CLINICAL TRIAL PROTOCOL

A Randomized, Assessor-blind Trial Comparing MENOPUR® (menotropins for injection) and Recombinant FSH (Follicle Stimulating Hormone) in a GnRH Antagonist Cycle with Single-Blastocyst Transfer in a High Responder Subject Population

000205

megaset–HR

EudraCT Number:	2008-006775-67
IND Number:	053954
Investigational Medicinal Product:	MENOPUR® (menotropins for injection)
Indication:	Development of multiple follicles and pregnancy in ovulatory women as part of an Assisted Reproductive Technology (ART) Cycle with ICSI
Phase:	4
Name and Address of Sponsor:	Ferring International PharmaScience Center US Inc. Reproductive Health & Urology 100 Interpace Parkway Parsippany, NJ 07054 973-796-1600
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A Randomized, Assessor-blind Trial Comparing MENOPUR® and Recombinant FSH in a GnRH Antagonist Cycle with Single-Blastocyst Transfer in a High Responder Subject Population

TRIAL SITES

25-30 infertility centers in the United States (US)

PLANNED TRIAL PERIOD		CLINICAL PHASE
First subject first visit:	August/September 2015	4
Last subject last visit:	December 2016	

OBJECTIVES

Primary Objective

- To demonstrate non-inferiority of MENOPUR® versus recombinant follicle-stimulating hormone (Gonal-f®) with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation (COS) following a gonadotropin-releasing hormone (GnRH) antagonist protocol.

Secondary Objectives

- To evaluate the positive β-human chorionic gonadotropin (hCG) rates and clinical pregnancy rates after stimulation with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate follicular development during stimulation with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate the serum endocrine profile during stimulation with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate the number of oocytes retrieved, the fertilization rate, and embryo quality, associated with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate the live birth rate associated with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate the adverse event (AE) profile of MENOPUR® and Gonal-f®

ENDPOINTS

The primary endpoint is the ongoing pregnancy rate, defined as the presence of at least 1 intrauterine pregnancy with a detectable fetal heartbeat at 10-11 weeks gestation (8-9 weeks after blastocyst transfer in the fresh cycle).

Secondary Endpoints

- Positive β-hCG rate (2 positive β-hCG tests; the first approximately 10-14 days after blastocyst transfer in the fresh cycle and a second confirmatory test approximately 2 days later).
- Clinical pregnancy rate (transvaginal ultrasound [TVUS] showing at least 1 intrauterine gestational sac with fetal heart beat at 6-7 weeks gestation, 4-5 weeks after blastocyst transfer in the fresh cycle).
- Early pregnancy loss (defined as 2 positive β-hCG tests but no ongoing pregnancy at 10-11 weeks gestation in the fresh cycle).
- Follicular development as assessed by TVUS (total number of follicles and number of follicles with a diameter of ≤9mm, 10-11 mm, 12-14 mm, 15-16 mm, and ≥17 mm on stimulation Day 6 and last day of stimulation).
- Endocrine profile:
    - Serum follicle-stimulating hormone (FSH), hCG, luteinizing hormone (LH), androstenedione, total testosterone, dehydroepiandrosterone: Day 1, Day 6, and last day of stimulation.
    - Progesterone (P4), estradiol (E2): Day 1, Day 6, last day of stimulation, and Visit 4 (morning following hCG trigger).
- Oocytes retrieved metaphase II oocytes, number of oocytes undergoing ICSI, fertilization rate, quality of embryos 3 days after oocyte retrieval, and the quality of blastocysts 5 days after oocyte retrieval.
- Aneuploidy rate.
- Endometrial assessment by TVUS (endometrial thickness in mm and echogenicity pattern on stimulation Day 6, last day of stimulation, and at the time of blastocyst transfer in the fresh cycle [transabdominal pelvic ultrasound or TVUS]).

Post-trial Endpoints

- Cumulative live birth rate for fresh and frozen blastocyst transfers (viable live birth greater >21 weeks gestation).
- Live birth rate for fresh blastocyst transfers (viable live birth greater >21 weeks gestation).
- Early pregnancy loss rate in frozen blastocyst transfer, defined as 2 positive β-hCG tests but no ongoing pregnancy at 10-11 weeks gestation in the frozen cycle.

- Late pregnancy loss rate (defined as a confirmed ongoing pregnancy but no live birth).
- Positive β-hCG rate, clinical pregnancy rate, and ongoing pregnancy rate for frozen blastocyst transfers.

Safety Endpoints

- AEs.
- Frequency of ovarian hyperstimulation syndrome (OHSS) (early OHSS if the onset is ≤9 days after hCG administration and late OHSS if the onset is >9 days after hCG administration).

METHODOLOGY

This is a Phase 4, randomized, open-label, assessor-blind, parallel-group, multicenter non-inferiority trial with the option for superiority. Approximately 600 females undergoing COS following a GnRH antagonist protocol at approximately 25-30 infertility centers in the US will be randomized 1:1 to receive either MENOPUR® or Gonal-f®. The primary endpoint is ongoing pregnancy rate.

On the second or third day of spontaneous menses, gonadotropins (either MENOPUR® or Gonal-f®) will be initiated at 150 IU for 5 days. From stimulation Day 6 onward, based on follicular response assessed by TVUS, dosing can be adjusted every day as needed by 75 IU per adjustment. However, the maximum gonadotropin dose will be 300 IU/day; gonadotropin dosing can continue for a maximum of 20 days.

Once the lead follicle measures ≥14 mm and/or serum E2 levels are ≥300 pg/mL, the GnRH antagonist (ganirelix acetate) will be initiated at a daily dose of 0.25 mg and continued throughout the gonadotropin treatment period. The stimulation day of the antagonist start will be recorded in the electronic case report form. A single injection of 250 µg hCG (Ovidrel®) will be administered to induce final follicular maturation as soon as 3 follicles of ≥17 mm are observed on TVUS. In the case of excessive ovarian response (>30 follicles of ≥12 mm each and/or E2 levels ≥5000 pg/mL), the hCG trigger will be replaced with a GnRH agonist trigger (4 mg leuprolide acetate) and the fresh blastocyst transfer cancelled, with cryopreservation of all resultant viable blastocysts following biopsy. Oocyte retrieval will take place roughly 36 hours after hCG administration, and oocytes will be inseminated by intracytoplasmic sperm injection (ICSI) 4±1 hours after retrieval; oocyte maturity will be recorded. Fertilization (number of pronuclei) will be checked on Day 1 following oocyte retrieval. Embryo quality will be assessed on Days 3 and 5 following oocyte retrieval; in the case of late blastulation, assessments will be made on Day 6 or Day 7, as needed.

On Day 5 following ICSI, a single blastocyst of the best quality available will be transferred; all remaining blastocysts will be frozen using the vitrification method. Laser-assisted trophectoderm biopsy for preimplantation genetic screening will be done on expanded blastocysts on Day 5; in the case of late blasulation, biopsy will be performed on Day 6 or Day 7, as needed. The PGS results will not be used to determine blastocyst selection for fresh transfer on Day 5. The evening of the

day after oocyte retrieval, vaginal progesterone inserts (ENDOMETRIN®; Ferring) will be initiated for luteal phase support and will continue until the day of the β-hCG test (10-14 days after blastocyst transfer). On the day that the progesterone inserts are initiated, only a single, 100 mg dose of ENDOMETRIN® will be given. On subsequent days, two (2) doses of ENDOMETRIN® (100 mg/BID for a total of 200 mg/day) will be given. ENDOMETRIN® will be continued for a maximum of 10 weeks total if pregnancy is confirmed. For subjects with no ongoing pregnancy in the fresh cycle, single frozen blastocyst transfer can be initiated within 6 months of a subject's date of randomization.

NUMBER OF SUBJECTS

Approximately 600 infertile females are to be randomized (300 subjects per group).

MAIN CRITERIA FOR INCLUSION/EXCLUSION

Subjects are to be aged 21 to 35 years with regular ovulatory menstrual cycles of 21 to 45 days, with a body mass index between 18 and 30 kg/m^2, infertility for a period of ≥1 year (≥6 months if receiving donor sperm), and who have a serum anti-Müllerian hormone (AMH) ≥5 ng/mL at screening. Key exclusion criteria include endometriosis stage III-IV, history of recurrent miscarriage, and previous poor response to a COS cycle.

MEDICINAL PRODUCTS

Investigational Medicinal Products (IMPs):

Each IMP will be administered subcutaneously once daily for up to 20 days at a dose of 75 IU to 300 IU.

- MENOPUR® (menotropins for injection) manufactured by Ferring Pharmaceuticals Inc., will be provided as a vial with powder (75 IU FSH activity and 75 IU LH activity) and a vial with diluent. After reconstitution, each vial delivers 75 IU of FSH activity and 75 IU of LH activity.
- Gonal-f®, (follitropin alpha for injection) a human follicle stimulating hormone (FSH) preparation of recombinant DNA origin manufactured by EMD Serono Inc., will be provided as pen and cartridges filled with either 300 or 450 IU of FSH activity.

Concomitant Therapy (Non-investigational Medicinal Products [NIMPs]):

The NIMPs include the following:

- Ganirelix® (ganirelix acetate injection), manufactured by Merck, will be provided as a pre-filled syringe (0.5 mL) delivering 0.25 mg Ganirelix. A daily dose of 0.25 mg will be continued throughout the gonadotropin treatment period.
- Ovidrel® (choriogonadotropin alfa), manufactured by EMD Serono Inc., will be provided as a pre-filled syringe (0.5 mL) delivering 250 μg choriogonadotropin alfa, to be administered as a single injection as soon as 3 follicles of ≥17 mm are observed on TVUS.
- ENDOMETRIN® (progesterone), manufactured by Ferring Pharmaceuticals Inc., will be

provided as inserts to be administered vaginally. On the day that the progesterone inserts are initiated, only a single, 100 mg dose of ENDOMETRIN® will be given. On subsequent days, ENDOMETRIN® will be administered 2 times daily, each delivering 100 mg of progesterone (200 mg/day). ENDOMETRIN® will be initiated the evening of the day after oocyte retrieval and will continue until the day of the second β-hCG test (if negative) or if pregnancy is confirmed by the second β-hCG test for a maximum of 10 weeks total.

DURATION OF TREATMENT

Subjects are treated with IMPs (either HP-hMG or Gonal-f®) for a maximum of 20 days.

STATISTICAL METHODS

Sample Size Calculation

The study has at least 80% power, with 275 subjects per treatment group, to demonstrate the non-inferiority of MENOPUR® to Gonal-f® in the ongoing clinical pregnancy rate at the 1-sided significance level of 0.025 with a 12% non-inferiority margin, by assuming an ongoing pregnancy rate of 50% for both treatment groups (Yeh et al. 2014). Assuming that 8% of the subjects may not be eligible for the per protocol analysis set, approximately 600 subjects will be randomized (1:1) into this study.

Efficacy:

The primary objective of the trial is to demonstrate the non-inferiority of MENOPUR® versus Gonal-f® with respect to ongoing pregnancy rate in women undergoing COS following a GnRH antagonist protocol. The non-inferiority limit for the difference between treatments (MENOPUR® minus Gonal-f®) will be -12% (absolute). The non-inferiority hypothesis to be tested for the primary endpoint will be:

H_0: $\pi_{MENOPUR} - \pi_{Gonal\text{-}f} \leq -12\%$
against the alternative
H_1: $\pi_{MENOPUR} - \pi_{Gonal\text{-}f} > -12\%$, where
$\pi_{MENOPUR}$ and $\pi_{Gonal\text{-}f}$ denote the ongoing pregnancy rate of subjects treated with MENOPUR® and Gonal-f®, respectively, in a single fresh blastocyst transfer following a GnRH antagonist protocol.

The null hypothesis (H_0) will be tested against the alternative by constructing a 2-sided 95% confidence interval for the difference in ongoing pregnancy rates. Subjects who do not have at least 1 intrauterine pregnancy with a detectable fetal heartbeat at 10-11 weeks gestation (8-9 weeks after blastocyst transfer in the fresh cycle), due to missing data, early withdrawal, or any other reason will be considered treatment failures (i.e., not having ongoing pregnancy). If the lower-limit of the 95% confidence interval is greater than the non-inferiority limit (-12%), the null hypothesis will be rejected and it will be claimed that MENOPUR® is non-inferior to Gonal-f® with respect to ongoing pregnancy rate. The primary efficacy analysis will be conducted for the modified intent-to-treat population, defined as all randomized (as planned) subjects who received at least 1 dose of IMP. If the lower bound of the confidence interval is above 0%, superiority will be declared.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AMH	anti-Müllerian hormone
ART	assisted reproductive technology
BMI	body mass index
COS	controlled ovarian stimulation
CRO	contract research organization
DHEA	dehydroepiandrosterone
E2	estradiol
eCRF	electronic case report form
EOT	end of treatment
EudraCT	European Union Clinical Trial Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
ICSI	intracytoplasmic sperm injection
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	intent-to-treat
IVF	in vitro fertilization
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MERiT	Menotrophin vs. Recombinant FSH in vitro Fertilization Trial
mITT	modified intent-to-treat
NIMP	Non-Investigational Medicinal Product
OHSS	ovarian hyperstimulation syndrome
P4	progesterone
PGS	preimplantation genetic screening
PP	per protocol
rFSH	recombinant follicle-stimulating hormone
SAE	serious adverse event

SOC	system organ class
TSH	thyroid stimulating hormone
TVUS	transvaginal ultrasound
US	United States

1 INTRODUCTION

1.1 Background

The Menotrophin vs. Recombinant FSH in vitro Fertilization Trial (MERiT) study was a large, randomized, open-label, multicenter, multinational study comparing treatment outcomes of controlled ovarian stimulation (COS) using MENOPUR® (n=363) with those using recombinant follicle-stimulating hormone (rFSH) α (Gonal-f®, Merck KGaA, Darmstadt, Germany, n=368) in in vitro fertilization (IVF) cycles using a long gonadotropin-releasing hormone (GnRH) agonist down-regulation protocol (Andersen, 2006). The results of this study conducted in 2005 demonstrated non-inferiority of MENOPUR® to Gonal-f® in ongoing pregnancy rates. Meta-analyses have indicated that menotropins provide higher live birth rates than Gonal-f® in the long GnRH agonist protocol (van Wely et al. 2011). A randomized, open-label, assessor-blind, parallel-group, multicenter trial comparing the efficacy of MENOPUR® and rFSH (Puregon®: Schering-Plough Organon) was conducted in subjects undergoing COS following a GnRH antagonist protocol; this study, called MEGASET, randomized 749 subjects in Europe (Belgium, Czech Republic, Denmark, Poland, Spain, Sweden, and Turkey) (Devroey, 2012). The ongoing pregnancy rates in the MENOPUR® and Puregon® groups were 28.9% and 26.7%, respectively, in the intent-to-treat (ITT) population and 30.0% and 27.0%, respectively, in the per protocol (PP) population. The non-inferiority of MENOPUR® to Puregon®, with respect to the ongoing pregnancy rate, was demonstrated for both the ITT and PP populations.

A retrospective analysis of data from both MERiT and MEGASET evaluated the impact of gonadotropin treatment on ovarian response and clinical outcome in women at risk of a high response and who were undergoing IVF/intracytoplasmic sperm injection (ICSI) treatment (Arce, 2014). Women at risk of a high response were defined as those with anti-Müllerian hormone (AMH) levels >75th percentile (i.e., equivalent to >5.2 ng/mL [37.4 pmol/L] in both studies), corresponding to 155 women in the MERiT study and 188 women in the MEGASET study. High ovarian response was defined as ≥15 oocytes retrieved. Treatment with MENOPUR® versus rFSH was associated with a lower median number of oocytes retrieved in women at risk of a high response, irrespective of the down-regulation protocol (Arce, 2014). When the data of women with high AMH from both protocols were integrated, MENOPUR® treatment was associated with a significantly lower incidence of high response (32% versus 49%, p=0.001) and increased live birth rate per started cycle (34% versus 22%, p=0.012) compared with rFSH treatment (Arce, 2014).

1.2 Scientific Justification for Conducting the Trial

The current study has a similar design as the MEGASET study conducted in Europe. The aim of this study is to demonstrate non-inferiority of MENOPUR® versus rFSHα (Gonal-f®) with respect to ongoing pregnancy rate in potential high-responders undergoing IVF/ICSI treatment, using an initial gonadotropin dose of 150 IU within a GnRH antagonist-controlled protocol. Subjects will be classified as high ovarian responders based on a serum level of AMH ≥5ng/mL. The AMH

measurements will be determined at a single reference laboratory (ReproSource, Inc., Woburn, MA) utilizing materials and reagents from Beckman Coulter-DSL (Chaska, MN).

1.3 Benefit/Risk Aspects

This study will be conducted using approved drugs with well-established efficacy and safety profiles; thus, the benefit/risk aspects are expected to be similar to what is outlined in the package insert for MENOPUR® (menotropins for injection [package insert] 2014) and Gonal-f RFF® Redi-ject™ (follitropin alfa injection [package insert] 2014).

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To demonstrate non-inferiority of MENOPUR® versus recombinant follicle-stimulating hormone (Gonal-f®) with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation (COS) following a gonadotropin-releasing hormone (GnRH) antagonist protocol.

Secondary Objectives

- To evaluate the positive β-human chorionic gonadotropin (hCG) and clinical pregnancy rates after stimulation with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate follicular development during stimulation with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate the serum endocrine profile during stimulation with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate the number of oocytes retrieved, the fertilization rate, and embryo quality associated with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate the live birth rate associated with MENOPUR® and Gonal-f® following a GnRH antagonist protocol.
- To evaluate the adverse event (AE) profile of MENOPUR® and Gonal-f®

2.2 Endpoints

Primary Endpoint

- Ongoing pregnancy rate, defined as the presence of at least 1 intrauterine pregnancy with a detectable fetal heartbeat at 10–11 weeks of gestation (8-9 weeks after blastocyst transfer in the fresh cycle).

Secondary Endpoints

- Positive β-hCG rate (2 positive β-hCG tests; the first approximately 10-14 days after blastocyst transfer in the fresh cycle and a second confirmatory test approximately 2 days later).
- Clinical pregnancy rate (transvaginal ultrasound [TVUS] showing at least 1 intrauterine gestational sac with fetal heart beat at 6-7 weeks gestation, 4-5 weeks after blastocyst transfer in the fresh cycle).
- Early pregnancy loss (defined as 2 positive β-hCG tests but no ongoing pregnancy at 10-11 week's gestation in the fresh cycle).

- Follicular development as assessed by TVUS (total number of follicles and number of follicles with a diameter of ≤9 mm, 10-11 mm, 12-14 mm, 15-16 mm, and ≥17 mm on stimulation Day 6 and the last day of stimulation).
- Endocrine profile:
  - Serum follicle-stimulating hormone (FSH), hCG, luteinizing hormone (LH), androstenedione, total testosterone, dehydroepiandrosterone (DHEA): Day 1, Day 6, and last day of stimulation.
  - Progesterone (P4), estradiol (E2): Day 1, Day 6, last day of stimulation, and Visit 4 (morning following hCG administration).
- Oocytes retrieved metaphase II oocytes, number of oocytes undergoing ICSI, fertilization rate, quality of embryos 3 days after oocyte retrieval, and the quality of blastocysts 5 days after oocyte retrieval.
- Aneuploidy rate.
- Endometrial assessment by TVUS (endometrial thickness in mm and echogenicity pattern on stimulation Day 6, the last day of stimulation, and at the time of blastocyst transfer in the fresh cycle [transabdominal pelvic ultrasound or TVUS]).

Post-trial Endpoints

- Cumulative live birth rate for fresh and frozen blastocyst transfers (viable live birth >21 weeks gestation).
- Live birth rate for fresh blastocyst transfers (viable live birth >21 weeks gestation).
- Early pregnancy loss rate in frozen blastocyst transfer, defined as 2 positive β-hCG tests but no ongoing pregnancy at 10-11 weeks gestation in the frozen cycle.
- Late pregnancy loss rate (defined as a confirmed ongoing pregnancy but no live birth).
- Positive β-hCG rate, clinical pregnancy rate, and ongoing pregnancy rate for frozen blastocyst transfers.

Safety Endpoints

- AEs.
- Frequency of ovarian hyperstimulation syndrome (OHSS) (early OHSS if the onset is ≤9 days after hCG administration and late OHSS if the onset is >9 days after hCG administration).

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

A trial flow diagram is presented in Figure 1.

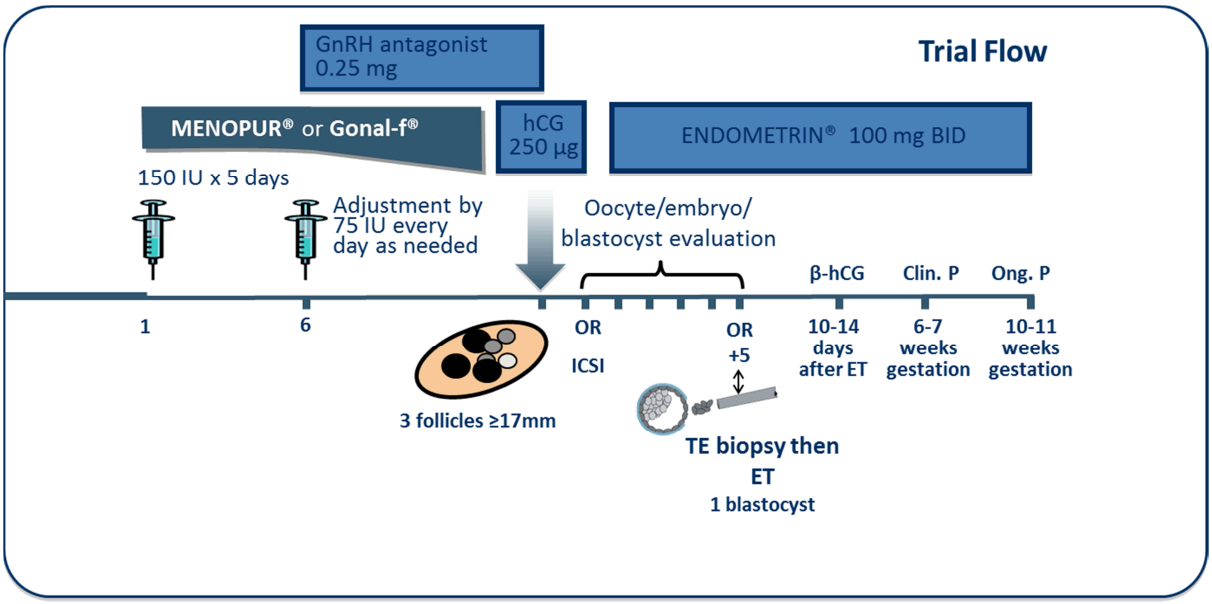

Figure 1 Trial Flow Diagram

3.1.2 Overall Design and Control Methods

This is a Phase 4, randomized, open-label, assessor-blind, parallel-group, multicenter study to be conducted at approximately 25-30 infertility centers in the United States (US). Approximately 600 females undergoing COS following a GnRH antagonist protocol will be randomized to receive either MENOPUR® or Gonal-f®. The study is designed to demonstrate non-inferiority of MENOPUR® versus Gonal-f® for ongoing pregnancy rates in a predefined high-responder subject population. High responders will be defined as subjects who have a serum AMH ≥5 ng/mL. All AMH measurements will be determined at a single reference laboratory (ReproSource, Inc., Woburn, MA), utilizing materials and reagents from Beckman Coulter-DSL (Chaska, MN).

Subjects will be randomized 1:1 to undergo COS with either MENOPUR® or Gonal-f® in a GnRH antagonist cycle. Gonadotropins (either MENOPUR® or Gonal-f®) will be started on the second or third day of spontaneous menses. The gonadotropin dose will be initiated at 150 IU for the first 5 days. From stimulation Day 6 onward, based on follicular response assessed by TVUS, dosing can be adjusted every day as needed by 75 IU per adjustment. However, the maximum gonadotropin dose will be 300 IU/day; gonadotropin dosing can continue for a maximum of 20 days. Coasting is prohibited.

If the lead follicle measures ≥14 mm and/or serum E2 levels are ≥300 pg/mL, the GnRH antagonist Ganirelix® (ganirelix acetate) will be initiated at a daily dose of 0.25 mg and continued throughout the gonadotropin treatment period. The stimulation day of the antagonist start will be recorded in the electronic case report form (eCRF). A single injection of 250 µg hCG (Ovidrel®) will be administered to induce final follicular maturation as soon as 3 follicles of ≥17 mm are observed on TVUS. If a subject has >30 follicles that are ≥12 mm each, she will receive 4 mg of leuprolide acetate administered subcutaneously at least 12 hours after the last dose of the GnRH antagonist. If the GnRH agonist trigger was required, TVUS-guided oocyte retrieval will be performed approximately 36 hours later, and all resultant viable blastocysts will be vitrified after trophectoderm biopsy, with no fresh blastocyst transfer to decrease risk of OHSS.

In order to minimize the risk of empty follicle syndrome, the subject will return the morning after hCG trigger to draw serum hCG, E2, and P4 levels. If the hCG level is <50 IU/L and/or P4 is <3.5 ng/mL, then a booster/rescue second dose of hCG must be given on that day as soon as possible. If the subject received the GnRH agonist trigger, the bloods drawn will be LH, E2, and P4 levels. If, after the GnRH agonist trigger, the LH is <15 IU/L and/or the P4 <3.5 ng/mL, a rescue/booster dose of hCG (Ovidrel®) should be given as soon as possible. Delay of oocyte retrieval will be left to the clinician's discretion and will be based on the time at which the rescue dose was administered.

Oocyte retrieval will take place approximately 36 hours after hCG administration. Oocytes will be inseminated using partner sperm by ICSI 4±1 hours after retrieval; oocyte maturity will be recorded. Fertilization (number of pronuclei) will be checked on Day 1 following oocyte retrieval. Embryo quality will be assessed on Days 3 and 5 following oocyte retrieval; in the case of late blastulation, assessments will be made on Day 6 or 7, as needed. On Day 5 following ICSI, a single blastocyst of the best quality available will be transferred; all remaining biopsied blastocysts will be frozen using the vitrification method. Laser-assisted trophectoderm biopsy for preimplantation genetic screening (PGS) will be done on Day 5; in the case of late blasulation, biopsy will be performed on Day 6 or Day 7, as needed. PGS results will not be used to select the blastocyst for fresh transfer. No fresh transfers will be done on Day 6 or Day 7 blastocysts.

The evening of the day after oocyte retrieval, vaginal progesterone inserts (ENDOMETRIN®; Ferring) will be initiated for luteal phase support. On the day that the progesterone inserts are initiated, only a single, 100 mg dose of ENDOMETRIN® will be given. On subsequent days, two (2) doses of ENDOMETRIN® (100 mg / BID for a total of 200 mg/day) will be given. ENDOMETRIN® will be continued until the day of the β-hCG test (10-14 days after blastocyst transfer) if negative for pregnancy or if pregnancy is confirmed, will be continued for a maximum of 10 weeks.

Positive β-hCG will be confirmed by 2 positive β-hCG tests, the first performed approximately 10-14 days after blastocyst transfer with a second positive test 2 days later. Clinical pregnancy will be confirmed by TVUS, indicating at least 1 intrauterine gestational sac with fetal heart beat at 6-7

weeks gestation (4-5 weeks after blastocyst transfer). Ongoing pregnancy will be confirmed by at least 1 intrauterine viable fetus at 10-11 weeks gestation (8-9 weeks after blastocyst transfer).

For subjects with no ongoing pregnancy in the fresh cycle or for those receiving agonist trigger, single frozen blastocyst transfer cycles can be initiated within 6 months of a subject's initial date of randomization. Single blastocyst transfer is mandatory. The PGS results can be used to select a euploid blastocyst for frozen blastocyst transfer. Frozen-thawed blastocyst transfer cycle data will be collected, including blastocyst transfer information (to include embryo grade, euploid status, endometrial thickness, presence of blood/mucus on transfer catheter tip, and whether blastocyst is retained in the catheter requiring a second pass), β-hCG test results, clinical pregnancy, ongoing pregnancy, and live birth.

In women undergoing COS, an excessive response to follicular-stimulating agents may lead to the development of OHSS, which represents a spectrum that can be categorized as mild, moderate, or severe. Subjects who have an excessive response to ovarian stimulation (>30 follicles that are ≥12 mm each and/or serum E2 ≥5000 pg/mL) will have the cycle cancelled and converted to freeze all with GnRH agonist trigger. That is, the subject will receive 4 mg of leuprolide acetate administered subcutaneously at least 12 hours after the last dose of the GnRH antagonist; TVUS-guided oocyte retrieval will be performed approximately 36 hours later, and all resultant blastocysts will be vitrified after trophectoderm biopsy, with no fresh blastocyst transfer, to decrease the risk of OHSS.

All cases of OHSS will be considered AEs and will be recorded in the source documents for that subject and on the AE page in the eCRF. Severe OHSS that requires medical or surgical intervention (i.e., paracentesis, hospitalization) is considered a serious adverse event (SAE). See Section 7.1.6 for definitions of mild, moderate, and severe OHSS.

Post-trial follow-up extends to collection of delivery information (live birth and neonatal health to include APGAR scores, birth weight, gestational age at birth, presence of congenital anomaly/birth defect, and cause of neonatal death, if applicable), which will be collected for all subjects with an ongoing pregnancy in the fresh cycle or the 6-month post-randomization frozen-thawed blastocyst transfer cycles. Live birth rate after the fresh cycle and cumulative live birth rate after fresh and 6-month post-randomization frozen-thawed blastocyst transfer cycles will be evaluated as part of the post-trial follow-up.

3.2 Planned Number of Trial Sites and Subjects

The study is planned to be conducted in 25-30 infertility centers in the US. Approximately 600 infertile females are to be randomized (1:1).

3.3 Discussion of Overall Trial Design and Choice of Control Groups

3.3.1 Trial Design

This is a multicenter, randomized, open-label, assessor-blind, parallel-group study to be conducted in female subjects undergoing COS following a GnRH antagonist protocol. Each study center will

follow the study center's standard practice for assisted reproductive technology (ART) unless otherwise noted in this protocol. Subjects who are potential high ovarian responders will be enrolled; high ovarian responders will be classified based on a high serum level of AMH ≥5 ng/mL at the start of stimulation. Eligible subjects will be randomly assigned to 1 of 2 treatment arms, either MENOPUR® or Gonal-f®; COS will continue for up to 20 days.

The primary objective of the trial is to demonstrate the non-inferiority of MENOPUR® versus Gonal-f® with respect to ongoing pregnancy rate in women undergoing COS following a GnRH antagonist protocol. The non-inferiority limit for the difference between treatments (MENOPUR® minus Gonal-f®) will be -12% (absolute).

3.3.2 Selection of Endpoints

The efficacy endpoints in this study (ongoing pregnancy rate, positive β-hCG rate, clinical pregnancy rate, live birth rate, fertilization rate, number of oocytes retrieved, embryo quality, aneuploidy rate, and pregnancy loss) are typical endpoints to demonstrate the effectiveness of products used for ovarian stimulation and pregnancy in infertile subjects. Safety endpoints of AEs, laboratory results, and OHSS are also typical.

3.3.3 Blinding

MENOPUR® is provided in a vial (powder), while Gonal-f® is provided in a pen and cartridge system. Therefore, a double-blind design is not feasible. The trial; however, is assessor-blind, ensuring unbiased evaluation by the individual performing the ultrasound monitoring, embryologists, and central laboratory personnel. Furthermore, the primary endpoint for this trial is ongoing pregnancy rate, a clinically objective assessment.

3.3.4 Selection of Doses in the Trial

Either MENOPUR® or Gonal-f® will be administered subcutaneously once daily for up to 20 days at a dose of 75 IU to 300 IU.

3.3.5 Selection and Timing of Dose for Each Subject

The dose of the investigational medicinal product (IMP) (MENOPUR® or Gonal-f®) will be initiated at 150 IU for the first 5 days. From stimulation Day 6 onward, based on follicular response assessed by TVUS, dosing can be adjusted every day, as needed, by 75 IU per adjustment. However, the maximum gonadotropin dose will be 300 IU/day; gonadotropin dosing can continue for a maximum of 20 days.

3.3.6 Withdrawal Criteria

A subject that withdraws from the study will not be replaced. Every subject has the right to refuse further participation in the study at any time and without providing reasons. A subject's participation is to terminate immediately upon her request. The Investigator should seek to obtain the reason and record this in the source documents and eCRF.

If, at the time of refusal, a dose of the study product has already been administered, the subject must be advised to consider follow-up safety investigations that will include all procedures outlined for the end of treatment (EOT) Visit.

The subject can also be withdrawn from the study at any time at the discretion of the Investigator; the reason should be discussed with the Sponsor prior to discontinuation and fully documented in the source documents and eCRF.

3.3.7 Follow-up Procedures

Subjects will return to the study center for regular scheduled clinic visits as required per protocol for measurement of hormone levels, TVUS, pregnancy testing, and other safety assessments. Unscheduled visits are allowed, per Investigator discretion and standard of care. Approximately 10-14 days after blastocyst transfer, all subjects will have a serum pregnancy test; subjects with a positive test result will have a second confirmatory test performed 2 days later.

Clinical pregnancy will be confirmed by TVUS, indicating at least 1 intrauterine gestational sac with fetal heart beat at 6-7 weeks gestation (4-5 weeks after blastocyst transfer). Ongoing pregnancy will be confirmed by at least 1 intrauterine viable fetus at 10-11 weeks of gestation (8-9 weeks after blastocyst transfer).

For subjects with no ongoing pregnancy in the fresh cycle, single frozen blastocyst transfers can be initiated within 6 months of the date of the subject's initial randomization. The PGS results can be used to select a euploid blastocyst for frozen transfer(s).

Post-trial follow-up extends to collection of delivery information (live birth and neonatal health), which will be collected for all subjects with an ongoing pregnancy in the fresh cycle or the 6-month post-randomization frozen-thawed blastocyst transfer cycles. Frozen-thawed blastocyst transfer cycle data will be collected, including blastocyst transfer information, β-hCG test results, clinical pregnancy, and ongoing pregnancy. Live birth rate after the fresh cycle and cumulative live birth rate following the fresh and 6-month post randomization start frozen-thawed cycles (if applicable) will be evaluated as part of the post-trial follow-up.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

To be eligible for participating in the trial, subjects must satisfy the following criteria:

1. Signed informed consent, prior to any study-related procedure.
2. Females aged 21 to 35 years with regular ovulatory menstrual cycles of 21 to 45 days, with a BMI between 18 and 30 kg/m^2 who desire pregnancy.
3. Subjects must be high responders, defined as subjects who have a serum AMH ≥5 ng/mL at screening.
4. Documented history of infertility (e.g., unable to conceive for at least 12 months or for at least 6 months if receiving donor sperm) with a Day 2 or Day 3 serum FSH level between 1 and 12 IU/L (inclusive), the results of which should be obtained within 6 months prior to screening. The highest FSH result within 6 months prior to screening will be considered for inclusion. Patients with documented bilateral tubal occlusion established as a cause of infertility are eligible at diagnosis.
5. Male partner with semen analysis that is at least adequate for ICSI at screening or within 6 months prior to the screening date. Partners with severe male factors requiring invasive or surgical sperm retrieval may not be used. Use of donor sperm is allowed.
6. Willing to accept transfer of 1 blastocyst per cycle.
7. At least 1 cycle with no fertility medication immediately prior to screening.
8. Hysterosalpingography, hysteroscopy, or saline hysterosonogram documenting uterine anatomy appropriate for ART at screening or within 12 months prior to screening.
9. TVUS documenting presence and adequate visualization of at least 1 ovary, without evidence of abnormality (e.g., no endometrioma, no dermoid cysts) and normal adnexa (e.g., no hydrosalpinx) at screening.
10. Total testosterone, prolactin, and thyroid-stimulating hormone (TSH) within the normal limits for the clinical laboratory or considered not clinically significant by the Investigator at screening or within 12 months prior to screening. Note: Subjects with high TSH levels who receive replacement therapy and are considered adequately controlled can be enrolled at the discretion of the Investigator.
11. Pap smear test results that are appropriate for ART, in the opinion of the Investigator, at screening or within the last 24 months prior to screening.
12. Negative serum hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus (HIV) antibody, and rapid plasma reagin tests at screening or within 6 months prior to screening.
13. Willing and able to comply with the protocol for the duration of the study.

4.1.2 Exclusion Criteria

Subjects with any of the following are to be excluded from study participation:

1. Known stage III-IV endometriosis (American Society for Reproductive Medicine, 2012).
2. Oocyte donor or embryo recipient; gestational or surrogate carrier.
3. History of recurrent miscarriage not followed by a live birth (recurrent is defined as two (2) or more consecutive miscarriages)
4. Previous IVF or ART failure due to a poor response to gonadotropins. Poor response is defined as development of ≤2 mature follicles or history of 2 previous failed cycle cancellations prior to oocyte retrieval due to poor response.
5. Inadequate number of oocytes, defined as fewer than 5 oocytes retrieved in previous ART attempts.
6. Early follicular phase total antral follicle count (diameter 2-10 mm) <10 for both ovaries combined (results obtained at screening or within 12 months prior to screening).
7. Subject's male partner, with obvious leukospermia (>2 million white blood cells/mL) or signs of infection in semen sample within 6 months of the subject's screening. If either of these conditions exists, the male should be treated with antibiotics and retested prior to the subject's randomization.
8. Known abnormal karyotype of subject or her partner.
9. The use of hormonal birth control within 3 months prior to screening.
10. Use or plan to use any of the following medications during the pre-treatment and treatment phase: hormonal drug products (including estrogen, androgen supplementation, i.e., DHEA, androgen patch) progesterone creams, progesterone in oil injections, hydrocortisone, and other steroid drug products, and fertility modifiers such as insulin sensitizers. Occasional use of inhaled or topical corticosteroids may be permitted.
11. The presence of any uncontrolled systemic disease.
12. Currently breastfeeding, pregnant, or has a contraindication to pregnancy that would preclude participation in the trial.
13. Presence of abnormal uterine bleeding of undetermined origin.
14. Findings at the gynecological examination that preclude gonadotropin therapy, in the opinion of the Investigator.
15. History of chemotherapy (except for gestational conditions) or radiotherapy.
16. Current or recent substance abuse, including alcohol.
17. Current or recent (3 months prior to screening) smoking more than 3 cigarettes per day.
18. Documented intolerance or allergy to any of the medications used, including the study medication.
19. Participation in any experimental drug study within 30 days prior to screening.

20. Refusal or inability to comply with the requirements of the protocol for any reason, including scheduled clinic visits and laboratory tests.
21. Known mental incapacity or language barrier precluding adequate understanding of the informed consent information and the study activities.
22. Clinic staff member directly involved in the conduct of the study. Any other staff member interested in participating must obtain Institutional Review Board (IRB) approval prior to participation.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The site will recruit subjects based on the inclusion/exclusion criteria and local recruitment practices. Recruitment materials cannot be used prior to IRB approval.

4.2.2 Randomization

Randomization list will be generated by the study statistician prior to the first subject's first visit. Each subject will be randomized to 1 of the 2 treatment arms, MENOPUR® or Gonal-f®, immediately prior to administration of study drug. Randomization numbers will be allocated sequentially to the subjects in the order in which the subjects are randomized.

Under no circumstances will subjects be permitted to re-randomize for a second time in this study.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

Any concomitant therapies used during the study or within 1 month prior to screening will be recorded in the source documents and eCRF, along with the main reason for their prescription/use.

4.3.2 Prohibited Therapy

Use of any medications other than the study medication provided for this study should be avoided from the screening period until completion of the study. Occasional use of over-the-counter medications or prescription drugs may be allowed, except for those listed in Section 4.1.2.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products

Each IMP will be administered subcutaneously once daily for up to 20 days at a dose of 75 IU to 300 IU.

- MENOPUR® (menotropins for injection) manufactured by Ferring Pharmaceuticals Inc., will be provided as a vial with powder (75 IU FSH activity and 75 IU LH activity) and a vial with diluent. After reconstitution, each vial delivers 75 IU of FSH activity and 75 IU of LH activity.
- Gonal-f® (follitropin alpha for injection) a human follicle stimulating hormone (FSH) preparation of recombinant DNA origin manufactured by EMD Serono Inc., will be provided as pen and cartridges filled with either 300 or 450 IU of FSH activity.

5.1.2 Non-Investigational Medicinal Products (NIMPs)

The NIMPs include the following.

- Ganirelix® (ganirelix acetate injection), manufactured by Merck, will be provided as a pre-filled syringe (0.5 mL) delivering 0.25 mg Ganirelix. A daily dose of 0.25 mg will be continued throughout the gonadotropin treatment period.
- Ovidrel® (choriogonadotropin alfa), manufactured by EMD Serono Inc., will be provided as a pre-filled syringe (0.5 mL) delivering 250 μg choriogonadotropin alfa, to be administered as a single injection as soon as 3 follicles of ≥17 mm are observed on TVUS.
- ENDOMETRIN® (Progesterone), manufactured by Ferring Pharmaceuticals Inc., will be provided as inserts to be administered vaginally. On the day that the progesterone inserts are initiated, only a single, 100 mg dose of ENDOMETRIN® will be given. On subsequent days, ENDOMETRIN® will be administered 2 times daily, each delivering 100 mg of Progesterone (200 mg/day). ENDOMETRIN® will be initiated the evening of the day after oocyte retrieval and will continue until the day of the second β-hCG test (if negative) or if pregnancy is confirmed by the second β-hCG test for a maximum of 10 weeks total.

5.2 Characteristics and Source of Supply

All medicinal (IMP and NIMP) products will be provided by Ferring Pharmaceuticals Inc. and will be handled according to the principles of Good Manufacturing Practice.

5.3 Packaging and Labeling

Packaging and labeling of the medicinal products will be performed under the responsibility of the IMP department at Ferring Pharmaceuticals A/S in accordance with Good Manufacturing Practice and national regulatory requirements.

All IMP will be provided to the investigational site as vials with powder and prefilled syringes with solvent MENOPUR® or as pen and cartridges filled with solution (Gonal-f®) in its original packaging. Subjects will self-administer study drug subcutaneously once daily for up to 20 days.

The label of the IMP and NIMP will contain 1 self-adhesive tear-off portion to be affixed to the subject dispensing log, or similar, maintained at the trial site.

5.4 Conditions for Storage and Use

The Investigator will ensure that the medicinal products will be stored in appropriate conditions in a secure location with controlled access as per the label for each drug. The storage compartment shall be monitored regularly with a minimum-maximum thermometer and the values shall be documented. Deviations in storage temperature must be reported to the Sponsor without delay and the IMP must not be used until acceptance from the Sponsor is received. See package inserts for specific storage and use instructions of MENOPUR® (menotropins for injection [package insert] 2014), Gonal-f RFF® Redi-ject™ (follitropin alfa injection [package insert] 2014), Ganirelix® (ganirelix acetate injection [package insert 2013]), Ovidrel® (choriogonadotropin alfa [package insert] 2014), and ENDOMETRIN® (Progesterone) [package insert] 2014).

The IMPs (MENOPUR® or Gonal-f®) will only be administered to subjects who meet the eligibility criteria and are randomized to a treatment group in the study.

5.5 Blinding/Unblinding

The study is assessor blind trial to individuals performing the ultrasound monitoring, embryologists, and central laboratory personnel.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMP will only be dispensed to subjects who meet the eligibility criteria and are randomized to a treatment arm in the study.

The Investigator or designee will maintain a drug-dispensing log detailing the dates and quantities of IMPs dispensed to, and used by, each subject. The monitor will verify drug accountability during the study. In order to monitor compliance, the subjects are to return the empty, partially used, and unused vials to the Investigator at each visit. The Investigator or designee will reconcile and document the return on the drug accountability log. Any discrepancies should be discussed with the subject at the time of the return.

5.6.2 Return and Destruction of Investigational Medicinal Products

The Monitor will check the supplies, the drug accountability, and inventory records. Following this check, the Investigator or designee will sign off the records.

The Sponsor must issue a written approval prior to any destruction of IMP/NIMP. Any destruction document must clearly identify the study code, batch number, subject numbers involved, and the quantities of IMP/NIMP destroyed, including treatment visits, if applicable.

All used IMP/NIMP can be destroyed at the study site after the drug accountability has been finalized and signed off by the Investigator. This includes residual liquid in a vial or ampoule (where no second dose can be withdrawn).

Used syringes and needles should be destroyed immediately after usage according to normal procedures at each study site.

Any unused IMP/NIMP will be returned for destruction, as instructed by the IMP Department, Ferring Pharmaceuticals A/S, and in accordance with local requirements, after the drug accountability has been finalized, verified by the monitor, signed off by the Investigator, and approved by the Sponsor.

5.7 Auxiliary Supplies

Sponsor will provide the site with syringes and needles for administration of MENOPUR® 75 IU.

6 TRIAL PROCEDURES

The trial procedures for subjects are shown in Table 1.

Table 1 Trial Assessments

	Screening Pre-treatment	Stimulation			Post Trigger	Oocyte retrieval	Transfer	Pregnancy monitoring				End
								β-hCG		Clinical	Ongoing	EOT[1]
Timing	<90 days before Visit 2	Day 1 (Cycle Day 2-3)	Day 6	Protocol stimulation monitoring, Ovidrel® hCG injection	Post-hCG dose	36 h (±2 h) after hCG	5 days after oocyte retrieval	10-14 days after blastocyst transfer		4-5 weeks after blastocyst transfer	8-9 weeks after blastocyst transfer	
Visit	Visit 1	Visit 2	Visit 3	Unscheduled	Visit 4	Visit 5	Visit 6	Visit 7a	Visit 7b	Visit 8	Visit 9	
Written informed consent	X											
Inclusion/exclusion criteria	X	X										
Demographics, medical/infertility history	X											
Physical examination, vital signs	X											X
Gynecological examination with Pap smear[2]	X											
Pregnancy test	X	X						X	X[3]			
Local laboratory (standard of care E2, P4, hCG, LH)		X	X	X	X[4]							
Central laboratory (E2, P4, hCG, testosterone, androstenedione, DHEA, FSH, LH)		X[5]	X	X[6]	X[7]							
Central laboratory (AMH, chemistry, hematology)	X											X[11]
Screening laboratory	X[8]											
Randomization, dispense IMP		X[9]										
TVUS (study-specific)	X	X	X	X	X		X[12]			X	X	
Oocyte retrieval						X						
Blastocyst transfer/freezing							X					
Drug accountability (IMP only)			X	X	X							X
Concomitant medications	X[10]	X	X	X	X	X	X	X		X	X	X
Adverse events		X	X	X	X	X	X	X		X	X	X

1. EOT assessments will be performed at the subject's last scheduled visit or the following day or within 2 weeks after the last scheduled visit in the case of premature discontinuation from the study.
2. Pap smear if not done in the previous 24 months.
3. For subjects who have a positive serum β-hCG at visit 7a. If conflicting results are obtained in the first 2 tests (visits 7a & 7b), a third test will be performed 2 days after the second test.
4. Including hCG or LH (if leuprolide acetate is given) in the morning.
5. No hCG on Day 1 of stimulation.
6. Blood samples for central and local laboratory testing must be drawn on the last day of stimulation. Since the final day of stimulation may not be known until the late afternoon or evening of the hCG trigger dose, an extra blood sample/tube will be collected and stored onsite for each day of stimulation monitoring to ensure the final day of stimulation is collected.
7. Only P4 and E2 will be collected and sent to the central laboratory for the post trigger/Visit 4.
8. Screening labs: total testosterone, TSH, prolactin within 12 months prior to screening; FSH (Day 2/3), HIV, rapid plasma reagin, hepatitis B antigen, and hepatitis C antibody within 6 months prior to screening.
9. The gonadotropin starting dose is 150 IU for the first 5 days, followed by individual adjustments according to the subject's follicular response. Dose adjustment should be 75 IU per adjustment.
10. Collect/document all medications taken within 30 days prior to screening.
11. No AMH to be drawn at EOT.
12. At Visit 6, a transabdominal or transvaginal ultrasound will be performed to assess endometrial thickness and echogenicity.

6.1 Visit 1 - Screening and Pre-stimulation Period

Screening can take place within 90 days prior to Visit 2.

After giving written informed consent, the subject will be screened based on the following:

- inclusion/exclusion criteria
- medical and infertility history (including well documented gynecological and menstrual history)
- complete physical examination, including vital signs and BMI
- gynecological examination (including Pap smear if not performed within the previous 24 months)
- record concomitant medications taken within 1 month of screening
- uterine cavity appropriate for ART on hysterosalpingography, hysteroscopy, or saline sonohysterogram within 12 months prior to screening
- normal ovaries and adnexa on TVUS (at screening)
- total antral follicle count (diameter 2-10 mm) ≥10 for both ovaries combined
- serum pregnancy, chemistry, hematology, AMH levels via the central laboratory, and FSH.

Screening will also be based on total testosterone, prolactin and TSH within 12 months of screening and FSH (Day 2/3), HIV, hepatitis B antigen, hepatitis C antibody, and rapid plasma reagin within 6 months of screening.

Copies of all reports must be filed in the subject's chart.

Each study center will follow its standard of practice guidelines for ICSI within the study parameters noted in this protocol. Evaluation of the partner's fertility potential (semen analysis) should be included in the work-up if it was not done within the previous 6 months.

Re-screens are not allowed.

6.2 Visit 2 - Randomization and Start of Controlled Ovarian Stimulation, Cycle Day 2-3

After all inclusion/exclusion criteria are met, subjects will be randomized to undergo COS with either MENOPUR® or Gonal-f® in a GnRH antagonist cycle. The study medication will be initiated on the second or third day of spontaneous bleeding, after documentation of a negative urine or serum pregnancy test completed at the local onsite laboratory. The starting total daily dose for subjects in both arms will be 150 IU for the first 5 days. A review of concomitant medications and updated medical history will also be completed and a TVUS will be performed. E2, P4, testosterone, androstenedione, DHEA, FSH, LH will be drawn.

6.3 Visit 3 - Stimulation Follow-up (Day 6) and Unscheduled Visits

After 5 days of treatment with a dose of 150 IU (Day 6 of stimulation), the subject will return to the clinic for monitoring and adjustment of gonadotropin dose, as needed. A TVUS will be performed and serum hormone levels (E2, P4) will be collected and evaluated via the local laboratory. The start/stop dates, dosages, duration of treatment, and results of all ultrasounds and blood analyses

obtained during the stimulation will be documented in the eCRF as well as concomitant medications and AEs.

Based on follicular response assessed by TVUS, dosing can be adjusted daily as needed by 75 IU per adjustment. However, the minimum daily total dose is 75 IU and the maximum total daily dose of study drug may not exceed 300 IU. Dosing with HP-hMG or Gonal-f® can continue for a maximum of 20 days.

When the lead follicle measures ≥14 mm and/or serum E2 levels are ≥300 pg/mL, the GnRH antagonist (ganirelix acetate) will be initiated at a daily dose of 0.25 mg and continued throughout the gonadotropin treatment period and the exact stimulation day of administration will be documented in the eCRF.

Subjects will be monitored per the center's standard practice during the stimulation dosing between Days 7 to 20 or until the stimulation phase is complete or study treatment is discontinued. Although these visits are not protocol-specific and can vary based on each centers standard of care, the results of the TVUS, E2 levels, P4 levels, concomitant medications, and AEs will be documented in the eCRF as unscheduled stimulation visits. The TVUS and blood results from the final day of stimulation (day of hCG trigger administration) will be documented in the eCRF and blood samples sent to the central laboratory. Since the final day of stimulation may not be known until the late afternoon or evening of the hCG trigger dose, an extra blood sample/tube will be collected and stored onsite for each day of stimulation monitoring to ensure the final day of stimulation is collected. Subjects will receive a single subcutaneous injection of Ovidrel® (choriogonadotropin alfa, r-hCG) to induce final follicular maturation when ≥3 follicles of ≥17 mm are detected on TVUS.

The time between two Ganirelix® injections as well as the time between the last Ganirelix injection and the hCG injection should not exceed 30h.

- When injecting Ganirelix in the morning, treatment with Ganirelix should be continued throughout the gonadotropin treatment period including the day of triggering final follicular maturation.

- When injecting Ganirelix in the afternoon, the last Ganirelix injection should be given in the afternoon prior to the day of triggering final follicular maturation.

Important Note: coasting is prohibited. If the criteria for hCG administration is not met after 20 days of treatment (i.e., subject does not have ≥3 follicles ≥17 mm in size), the subject will be discontinued from study treatment. An EOT Visit will be scheduled or completed at this time and the information will be documented in the eCRF.

Subjects are to return the pens and empty, partially used, and unused vials/cartridges of the IMP to the site in order to monitor compliance. The coordinator or designee will reconcile and document the returned drug product in the drug accountability log.

6.4 Visit 4 - Day Following Administration of Ovidrel®

The subject will return to the center (in the morning) the day following the Ovidrel® injection for P4 and E2 samples to be submitted to the central laboratory; serum hCG will be analyzed at the local lab. A TVUS will be performed. The date, time, and dosage of Ovidrel® will be recorded as well as study medication compliance. Adverse events and concomitant medications will be assessed and documented. Any symptoms of OHSS will be closely monitored.

The cycle will be cancelled in case of poor ovarian response (if the Investigator judges that ≥3 follicles of ≥17 mm cannot be reached after a minimum of 10 days of stimulation).

Subjects who have an excessive response to ovarian stimulation (>30 follicles of ≥12 mm and/or E2 ≥5000 pg/mL) will have the fresh transfer cancelled, and the hCG trigger will be replaced with a GnRH agonist trigger (4 mg leuprolide acetate). If leuprolide acetate is administered, a blood sample for LH will be collected and analyzed at the local lab. All resultant expanded blastocysts will be vitrified after trophectoderm biopsy, with no fresh blastocyst transfer in order to decrease the risk of OHSS. Following oocyte retrieval and blastocyst evaluation, an End of Trial (EOT) Visit will be scheduled or completed and the information will be documented in the eCRF.

In order to minimize the risk of empty follicle syndrome, the subject will return the morning after hCG trigger to draw serum hCG, E2, and P4 levels. If the hCG level is <50 IU/L and/or P4 is <3.5 ng/mL, then a booster/rescue second dose of hCG must be given on that day as soon as possible. If the subject received the GnRH agonist trigger, the bloods drawn will be LH, E2, and P4 levels. If, after the GnRH agonist trigger, the LH is <15 IU/L and/or the P4 <3.5 ng/mL, a rescue/booster dose of hCG (Ovidrel®) should be given as soon as possible. Delay of oocyte retrieval will be left to the clinician's discretion and will be based on the time at which the rescue dose was administered.

6.5 Visit 5 - Oocytes Retrieval/Insemination

A TVUS will be performed and oocytes retrieved roughly 36 hours after hCG administration. Oocytes will be inseminated using partner or donor sperm by ICSI 4±1 hours after retrieval.

Oocyte maturity will be assessed at the time of ICSI. Fertilization (number of pronuclei) will be checked on Day 1 following oocyte retrieval. Embryos must be cultured individually in separate dishes/droplets following the Day 1 assessment. Embryo quality will be assessed on Days 3 and 5 following oocyte retrieval; in the case of late blasulation, assessment will be performed on Day 6 or Day 7, as needed. A standardized embryo grading system will be used and documented in the eCRF. Adverse events and concomitant medications will be assessed and documented.

Each subject will be provided with vaginal progesterone inserts (200 mg/day – ENDOMETRIN®) to begin luteal support on the evening of the day after oocyte retrieval. The dose will be administered following the instructions provided in the package insert. Luteal phase support will continue until negative β-hCG (10-14 days after blastocyst transfer) or 8-9 weeks gestation, if pregnant.

6.6 Visit 6 - Blastocyst Transfer

On Day 5 following ICSI, a single blastocyst of the best quality available will be transferred; all remaining blastocysts will be frozen using the vitrification method. A transabdominal pelvic ultrasound or transvaginal ultrasound will be performed to assess the endometrial thickness and echogenicity pattern. Laser-assisted trophectoderm biopsy for preimplantation genetic screening (PGS) will be done on Day 5; in the case of late blasulation, biopsy will be performed on Day 6 or Day 7, as needed. All expanded blastocysts with Blastocyst Expansion and Hatching Status 3-6, Inner Cell Mass grading A or B, and Trophoectoderm Grading A, B, or C. (Gardner & Schoolcraft, 1999) should be biopsied. The results of the PGS will not be available prior to the fresh blastocyst transfer, but can be used for subsequent frozen blastocyst transfer cycles, if needed. Adverse events and concomitant medications will be assessed and documented.

The residual cells obtained from ART (including granulosa cells, immature eggs, eggs that do not fertilize, sperm that is left over after fertilization, or embryos that stop developing, developed abnormally, are aneuploid or that would be discarded after other embryos are selected for embryo transfer or freezing) may be considered for use for further research in a future sub-study. Some of the research may be genetic and/or may be used for some of the following reasons.

- To further our understanding of how patients' genetics affect the response to medications designed for ovarian stimulation.
- To develop new techniques to optimize our understanding of genetic and chromosomal regulation in eggs, sperm, and embryos.
- To improve embryonic efficiency by assessing genes, DNA, RNA, proteins, chromosomes and cellular pathologies.
- To characterize normal and abnormal expression of genes and their functions, as well as downstream effects of transcription and translation.
- To determine the frequency of embryo mosaicism and chromosomal irregularities (inversions, translocations, deletions, etc.)
- To study proteins and their structure, functions, and interactions.

Subjects who wish to participate in such a sub-study will be asked to consent to the donation of this material.

6.7 Visits 7, 8, and 9 - Pregnancy Monitoring

- **Visit 7**: All subjects will be required to return to the clinic approximately 10-14 days after blastocyst transfer for β-hCG assessment. If the first serum β-hCG is positive, a second confirmatory test will be performed approximately 2 days later. If the pregnancy test is negative, ENDOMETRIN® will be discontinued and EOT procedures completed. If conflicting results are obtained in the first 2 tests, a third test will be performed 2 days after the second test. If a positive β-hCG is confirmed, ENDOMETRIN ® will continue up to 10 weeks from the time it was initiated until the EOT Visit.
- **Visit 8**: Subjects who are pregnant will return to the clinic 4-5 weeks after blastocyst transfer for clinical pregnancy assessment (TVUS showing at least 1 intrauterine gestational sac with fetal heartbeat).

- **Visit 9:** Subjects with clinical pregnancy will return to the clinic 8-9 weeks after blastocyst transfer for assessment of ongoing pregnancy (presence of at least 1 intrauterine pregnancy with a viable fetus with a detectable fetal heartbeat).

  An End of Trial (EOT) Visit will be scheduled or completed for non-pregnant subjects and the information will be documented in the eCRF.

Non-pregnant subjects: Subjects without 2 positive β-hCG tests, clinical pregnancy, or ongoing pregnancy in the fresh cycle, may undergo a single frozen blastocyst transfer within 6 months of each subject's date of randomization. The PGS results can be used to select the euploid blastocyst for frozen transfer. Frozen-thawed blastocyst transfer cycle data will be collected, including blastocyst transfer information (endometrial thickness and echogenicity, grade of blastocyst, ploidy of blastocyst, presence of blood, or mucus within catheter tip), β-hCG serum results, clinical pregnancy, and ongoing pregnancy for the first frozen blastocyst transfer cycle following negative pregnancy.

Subjects may also return to the study center for regularly scheduled clinic visits as required per study center standard of care. The data collected during these visits will not be documented in the eCRF unless it is new or is a change in concomitant medications, pregnancy, or AEs.

6.8 End of Trial (EOT) Visit

EOT assessments will be performed at the subject's last scheduled visit. If the EOT visit cannot be scheduled on the same day as the last scheduled visit, it can be done the following day. In the case of premature discontinuation from the study, an EOT visit will be completed within 2 weeks after the subject's last scheduled visit.

A physical examination will be done and vital signs will be recorded. The following laboratory tests will be performed by a central laboratory (no AMH will be drawn):

- Serum chemistry: non-fasting glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase.
- Hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count.

Adverse events and concomitant medications will be assessed and documented and drug accountability will be performed.

6.9 Pregnancy Follow-Up

After confirmation of ongoing pregnancy in the fresh cycle or the 6-month post-treatment frozen-thawed blastocyst transfer cycle, the site will be required to collect delivery information (live birth and neonatal health). The follow-up will be conducted by the study center via telephone or mail and recorded in the eCRF. The site will also document miscarriage/pregnancy loss (spontaneous and/or induced), date of live birth, number of deliveries, gestational age at delivery, birth weight at deliveries, gender, and congenital anomalies/birth defects. Live birth rate after the fresh cycle and

cumulative live birth rate after fresh and 6-month post-treatment frozen-thawed transfer cycles will be evaluated as part of the pregnancy follow-up.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Endpoints

7.1.1 Pregnancy Tests and Pregnancy Monitoring

Positive β-hCG will be based on the detection of 2 positive β-hCG tests in serum via central laboratory. β-hCG pregnancy tests will be performed for all subjects 10-14 days after blastocyst transfer, with a second test approximately 2 days later, if the first test is positive. If conflicting results are obtained in the first 2 tests, a third test will be performed 2 days after the second test. Subjects who achieve pregnancy (2 positive serum pregnancy tests) will be followed up for clinical and ongoing pregnancy at 2 additional study visits.

Clinical pregnancy will be based on detection of intrauterine gestational sac and/or fetal heart movement on TVUS at approximately 4-5 weeks post-blastocyst transfer. Ongoing pregnancy will be based on detection of at least 1 intrauterine viable fetus at 10-11 weeks gestation (8-9 weeks after blastocyst transfer).

7.1.2 Oocyte Retrieval and Blastocyst Transfer

Information regarding the total number of oocytes retrieved, the number of mature oocytes obtained, number of oocytes undergoing ICSI, and number of fertilized (2PN) oocytes will be documented in the eCRF. Blastocyst transfer cycle data will be collected and documented in the eCRF including: endometrial thickness in mm, grade of blastocyst transferred, and presence of blood or mucus within the catheter tip after transfer is completed.

7.1.3 Transvaginal Ultrasounds

Transvaginal ultrasounds (including ovaries, adnexa, endometrial thickness in mm, follicular development - diameter of each follicle in mm, hyper- or hypo-echogenicity will be documented and recorded in the eCRF), and if pregnant, presence of intrauterine gestational sac, fetal pole, and/or fetal heartbeat, will be collected. Other ultrasounds may be performed throughout the ICSI treatment per standard practice but will not be documented in the eCRF.

7.1.4 Central Laboratory Tests

The following laboratory tests will be performed by a central laboratory:

- Screening and EOT Visit: serum chemistry: non-fasting glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase.
- Screening and EOT Visit: hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count.
- Screening: AMH (all subjects will have an AMH sample taken). This must be at least 3 months after the cessation of any hormonal birth control and may be repeated 1 additional time to determine eligibility.

- Day 1, Day 6, final day of stimulation: FSH, hCG, LH, androstenedione, total testosterone, and DHEA.
- Day 1, Day 6, final day of stimulation, and Visit 4 (in the morning following hCG administration): E2, P4.

The Investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether or not abnormal results are clinically significant. The laboratory report will be signed and dated by the Investigator.

7.1.5 Local Laboratory Tests

The following laboratory tests will be performed at each site's local or reference laboratory per standard practice and will be reviewed by the Investigator. All blood draws should be non-fasting. The results must be available and documented in the subject's chart and eCRF (if applicable).

- Hormones: total testosterone, prolactin, and TSH should be drawn at screening or within 12 months prior to screening and documented to be within normal limits or considered not clinically significant by the investigator. Early follicular phase (Day 2/3) serum levels of FSH should be documented between 1- 12 IU/L (inclusive) at screening or in the preceding 6 months prior to screening.
- Other laboratory assessments: negative serum hepatitis B surface antigen, hepatitis C antibody, HIV antibody, and rapid plasma reagin tests are to be done at screening or within 6 months prior to screening and documented to be within normal limits.
- FSH (cycle Day 2-3) within 6 months of screening.
- E2, P4, LH, and serum β-hCG tests collected at various time points during stimulation and luteal support.

7.1.6 Ovarian Hyperstimulation Syndrome Monitoring

In women undergoing COS, an excessive response to follicular stimulating agents may lead to the development of OHSS, which has a spectrum that can be categorized as mild, moderate, or severe. If OHSS is suspected, the subject should have a TVUS to document ovarian size and presence of ascites, as well as serum chemistry and hematology (see screening laboratories).

Table 2 Classification of Mild, Moderate, and Severe OHSS

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.[1]
Moderate OHSS	Grade 3: Features of mild OHSS plus ultrasonic evidence of ascites.[2]
Severe OHSS	Grade 4: Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax (or breathing difficulties). Paracentesis due to OHSS symptoms.[3] 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.[4] Hospitalization due to OHSS symptoms.

1. 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.
2. For subjects with transvaginal evidence of ascites, the size of the fluid pockets in the pelvis (Douglas pouch, vesicouterine pouch, etc.) should be estimated by measuring the greatest diameter and its greatest perpendicular diameter, and multiplying these 2 numbers (the unit will be cm^2). Peritoneal fluid is the total size of all fluid pockets in the pelvis.
3. In case of paracentesis, the volume of fluid drained should be measured.
4. Hemoconcentration is defined as hematocrit >45 %. Electrolyte disturbances are 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 AEs and will be recorded in the source documents for that subject and on the AE page in the eCRF. Severe OHSS that requires medical or surgical intervention (i.e., paracentesis or hospitalization) is considered an SAE (see Section 8.4).

Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation. Classification of grade is according to Golan's classification system (Golan, 1989) and all OHSS cases will be graded as mild, moderate, or severe. Preventive interventions for early OHSS cover cycle cancellation due to excessive ovarian response, triggering of final follicular maturation with GnRH agonist, and administration of dopamine agonist (the latter is only considered as preventive intervention in subjects with ≥20 follicles of ≥12 mm).

Late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation.

7.1.7 Concomitant Medications

At each study visit, subjects will be queried regarding use of any medication other than study drug since the last visit. Any use of prior medication or concomitant medication will be recorded in the source documents and 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 AE, the AE should be recorded in the source documents for that subject and on the AE page in the eCRF.

7.2 Other Assessments

7.2.1 Physical and Gynecological Examinations

A complete physical and gynecological examination will be performed at screening (including height, weight, BMI calculation, and pelvic and breast examinations). In addition, a Pap smear will be performed at screening if not done in the previous 24 months. If done in the previous 24 months, a copy of the report must be filed in the subject's chart.

7.2.2 Medical History/Menstrual History

A complete medical and gynecological history will be obtained at screening and will include a review of prior medical history, menstrual history, concurrent conditions by body system, history of alcohol, tobacco, and drug use, and female reproductive status. Medical history findings will be recorded in the subject's chart and eCRF.

7.2.3 Vital Signs

Blood pressure, heart rate, and temperature will be measured at screening. Blood pressure and heart rate are to be measured while the subject is seated under resting conditions.

7.2.4 Number of Oocytes Retrieved

The number of oocytes retrieved will be recorded at the oocyte retrieval visit.

7.2.5 Metaphase II Oocytes

Maturity stage will be assessed prior to undergoing ICSI. Maturity stage will be categorized as germinal vesicle, metaphase I, metaphase II, degenerated, or other.

7.2.6 Fertilization Rate

The number of pronuclei will be counted on Day 1 post-insemination and recorded. Fertilization rate is the number of 2PN oocytes divided by the number of oocytes retrieved.

7.2.7 Number and Quality of Embryos on Day 3

Each embryo will be evaluated on Day 3 post-insemination. The quality evaluation will consist of assessment of cleavage stage and embryo morphology parameters (blastomere uniformity, cell size, degree of fragmentation, and visual signs of multinucleation).

Cleavage stage will be defined by the number of blastomeres.

Blastomere uniformity will be classified as equally sized blastomeres or unequally sized blastomeres (largest blastomere >25% larger in average diameter compared to the smallest blastomere).

Cell size will be classified as stage-specific cell size or not stage-specific cell size.

Degree of fragmentation will be classified as 1 of the following: 0%, 1-10%, 11-20%, 21-25%, 26-30%, 31-50%, or >50% fragmentation, or totally fragmented (no blastomeres recognized).

Visual sign of multinucleation will be evaluated as a yes or no.

7.2.8 Number and Quality of Blastocysts on Day 5

Blastocyst Expansion and Hatching Status, Blastocyst Inner Cell Mass Grading, and Trophectoderm Grading

The quality evaluation of blastocysts on Day 5 after oocyte retrieval will consist of assessment of 3 parameters: blastocyst expansion and hatching status, blastocyst inner cell mass grading, and trophectoderm grading. The scoring is based on the classification system by Gardner & Schoolcraft, 1999, with the addition of D-categories for inner cell mass and trophectoderm.

Blastocyst expansion and hatching status will be assessed as 1 of the following:

1: An early blastocyst, blastocoel being less than half volume of that of the embryo.

2: A blastocyst with a blastocoel whose volume is half of, or greater than half of, that of the embryo.

3: A blastocyst with a blastocoel completely filling the embryo.

4: An expanded blastocyst with a blastocoel volume larger than that of the early embryo, with a thinning zona.

5: A hatching blastocyst with the trophectoderm starting to herniate through the zona.

6: A hatched blastocyst, in which the blastocyst has completely escaped from the zona.

For blastocysts with expansion and hatching status 3-6, blastocyst inner cell mass grading and trophectoderm grading will be evaluated.

Blastocyst inner cell mass grading will be assessed as 1 of the following:

A: Tightly packed, many cells.

B: Loosely grouped, several cells.

C: Very few cells.

D: Degenerative or no inner cell mass.

Trophectoderm grading will be assessed as 1 of the following:

A: Many cells forming a cohesive epithelium.

B: Few cells forming a loose epithelium.

C: Very few, large cells.

D: Degenerative or very large cells.

Blastocysts with expansion and hatching status 3-6 will have a score combining the 3 parameters (blastocyst expansion and hatching status, inner cell mass, and trophectoderm); e.g., 4AB for a blastocyst with blastocyst expansion and hatching status 4, inner cell mass grading A, and trophectoderm grading B.

7.2.9 Overall Blastocyst Quality on Day 5

The overall blastocyst quality on Day 5 is based on the blastocyst expansion and hatching status, inner cell mass grading, and trophectoderm grading.

Excellent-quality blastocysts are defined as those with blastocyst expansion and hatching status 4, 5, or 6, inner cell mass grading A, and trophectoderm grading A or B. The number and percentage of excellent-quality blastocysts on Day 5 is a secondary endpoint. This will be based on the best overall quality score of the Day 5 post-insemination assessments.

Good-quality blastocysts are defined as those with blastocyst expansion and hatching status 3, 4, 5, or 6, inner cell mass grading B, and trophectoderm grading A or B. The number and percentage of good-quality blastocysts on Day 5 will be based on the best overall quality score. The number and percentage of excellent-quality blastocysts and good-quality blastocysts on Day 5 will be calculated. The best blastocyst based on Day 5 morphology will be transferred.

All expanded blastocysts with Blastocyst Expansion and Hatching Status 3-6, Inner Cell Mass grading A or B, and Trophoectoderm Grading A, B, or C. should be biopsied.

7.2.10 Compaction Assessment in Morulas

Embryos that have not reached the blastocyst stage on Day 5, but are morulas, will also be evaluated. Morulas will be categorized as 1 of the following 3 options:

- Compacted: complete compaction. Tightly compacted cells. Individual cell membranes are no longer visible.
- Compacting: early stage. Cells can be distinguished.

Abnormal compaction: regional or partial compaction, or few cells (<8) in compaction

Day 5 morulas may be considered for extended culture as per the investigator/site standard of care. Day 6 or Day 7 viable blastocysts can then undergo trophectoderm biopsy and vitrification. All expanded blastocysts with Blastocyst Expansion and Hatching Status 3-6, Inner Cell Mass grading A or B, and Trophoectoderm Grading A, B, or C. should be biopsied.

The quality of Day 6 or Day 7 embryos should be assessed and recorded on the eCRF according to the criteria specified in section 7.2.9.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An AE 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.
- AEs commonly observed and AEs 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 (findings from assessments and examinations done during screening are not AEs, 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 (EOT).

The sources of AEs 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 AEs in the AE Log provided in each subject's eCRF with information about:

- AE description.
- Date and time of onset (time can be omitted, if not applicable).
- Intensity.
- Causal relationship to IMP.

- Action taken to IMP.
- Other action taken.
- Date and time of outcome (time can be omitted, if not applicable).
- Outcome.
- Seriousness.

Each of the items in the AE 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 AE more than once and the subject recovers in between the events, the AEs should be recorded separately. If an AE 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]

Note the following: a procedure is not an AE; the reason for conducting the procedure is. Hospitalization is not an AE; the reason for hospitalization is. Death is not an AE, but the cause of death is (an exception is sudden death of unknown cause, which is an AE).

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 AE 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 AE 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).

[a] Exception: if an AE with onset before the first IMP administration (i.e., a pre-treatment AE) changes in intensity, this must be recorded as 2 separate events. The initial AE should be recorded with outcome "not yet recovered" and the date and time of outcome is when the intensity changed. The second AE should be recorded with date and time of onset when the intensity changed.

Causal Relationship to IMP

The possibility of whether the IMP caused the AE must be classified as 1 of the following:

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

Examples:

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

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

Examples:

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

Action Taken to IMP

The action taken to the IMP in response to an AE must be classified as 1 of the following:

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

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 AE, 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 AE must be classified as 1 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 Pregnancy and Pregnancy Outcome

Subjects who achieve pregnancy (2 positive β-hCG tests) will be followed for clinical pregnancy (intrauterine gestational sac and/or fetal heart movement approximately 4-5 weeks after embryo transfer) and ongoing pregnancy (approximately 8-9 weeks after embryo transfer). Pregnant subjects will complete their final study visit approximately 8-9 weeks after embryo transfer (or sooner, if there is a loss of pregnancy). Subjects with ongoing pregnancy will be followed by telephone or mail for live birth data and information will be recorded in the eCRF. Pregnancy loss will be recorded on a pregnancy follow-up form in the eCRF.

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

An event is defined an SAE 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, which 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. An overnight stay for observation, a stay at an emergency room, or treatment on an outpatient basis does not constitute a hospitalization. However, medical judgment must always be exercised and when in doubt the case should be considered serious (i.e., if the 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 AEs 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. If in doubt, the decision should be left to medical judgment by the Investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IMP.
is an **important medical event**	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 1 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 judgment 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.

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported immediately to the contract research organization (CRO) and/or Ferring Pharmaceuticals as soon as it becomes known to the Investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The Investigator is responsible for submitting the completed SAE Report Form with the fullest possible details to the CRO and/or 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:

Completion of the Demographics Log, AE 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, details such as the subject's name, address, and hospital identification number should be concealed and instead the subject number should be provided.

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

Expedited Reporting by Ferring

Ferring will report all AEs that are serious, unexpected, and with a reasonable possible causality to the IMP, as judged by either the Investigator or Ferring, to the relevant parties within the stipulated timelines.

The expectedness is assessed by Ferring according to the Package Inserts for both the IMP and Non IMP products.

Serious AEs will be considered reportable regardless of whether or not the IMP or Non IMP was used in accordance with the provisions in the protocol, Package Inserts, and labeling.

8.5 Follow-up of Adverse Events and Serious Adverse Events

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

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

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

8.5.2 Collection of Serious Adverse Events with Onset after Last Trial

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

9 STATISTICAL METHODS

This section details the planned statistical analyses for the primary endpoint and outlines the secondary endpoints. All analyses and further descriptions of the statistical methodology for the primary and secondary endpoints will be included in the Statistical Analysis Plan available before the first subject signs their informed consent. Any deviations from the protocol-specified statistical analysis will be described in the Statistical Analysis Plan or final report, as appropriate. A separate Statistical Analysis Plan will be prepared to cover the post-trial information.

9.1 Determination of Sample Size

The study has at least 80% power, with 275 subjects per treatment group, to demonstrate the non-inferiority of MENOPUR® to Gonal-f® in the ongoing clinical pregnancy rate at the 1-sided significance level of 0.025 with a 12% non-inferiority margin, by assuming an ongoing pregnancy rate of 50% for both treatment groups (Yeh et al. 2014). Assuming that 8% of the subjects may not be eligible for the PP analysis set, approximately 600 subjects will be randomized (1:1) into this study.

9.2 Subject Disposition

The number and percentage of subjects within each analysis set, randomized subjects treated with IMP, and subjects prematurely discontinued from 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

Major protocol deviations will be defined and documented prior to database lock. Details will be provided in the Statistical Analysis Plan and/or in the Clean File document.

9.4 Analysis Sets

9.4.1 Intent-to-Treat (ITT) Analysis Dataset

The ITT analysis set comprises all randomized (as planned) subjects.

9.4.2 Modified Intent-to-Treat (mITT) Analysis Dataset

The mITT analysis set comprises all randomized (as planned) subjects who received at least 1 dose of IMP.

9.4.3 Per Protocol (PP) Analysis Dataset

The PP analysis set comprises all mITT subjects except those excluded as a result of major protocol deviations.

9.4.4 Safety Analysis Dataset

All subjects who received at least 1 dose of IMP will be included in the safety population.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for the subjects in the mITT, PP, and safety analysis sets by treatment group, separately.

9.5.2 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical classification first level (alphabetically) and Anatomical Therapeutic Chemical classification second level (in decreasing order of frequency).

9.6 Efficacy Endpoint Assessments

9.6.1 General Considerations

All primary, secondary, and post-trial efficacy analyses will be conducted for the mITT analysis set. Analyses for the mITT, PP, and ITT analysis sets will be conducted according to the randomized treatment. Analyses for the safety analysis set will be conducted according to the actual treatment received. Continuous variables will be described with the number of non-missing values, mean, standard deviation, median, and minimum/maximum values. Categorical variables will be described with the number and percentage of subjects with each level. Missing values will not be included in the calculation of percentages unless otherwise specified. All individual subject data will be listed.

9.6.2 Primary Efficacy Endpoint

The primary objective of the trial is to demonstrate that MENOPUR® is non-inferior to recombinant FSH with respect to ongoing pregnancy rate in a single fresh treatment cycle following a GnRH antagonist protocol. Ongoing pregnancy is defined as presence of at least 1 intrauterine pregnancy with a detectable fetal heartbeat at 10-11 weeks gestation (8-9 weeks after blastocyst transfer in the fresh cycle). The non-inferiority limit for the difference between treatments (MENOPUR® versus Gonal-f®) is -12% (absolute). The non-inferiority hypothesis to be tested for the primary endpoint is:

$$H_0: \pi_{MENOPUR} - \pi_{Gonal\text{-}f^{®}} \leq -12\%$$

against the alternative

$$H_1: \pi_{MENOPUR} - \pi_{Gonal\text{-}f^{®}} > -12\%,$$

where $\pi_{MENOPUR}$ and $\pi_{Gonal\text{-}f^{®}}$ denote the ongoing pregnancy rate of subjects randomized and treated with MENOPUR® and Gonal-f®, respectively, in a single fresh embryo transfer following a GnRH antagonist protocol.

The null hypothesis (H_0) will be tested against the alternative by constructing a 2-sided 95% confidence interval for the difference in ongoing pregnancy rates. If the lower-limit of the 95% confidence interval is greater than the non-inferiority limit (-12%), the null hypothesis will be

rejected and it would be claimed that MENOPUR® is non-inferior to Gonal-f® with respect to ongoing pregnancy rate in a single fresh embryo transfer following a GnRH antagonist protocol.

If the 95% confidence interval for the treatment difference not only lies above the non-inferiority limit (-12%) but also above zero then there is evidence of superiority in terms of statistical significance at the 2-sided 5% level. With evidence of superiority, the corresponding 2-sided p-value will be reported. There is no need for a multiplicity adjustment since it is a simple closed test procedure.

Due to the expected large sample size, the confidence interval will be established based on the asymptotic normal distribution as follows:

$$\hat{\pi}_{MENOPUR} - \hat{\pi}_{Gonal-f} \pm Z_{(1-\alpha/2)} \sqrt{\frac{\hat{\pi}_{MENOPUR}(1-\hat{\pi}_{MENOPUR})}{N_{MENOPUR}} + \frac{\hat{\pi}_{Gonal-f}(1-\hat{\pi}_{Gonal-f})}{N_{Gonal-f}}}$$

where

$\hat{\pi}_{MENOPUR}$: is the observed ongoing pregnancy rate of subjects randomized to MENOPUR® in a single fresh treatment cycle following a GnRH antagonist protocol.

$\hat{\pi}_{Gonal-f}$: is the observed ongoing pregnancy rate of subjects randomized to Gonal-f® in a single fresh treatment cycle following a GnRH antagonist protocol.

$N_{MENOPUR}$: is the number of subjects randomized to MENOPUR®.

$N_{Gonal-f}$: is the number of subjects randomized to Gonal-f®.

$Z_{(1-\alpha/2)}$: is the 1-α/2 percentile in the standard normal distribution.

α : is the significance level, i.e., 0.05.

Subjects who do not have at least 1 intrauterine pregnancy with a detectable fetal heartbeat at 10–11 weeks gestation (8-9 weeks after blastocyst transfer in the fresh cycle), due to missing data, early withdrawal, or any other reason will be considered treatment failures (i.e., not having ongoing pregnancy).

The primary endpoint analysis will be based on the mITT analysis set.

Sensitivity analyses for the primary endpoint will be conducted for both the ITT analysis set and the PP analysis set.

9.6.3 Secondary Endpoints

All secondary endpoints will be summarized using tables and figures, as appropriate. Additional details will be specified in the Statistical Analysis Plan. The secondary endpoints include:

- Positive β-hCG rate and clinical pregnancy rate in the fresh cycle will be analyzed using the same method that is applied to the primary efficacy analysis.
- Early pregnancy loss is defined as 2 positive β-hCG tests but no ongoing pregnancy at 10-11 week's gestation in the fresh cycle. Descriptive statistics will be provided by treatment group.
- The follicle cohort on stimulation Day 6 and last day of stimulation will be summarized by treatment on the follicle level (number of follicles ≤9mm, 10-11 mm, 12-14 mm, 15-16 mm, and ≥17 mm) and subject level (largest follicle size, average follicle size, average size of 3 largest follicles, and average number of follicles ≥17 mm, ≥15 mm, and ≥12 mm. Tables will be produced for all subjects and for subjects with oocytes retrieved.
- The endocrine profile will be summarized using descriptive statistics by scheduled visit, as well as for the change from baseline, if appropriate. Any subject who receives antagonist earlier than Day 6 will be excluded from Day 6 endocrine analysis.
    - Serum FSH, hCG, LH, androstenedione, total testosterone, DHEA: Day 1, Day 6, and final day of stimulation.
    - P4, E2: Day 1, Day 6, final day of stimulation, and Visit 4 (in the morning following hCG trigger).
- The number of oocytes retrieved, the number of metaphase II oocytes, and the number of normally fertilized (2PN) oocytes will be summarized by frequency distribution and by descriptive statistics for each treatment group.
- The fertilization rate will be expressed as a percentage for each subject and calculated as 100 times the ratio of the number of fertilized 2PN oocytes to the number of oocytes retrieved. Descriptive statistics will be provided by treatment group.
- The quality of embryos 3 days after oocyte retrieval will be assessed by cleavage stage, blastomere uniformity, cell size, the degree of fragmentation, and visual signs of multinucleation. Frequency distributions and descriptive statistics will be provided for each treatment group at the embryo level, as appropriate.
- The quality of blastocysts 5 days after oocyte retrieval will be assessed by blastocyst expansion and hatching status, blastocyst inner cell mass grading, and trophectoderm grading. Frequency distributions will be provided for each treatment group at the blastocyst level.
- The best quality blastocyst 5 days after oocyte retrieval at the subject level will be summarized for excellent-quality blastocysts and good-quality blastocysts separately by treatment using descriptive statistics.
- The aneuploidy rate will be expressed as a percentage for each subject and calculated as 100 times the ratio of the number of aneuploid blastocysts to the total number of blastocysts. Descriptive statistics will be provided by treatment group.

- Endometrial thickness and the echogenicity pattern will be summarized by frequency distribution and by descriptive statistics, as appropriate, for each treatment group at stimulation Day 6, the last day of stimulation, and at the time of blastocyst transfer in the fresh cycle.

9.6.4 Post-Trial Endpoints

All post-trial endpoints will be summarized using tables and figures, as appropriate. Additional details will be specified in the separate Statistical Analysis Plan for the post-trial endpoints. The post-trial endpoints include:

- Cumulative live birth rate for fresh and frozen blastocyst transfer (defined as the proportion of subjects with at least 1 viable live birth greater >21 weeks gestation).
- Live birth rate for fresh blastocyst transfer (defined as the proportion of subjects with at least 1 viable live birth greater >21 weeks gestation).
- Early pregnancy loss rate in frozen blastocyst transfer is defined as 2 positive β-hCG tests but no ongoing pregnancy at 10-11 weeks gestation in the frozen cycle.
- Late pregnancy loss rate (defined as a confirmed ongoing pregnancy but no viable live birth greater >21 weeks gestation).
- Positive β-hCG rate, clinical pregnancy rate, and ongoing pregnancy rate for frozen blastocyst transfers.

Descriptive statistics will be provided in each of the respective post-trial endpoints.

9.7 Extent of Exposure and Treatment Compliance

The number of days exposed and the total amount of IMP and NIMP administered will be summarized and listed per subject and treatment. Subjects that deviate from the planned treatment will also be listed.

9.8 Safety

9.8.1 General Considerations

Missing values will be treated as missing, except for causality, intensity, seriousness, and outcome of AEs. A worst-case approach will be used: if causality is missing, the AE will be regarded as related to the IMP; if the intensity of an AE is missing, the AE will be regarded as severe; if seriousness is missing, the AE will be regarded as serious; if outcome is missing, and no date of outcome is present, the outcome is regarded as ‘ongoing’.

Data will be presented by summary tables and listings only. Categorical data will be summarized by treatment using the number and percentage of subjects in each category. For calculation of percentages, the denominator will be the total number of subjects in the respective treatment group in the safety analysis set. Continuous data will be summarized by treatment using number, mean, standard deviation, median, minimum, and maximum.

All individual subject data will be listed per subject and treatment as observed including any derived values.

9.8.2 Adverse Events

Adverse events will be coded using MedDRA.

A treatment-emergent AE is defined as an AE that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state. Only treatment-emergent AEs will be presented in summary tables.

All data will be listed per subject and AE.

Written narratives will be issued for all SAEs and AEs leading to withdrawal. If causality is missing, the AE will be regarded as being reasonably possibly related to IMP. Related AEs (judged as being reasonably possibly related to IMP) will be termed adverse drug reactions.

Overview of Treatment Emergent Adverse Events

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

- All AE.
- Severe AEs.
- Adverse drug reactions.
- AEs leading to discontinuation.
- SAEs.
- Deaths.

Incidence of Adverse Events

Treatment-emergent AEs in each treatment group will be tabulated by system organ class (SOC) and preferred term. The following will be presented: number of subjects reporting an AE, the percentage of subjects with an AE, and the number of events reported.

For each treatment the following counts are done:

- For number of subjects experiencing a particular event, counting will be done by subject and not by event. This is valid for both the SOC and preferred term, i.e., a subject will only be counted once in each SOC and once within each preferred term.
- For total number of events counting will be done by event. This is valid for both the SOC and preferred term, i.e., an event occurring more than once for the same subject will be counted for each occurrence.

This counting and data presentation will be applied for the various incidences of AE tables described below.

Incidence of OHSS

OHSS for each treatment group will be tabulated by classification (mild, moderate, severe) and grade (1, 2, 3, 4, 5). The tabulation will be made for OHSS overall as well as separately for early OHSS and late OHSS.

Incidence of AEs by Relationship to IMP

Treatment-emergent AEs for each treatment group will be tabulated by SOC, preferred term, and relationship to IMP. One summary table will be prepared per type of relationship (related/not related).

Incidence of AEs by Intensity

Treatment-emergent AEs for each treatment group will be tabulated by SOC, preferred term, and intensity. One summary table will be prepared per type of intensity (mild/moderate/severe).

Incidence of Adverse Drug Reactions by Intensity

Adverse drug reactions for each treatment group will be tabulated by SOC, preferred term and intensity for all IMP-related AEs.

Adverse Events Leading to Discontinuation

Adverse events leading to discontinuation for each treatment group will be listed and tabulated by SOC and preferred term.

Serious Adverse Events

Serious AEs for each treatment group will be listed and tabulated by SOC and preferred term.

Deaths

A separate data listing will be provided for all deaths (deaths occurring at any time during the trial, i.e., pre-treatment, during treatment, or post-treatment), if any.

9.8.3 Vital Signs

Vital signs will be summarized by treatment group. All vital signs values will be listed per subject, treatment group, and time point. Values outside the reference range will be flagged.

9.8.4 Physical Examination

Physical examinations will be summarized and all subjects with any abnormal finding will be listed per subject for the safety analysis set.

9.8.5 Gynecological Examination

Gynecological examinations will be summarized and all subjects with any abnormal finding will be listed by subject for the safety analysis set.

9.8.6 Clinical Laboratory Variables

Baseline and EOT 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 EOT will be summarized by treatment group using descriptive statistics.

9.9 Interim Analyses

No interim analysis is planned.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – International Conference on Harmonization (ICH) Definition

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

Source Documents - ICH Definition

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

Trial-Specific Source Data Requirements – Ferring

Any study specific source data will be described and defined in the monitoring manual produced for this study.

10.2 eCRF/Case Report Form

An electronic data capture system provided by an independent third-party will be used. 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 3 working days after the subject has attended a visit or after the data become available, as applicable.

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.

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

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, ICH-Good Clinical Practice (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.

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 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 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 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, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g., the confidential subject identification code and the signed informed consent 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 IRBs 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 IRB approval.

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 an answer to a query in the eCRF, in a protocol deviation report in the eCRF, or a combination of both. A log of significant 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 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 and submitted for comments and signature(s) to the signatory Investigator(s). The name of the signatory Investigator and contact details are specified in the contact list attachment in the protocol.

13.2 Confidentiality and Ownership of Trial Data

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

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, 1 or more manuscripts for joint publication may be prepared in collaboration between the Investigator(s) offered authorship and Ferring. In a multi-site trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the International Committee of Medical Journal Editors criteria (see current official version: http/www.ICMJE.org). The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the Investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

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

If the Investigator wishes to independently publish/present any results from the trial, the draft manuscript/presentation must be submitted in writing to Ferring for comment prior to submission. Comments will be given within 4 weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent application is published. Under such conditions, the publication will be modified or delayed at the Investigator's discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

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, which is sponsored by the National Institutes of Health.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Institutional Review Board

An IRB will review the protocol and any amendments and advertisements used for recruitment. The 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 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 Authority 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

At the end of the trial the IRBs will be notified in writing.

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 IRBs (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 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.

14.6 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP, and 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 company, which 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, which 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 2 years after the completion or discontinuation of the study, if no further instructions are given by Ferring.

The Investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous case report form/eCRF data for Ferring. The Investigator must arrange for the retention of this subject Identification Log and signed informed consent documents 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

American Society for Reproductive Medicine. Endometriosis: a guide for patients. 2012.

Andersen AN, Devroey P, Arce JC. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Hum Reprod. 2006;21(12):3217-27.

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Arce JC, Klein BM, La Marca A. The rate of high ovarian response in women identified at risk by a high serum AMH level is influenced by the type of gonadotropin. Gynecol Endocrinol. 2014;30(6):444-50.

Golan A, Ron-El R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian Hyperstimulation Syndrome: An Update Review. Obstetrical and Gynecological Survey. 1989;44:6:430-440.

MENOPUR® (menotropins for injection) [package insert] Parsippany, NJ: Ferring Pharmaceuticals Inc.; February, 2014.

Gonal-f RFF® Redi-ject™ (follitropin alfa injection) [package insert] Rockland, MA: EMD Serono Inc.; January, 2014.

Ganirelix acetate injection [package insert] Whitehouse Station, NJ: Merck & Co. Inc.; December, 2013.

Ovidrel® (choriogonadotropin alfa) [package insert] Rockland, MA: EMD Serono Inc.; September, 2014.

ENDOMETRIN® (progesterone) [package insert] Parsippany, NJ: Ferring Pharmaceuticals Inc.; June, 2014.

van Wely M, Kwan I, Burt AL, et al. Recombinant versus urinary gonadotropin for ovarian stimulation in assisted reproductive technology cycles. Cochrane Database Syst Rev. 2011;(2):CD005354.

Gardner DK, Schoolcraft WB. In vitro culture of human blastocysts. In: Towards reproductive certainty (Eds Jansen R & Mortimer D). The plenary proceedings of the 11th world congress on in vitro fertilization and human reproductive genetics. The Parthenon Publishing Group. 1999. 378-88.

Yeh JS, Steward RG, Dude AM, et al. Pregnancy outcomes decline in recipients over age 44: an analysis of 27,959 fresh donor oocyte in vitro fertilization cycles from the Society for Assisted Reproductive Technology. Fertil Steril. 2014;101(5):1331-6.

PROTOCOL DOCUMENT APPROVAL

The Principal Investigator and Ferring agree to conduct the trial as outlined in this Protocol with reference to national/local regulations and in accordance with current Good Clinical Practice (GCP) guidelines. Any modification to the Protocol must be agreed upon by both the Principal Investigator and Ferring and be documented in writing. By written agreement to this Protocol, the Principal Investigator agrees to allow direct access to all documentation, including source data, to authorized individuals representing Ferring (including monitoring staff and auditors) to Institutional Review Boards (IRBs) and/or to domestic and foreign regulatory authorities.

FERRING REPRESENTATIVE

_____ _____
Date

[redacted] Reproductive Health and Urology

PRINCIPAL INVESTIGATOR

_____ _____
Date

Print Name: _____
Site Name: _____
Address: _____
_____
_____