Cover page for Protocol

Sponsor name	Ferring Pharmaceuticals A/S
NCT Number	NCT04163458
Sponsor trial ID:	000303
Official title of study	A Randomized, Double-blind Double-dummy Trial Comparing MENOPUR Solution for Injection in a Pre-filled Pen and MENOPUR Powder and Solvent for Solution for Injection (Menotropins for Injection) in a GnRH Agonist Cycle in Women Aged 18-42 Years Undergoing an Assisted Reproductive Technology Program
Document Date	19 Mar 2020

CLINICAL TRIAL PROTOCOL

A randomized, double-blind double-dummy trial comparing MENOPUR solution for injection in a pre-filled pen and MENOPUR powder and solvent for solution for injection (menotropins for injection) in a GnRH agonist cycle in women aged 18-42 years undergoing an assisted reproductive technology program

Trial 000303

CLARA
(Comparison of MENOPUR Liquid and Powder in Women Undergoing ART)

IND Number:	053954
Investigational Medicinal Product:	MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL MENOPUR powder and solvent for solution for injection, 75 IU
Indication:	Development of multiple follicles and pregnancy in ovulatory women undergoing controlled ovarian stimulation as part of an assisted reproductive technology (ART) cycle
Phase:	3
Name and Address of Sponsor:	Ferring Pharmaceuticals, Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: [redacted]
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A randomized, double-blind double-dummy trial comparing MENOPUR solution for injection in a pre-filled pen and MENOPUR powder and solvent for solution for injection (menotropins for injection) in a GnRH agonist cycle in women aged 18-42 years undergoing an assisted reproductive technology program

Short title: CLARA (Comparison of MENOPUR Liquid and Powder in Women Undergoing ART)

SIGNATORY INVESTIGATOR

[redacted] MD.
[redacted]

TRIAL SITES

Up to 25 infertility centers in the United States (US).

PLANNED TRIAL PERIOD

First subject first visit (FSFV):	Q4 2019
Last subject last visit (LSLV):	Q4 2020
Last 4-weeks neonatal health follow-up:	Q1 2021
Last 6-months neonatal health follow-up:	Q3 2021

CLINICAL PHASE

3

BACKGROUND / RATIONALE

MENOPUR is a highly purified human menotropin, delivering follicle-stimulating hormone (FSH) activity and luteinizing hormone (LH) activity in a 1:1 ratio.

MENOPUR powder and solvent for solution for injection has been approved in the US since 2004, for the development of multiple follicles and pregnancy in ovulatory women undergoing controlled ovarian stimulation as part of an assisted reproductive technology (ART) cycle.

The currently available MENOPUR powder and solvent for solution for injection consists of a vial with powder containing 75 IU FSH activity and 75 IU LH activity and a vial with diluent.

As part of the global clinical development program for MENOPUR, Ferring has developed a new multi-dose liquid formulation of MENOPUR in a pre-filled pen, containing 625 IU/mL FSH activity and 625 IU/mL LH activity. This is intended to offer infertility patients a more convenient administration of MENOPUR. The drug substance (highly purified menotropin) in

the MENOPUR multi-dose liquid formulation is the same as in the currently approved MENOPUR.

The trial is designed to compare the pharmacodynamics of MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL to the currently approved MENOPUR powder and solvent for solution for injection, 75 IU.

Note: MENOPUR solution for injection in pre-filled pen 1200 IU/1.92 mL will in this document hereafter be referred to as MENOPUR liquid, and MENOPUR powder and solvent for solution for injection, 75 IU will hereafter be referred to as MENOPUR powder.

OBJECTIVES

Primary Objective

- To demonstrate non-inferiority of MENOPUR liquid versus MENOPUR powder with respect to the number of fertilized oocytes in women undergoing controlled ovarian stimulation.

Secondary Objectives

- To evaluate the pregnancy rates after stimulation with MENOPUR liquid and MENOPUR powder.
- To evaluate the follicular development during stimulation with MENOPUR liquid and MENOPUR powder.
- To evaluate the serum endocrine profile during stimulation with MENOPUR liquid and MENOPUR powder.
- To evaluate the number of oocytes retrieved, the number and quality of embryos, and the number and quality of blastocysts, associated with MENOPUR liquid and MENOPUR powder.
- To evaluate treatment efficiency of MENOPUR liquid and MENOPUR powder.
- To evaluate the safety profile of MENOPUR liquid and MENOPUR powder, including adverse events, routine safety laboratory parameters, local tolerability and immunogenicity.

ENDPOINTS

Primary Endpoint

- Number of fertilized (2 pronuclei [2PN]) oocytes at 19±2 hours after insemination.

Secondary Endpoints

- Positive βhCG rate (positive βhCG test 10-14 days after blastocyst transfer).

- Clinical pregnancy rate (transvaginal ultrasound showing at least 1 intrauterine gestational sac with fetal heart beat at 5-6 weeks after blastocyst transfer).
- Ongoing pregnancy rate (at least one intrauterine viable fetus 8-9 weeks after blastocyst transfer).
- Early pregnancy loss (defined as a positive βhCG test but no ongoing pregnancy at 8-9 weeks after blastocyst transfer).
- Follicular development as assessed by transvaginal ultrasound on stimulation day 6 and last day of stimulation.
- Endocrine profile:
  - Serum follicle-stimulating hormone (FSH) on day 6, last day of stimulation and at oocyte retrieval, and corresponding population pharmacokinetics (PK) analysis.
  - Serum Anti-Müllerian hormone (AMH) on last day of stimulation and at end-of-trial.
  - Human chorionic gonadotropin (hCG) and luteinizing hormone (LH) on day 6 and last day of stimulation.
  - Estradiol (E2) and progesterone (P4) on day 6 and last day of stimulation.
- Number of oocytes retrieved, number of metaphase II oocytes, fertilization rate, and number and quality of blastocysts 5 days after oocyte retrieval.
- Frequency of ovarian hyperstimulation syndrome (OHSS) (early OHSS if the onset is ≤9 days after triggering of final follicular maturation and late OHSS if the onset is >9 days after triggering of final follicular maturation).
- Total gonadotropin dose and number of stimulation days.
- Frequency and intensity of adverse events.
- Changes in circulating levels of clinical chemistry and hematology parameters and proportion of subjects with markedly abnormal changes.
- Frequency and intensity of injection site reactions (redness, pain, itching, swelling and bruising) assessed by the subject during the stimulation period.
- Frequency of treatment-induced anti-MENOPUR antibodies, overall as well as with neutralizing capacity.
- Technical malfunctions of the pen.

Post-trial Endpoints

- Live birth rate.
- Late pregnancy loss rate (defined as an ongoing pregnancy but no live birth).
- Neonatal health including serious adverse events (SAEs) at birth, and SAEs at 4 weeks and minimum 6 months after birth.

METHODOLOGY

This is a phase 3, randomized, double-blind double-dummy, parallel-group, multicenter non-inferiority trial. Approximately 400 females undergoing controlled ovarian stimulation as a part of a GnRH agonist protocol at infertility centers in the US will be randomized 1:1 to receive either MENOPUR liquid (including Placebo to MENOPUR powder) or MENOPUR powder (including Placebo to MENOPUR liquid). Randomization will be stratified by trial site and age group (<35 years and ≥35 years). The primary endpoint is the number of fertilized oocytes.

Pituitary downregulation will be done following a protocol using combined oral contraceptives (NORTREL; daily for at least 14 days but no more than 21 days) and a GnRH agonist (LEUPROLIDE ACETATE) which will be initiated at a dose of 0.1 mL (500 µg)/day starting 4 days before the last day on oral contraceptives. Downregulation will be assessed starting on or after day 10 of LEUPROLIDE ACETATE administration, but no later than day 20. In the event of spontaneous menses, subject should be instructed to continue LEUPROLIDE ACETATE and be seen at the center within 3 days to assess downregulation. If downregulation is confirmed (serum E2 ≤20 pg/mL (central laboratory) and transvaginal ultrasound showing no ovarian cysts), the subject is to be randomized and gonadotropins initiated within 3 days. If an ovarian cyst is detected and the E2 level is >20 pg/mL, the subject can undergo outpatient aspiration of the ovarian cyst at the discretion of her physician with assessment of estradiol >1 day later. Subjects can be reassessed to confirm downregulation a maximum of 3 times. The GnRH agonist dose will be reduced to 0.05 mL (250 µg)/day on stimulation day 1 and administration continued until end of gonadotropin administration.

Within 3 days of downregulation confirmation, subjects will be randomized to receive either MENOPUR liquid (including Placebo to MENOPUR powder) or MENOPUR powder (including Placebo to MENOPUR liquid) initiated at 225 IU for 5 days. From stimulation day 6 onward, based on follicular response assessed by transvaginal ultrasound, dosing can be adjusted every second day as needed by 75 IU per adjustment. However, the maximum gonadotropin dose will be 450 IU/day and the minimum dose will be 75 IU/day; gonadotropin dosing can continue for a maximum of 20 days, and coasting is not allowed. Subjects will self-inject the GnRH agonist and gonadotropins (including placebo) at home after receiving instruction by a member of the clinical trial staff (e.g. a trial nurse).

Injection of 2 x 5,000 IU hCG (NOVAREL) will be administered for the triggering of final follicular maturation as soon as 3 follicles of ≥17 mm are observed on transvaginal ultrasound. In the case of excessive ovarian response (>30 follicles of ≥12 mm each and/or E2 levels ≥5000 pg/mL (local laboratory)), the cycle will be cancelled. Oocyte retrieval will take place 36±2 hours after triggering of final follicular maturation, and oocytes will be inseminated by ICSI 4±2 hours after retrieval; oocyte maturity will be recorded. Fertilization (number of pronuclei) will be assessed 19±2 hours following ICSI. Blastocyst quality will be assessed on day 5 following oocyte retrieval.

All subjects will have single blastocyst transfer if they have at least one good-quality (i.e. grade 3BB or above) blastocyst available on day 5 following oocyte retrieval. If no good-quality blastocyst is available, they may have double blastocyst transfer, if at least two blastocysts are available. Transfer of day 6 (or later) blastocyst(s) is not allowed. Remaining blastocysts may be cryopreserved by vitrification. All cryopreserved blastocysts can be used by the subject after completion of the trial in accordance with local guidelines and/or regulations.

Vaginal progesterone inserts (ENDOMETRIN), 100 mg three times daily will be administered for luteal phase support starting the day after oocyte retrieval and continuing up to menses, negative βhCG, pregnancy loss or for a maximum of 10 weeks total if pregnancy is confirmed.

Blood samples will be collected throughout the trial for the purpose of evaluating the endocrine profile, clinical chemistry and hematology parameters as well as anti-MENOPUR antibodies. Endocrine parameters (FSH, LH, hCG, E2 and P4) are assessed at baseline (E2 at confirmation of downregulation and FSH, LH, hCG and P4 on stimulation day 1), day 6, and at end-of-stimulation (day of trigger), and furthermore, FSH is also assessed at oocyte retrieval. In addition, AMH is assessed on stimulation day 1, on the last day of stimulation, and at end-of-trial. Clinical chemistry and hematology are assessed at screening, last day of stimulation, and end-of-trial. Anti-MENOPUR antibodies are assessed at four occasions. The first sample is taken at the screening visit and is exclusively used to re-establish the anti-drug antibody analytical assays. The subsequent three samples are used for analysis of anti-MENOPUR antibodies in the individual subjects in the trial, and are taken prior to dosing on stimulation day 1 and at two occasions post-dosing: 7-10 days after the last MENOPUR liquid or MENOPUR powder dose (this may coincide with the transfer visit) and 21-28 days after the last MENOPUR liquid or MENOPUR powder dose (this may coincide with the βhCG test visit). Subjects with a treatment-induced anti-MENOPUR antibody response will be followed until the response has become negative or returned to the pre-dosing level. These subjects will be called in for assessments at 2 months after the last post-dosing anti-MENOPUR antibody sampling. If required, further assessments will be made at 3, 4, 6, 9 and 12 months after the last post-dosing anti-MENOPUR antibody sampling. The assessments will be terminated when two consecutive assessments are negative or indicate that the pre-dosing level has been reached, with a maximum follow-up period of one year. The assessments will also be terminated if the subject commences a new treatment cycle with any gonadotropin preparation.

Local tolerability of MENOPUR liquid or MENOPUR powder following subcutaneous administration will be assessed by the subject three times daily: immediately, 30 minutes and 24 hours after each injection. The assessment of injection site reactions will be made throughout the stimulation period and recorded by the subject in a diary.

Concerning post-trial follow-up, all subjects with an ongoing pregnancy will be followed. Data will be gathered on delivery information (live birth and neonatal health). In addition, data on neonatal SAEs will be collected at 4 weeks and minimum 6 months after birth.

NUMBER OF SUBJECTS

It is planned to randomize 400 subjects of whom 200 subjects will be randomized to MENOPUR liquid and 200 subjects will be randomized to MENOPUR powder. It is estimated that approximately 800 subjects should be screened to achieve 400 subjects eligible for randomization.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion criteria

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

1. Signed informed consents, prior to any trial-related procedure.
2. Females between the ages of 18 and 42 years. The subjects must be at least 18 years (including the 18th birthday) when they sign the informed consent and no more than 42 years (up to the day before the 43rd birthday) at the time of randomization who desire pregnancy.
3. Body mass index (BMI) between 17.5 and 38.0 kg/m^2 (both inclusive) at screening.
4. Regular menstrual cycles of 24 to 35 days, presumed to be ovulatory.
5. Documented history of infertility for at least 12 months before randomization for women ≤ 35 years or for at least 6 months for women ≥ 36 years. Women with documented bilateral tubal occlusion or male factor infertility requiring the use of donor sperm established as a cause of infertility are eligible at diagnosis.
6. Early follicular phase (cycle day 2-4) serum FSH level between 1 and 12 IU/L (results obtained within 3 months prior to randomization).
7. Serum Anti-Müllerian hormone (AMH) level greater than 1.0 ng/mL at screening (central laboratory).
8. 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.
9. At least 1 cycle with no fertility medication immediately prior to screening.
10. Hysterosalpingography, hysteroscopy, or saline hysterosonogram documenting uterine anatomy appropriate for ART at screening or within 12 months prior to screening.
11. Transvaginal ultrasound documenting presence and adequate visualization of both ovaries, without evidence of clinically significant abnormality (e.g., endometrioma ≥3 cm, no dermoid cysts) and normal adnexa (e.g., no hydrosalpinx) at screening. Both ovaries must be accessible for oocyte retrieval.
12. 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.

13. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests at screening or within 6 months prior to screening.
14. Confirmation of downregulation prior to randomization, defined as serum E2 ≤20 pg/mL (central laboratory) and transvaginal ultrasound showing no ovarian cysts.
15. Willing and able to comply with the protocol, including scheduled clinic visits and laboratory tests, for the duration of the trial.

Exclusion criteria

Subjects meeting any of the following criteria will not be eligible for trial participation:

1. More than two previous controlled ovarian stimulation cycles for IVF/ICSI
2. Known stage III-IV endometriosis (American Society for Reproductive Medicine, 2012)[10].
3. Oocyte donor or embryo recipient; gestational or surrogate carrier.
4. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy [excl. ectopic pregnancy] and before week 24 of pregnancy).
5. 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.
6. The use of hormonal preparations (except for thyroid medication) within 3 months prior to screening.
7. Use of fertility modifiers during the last menstrual cycle before start of downregulation, including dehydroepiandrosterone (DHEA) and metformin.
8. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
9. History or presence of heart disease, cardiovascular or cerebrovascular disease or disorder (e.g. coronary artery disease, hypertension).
10. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
11. Any known endocrine (total testosterone, prolactin and TSH) or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of controlled thyroid function disease.
12. Known tumors of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.

13. Known moderate or severe impairment of renal or hepatic function.
14. Any abnormal finding of clinical chemistry, hematology and vital signs at screening, which is judged clinically significant by the investigator.
15. Currently breastfeeding.
16. Pregnancy (negative urine pregnancy test must be documented at screening and prior to the first IMP administration), or contraindication to pregnancy.
17. Presence of abnormal uterine bleeding of undetermined origin.
18. Known abnormal cervical cytology of clinical significance observed within three years prior to randomization (unless the clinical significance has been resolved).
19. Findings at the gynecological examination at screening that preclude gonadotropin therapy in the opinion of the investigator or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
20. History of chemotherapy (except for gestational conditions) or radiotherapy.
21. Current or recent (12 months prior to randomization) abuse of alcohol or drugs, and/or current (last month) intake of more than 14 units of alcohol per week.
22. Current or recent (3 months prior to screening) smoking more than 10 cigarettes per day (or the equivalent).
23. Hypersensitivity to any active ingredient or excipients in the medicinal products used in this trial.
24. Participation in any experimental drug trial within 30 days prior to screening, including previous participation in the present trial.
25. Known mental incapacity or language barrier precluding adequate understanding of the informed consent information and the trial activities.
26. Clinic staff member directly involved in the conduct of the trial. Any other staff member interested in participating must obtain Institutional Review Board (IRB) approval prior to participation.

MEDICINAL PRODUCTS

Investigational Medicinal Products (IMPs)

- MENOPUR liquid (MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL; Ferring Pharmaceuticals), will be provided as a pre-filled injection pen (with integrated non-replaceable 3 mL cartridge), each pen delivers 625 IU/mL of FSH activity and 625 IU/mL of LH activity. The starting dose of 225 IU will be fixed for the first five stimulation days, followed by potential adjustments of 75 IU to a maximum dose of 450 IU or a minimum dose of 75 IU/day.

- Placebo to MENOPUR liquid (solution for injection in pre-filled pen; Ferring Pharmaceuticals), will be provided as a pre-filled injection pen (with integrated non-replaceable 3 mL cartridge).
- MENOPUR powder (MENOPUR powder and solvent for solution for injection, 75 IU; Ferring Pharmaceuticals), will be provided as vials with powder (75 IU FSH activity and 75 IU LH activity) and vials with diluent. After reconstitution, each vial delivers 75 IU of FSH activity and 75 IU of LH activity. The starting dose of 225 IU will be fixed for the first five stimulation days, followed by potential adjustments of 75 IU to a maximum dose of 450 IU or a minimum dose of 75 IU/day.
- Placebo to MENOPUR powder (powder and solvent for solution for injection; Ferring Pharmaceuticals), will be provided as vials with powder and vials with diluent.

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

- NORTREL 1/35 (norethindrone [1 mg] and ethinyl estradiol [0.035 mg]; Teva Pharmaceuticals USA, Inc.), will be provided as oral tablets to be administered at a dose of 1 mg/0.035 mg (1 tablet) daily for at least 14 days but no more than 21 days during the downregulation period.
- LEUPROLIDE ACETATE (leuprolide acetate; Sandoz), will be provided as a vial with sterile solution (14 mg/2.8 mL), to be administered at a dose of 0.1 mL (500 µg)/day during the downregulation period, followed by a dose of 0.05 mL (250 µg)/day from stimulation day 1 throughout the gonadotropin treatment period.
- NOVAREL (chorionic gonadotropin; Ferring Pharmaceuticals), will be provided as vials containing 5,000 IU chorionic gonadotropin per vial, 2 x 5,000 IU is to be administered by intramuscular injection according to label as soon as 3 follicles of ≥17 mm are observed on transvaginal ultrasound.
- ENDOMETRIN (progesterone; Ferring Pharmaceuticals), will be provided as inserts to be administered vaginally. Starting the day after oocyte retrieval, 100 mg three times daily will be administered for luteal phase support continuing up to menses, negative βhCG, pregnancy loss, or for a maximum of 10 weeks total if pregnancy is confirmed.

DURATION OF TREATMENT

The maximum period of exposure to MENOPUR liquid or MENOPUR powder is 20 days.

STATISTICAL METHODS

Sample size

The present trial is a pharmacodynamic comparison of a marketed product to a new formulation of the same. With 188 subjects per treatment group, the study has at least 85% power to demonstrate the non-inferiority of MENOPUR liquid to MENOPUR powder in the number of

fertilized oocytes at the 1-sided significance level of 0.025. This is based on the results for MENOPUR powder from the COMBINE trial conducted in a similar setting (GnRH agonist protocol, MENOPUR starting dose of 225 IU for the first five days, insemination by ICSI etc.) and in a similar population (infertile women between 18 and 42 years). The mean (SD) of the number of fertilized oocytes were 7.88 (5.15) with similar results in the two age groups (7.92 in the <35 years age group vs. 7.80 in the ≥35 years age group). The non-inferiority margin of -1.60 will retain 80% of the expected comparator effect.

After adjusting for 5% missing data, approximately 400 subjects will be randomized (1:1) into this trial, stratified by trial site and age (<35 years and ≥35 years).

Sample Size Monitoring

A blinded sample size reassessment will be done when data on the primary endpoint are available for 70% of the planned subjects or when 300 subjects are randomized, whichever comes first. The sample size reassessment will be done without breaking the blind and without inflating the type I error of the trial, in line with current regulatory guidelines. The expected maximum number of subjects to be randomized is 500 (250 subjects per treatment group), corresponding to a blinded one-sample (both groups pooled) standard deviation estimate of 5.8 and 85% power.

Primary endpoint

The primary objective of the trial is to demonstrate the non-inferiority of MENOPUR liquid versus MENOPUR powder with respect to the number of fertilized oocytes in women undergoing controlled ovarian stimulation. The non-inferiority limit for the difference between treatments (MENOPUR liquid minus MENOPUR powder) is set as -1.60. The non-inferiority hypothesis to be tested for the primary endpoint will be:

$$H_0: \mu_{\text{MENOPUR liquid}} - \mu_{\text{MENOPUR powder}} \leq -1.60$$

against the alternative

$$H_1: \mu_{\text{MENOPUR liquid}} - \mu_{\text{MENOPUR powder}} > -1.60$$

where $\mu_{\text{MENOPUR liquid}}$ and $\mu_{\text{MENOPUR powder}}$ denote the mean numbers of fertilized oocytes in subjects treated with MENOPUR liquid and MENOPUR powder, respectively.

The null hypothesis (H_0) will be tested against the alternative by constructing a 2-sided 95% confidence interval for the difference in the least squares mean number of fertilized oocytes between the two treatment groups. If the lower-limit of the 95% confidence interval is greater than the non-inferiority limit (-1.60), the null hypothesis will be rejected, and it will be claimed that MENOPUR liquid is non-inferior to MENOPUR powder with respect to the number of fertilized oocytes.

Due to the expected large sample size, the primary endpoint will be analyzed using a mixed effects two-way analysis of variance (ANOVA) model including the treatment group and the age group as fixed factors, as well as the trial site as a random effect. The least squares mean estimate of the treatment difference in the number of fertilized oocytes and the associated 95% confidence interval will be derived through an LSMEANS statement in the SAS PROC GLM procedure. For subjects who do not have any oocytes retrieved, or do not have fertilization assessment due to early withdrawal, or any other reason, the number of fertilized oocytes will be considered as zero.

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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

AMH	anti-Müllerian hormone
ART	assisted reproductive technology
BMI	body mass index
CRO	contract research organization
DHEA	dehydroepiandrosterone
E2	estradiol
e-CRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICH	International Council for Harmonisation
ICSI	intracytoplasmic sperm injection
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	intention-to-treat
IU	international units
IVF	in vitro fertilization
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
NAb	neutralizing antibody
NCU	neonatal care unit
NICU	neonatal intensive care unit
NIMP	Non-Investigational Medicinal Product
OHSS	ovarian hyperstimulation syndrome
P4	progesterone

PCU	pediatric care unit
PP	per protocol
SAE	serious adverse event
SOC	system organ class
TSH	thyroid-stimulating hormone
US	United States

Definition of Terms

MENOPUR liquid	MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL
MENOPUR powder	MENOPUR powder and solvent for solution for injection, 75 IU

Throughout this document, all trade names are written in capitals to comply with Ferring standard operating procedures.

1 INTRODUCTION

1.1 Background

MENOPUR is a highly purified human menotropin, delivering follicle-stimulating hormone (FSH) activity and luteinizing hormone (LH) activity in a 1:1 ratio.

MENOPUR powder and solvent for solution for injection has been approved in the United States (US) since 2004, for the development of multiple follicles and pregnancy in ovulatory women undergoing controlled ovarian stimulation as part of an assisted reproductive technology (ART) cycle.

The currently available MENOPUR powder and solvent for solution for injection consists of a vial with powder containing 75 IU FSH activity and 75 IU LH activity and a vial with diluent.[1]

As part of the global clinical development program for MENOPUR, Ferring has developed a new multi-dose liquid formulation of MENOPUR in a pre-filled pen, containing 625 IU/mL FSH activity and 625 IU/mL LH activity. This is intended to offer infertility patients a more convenient administration of MENOPUR. The drug substance (highly purified menotropin) in the MENOPUR multi-dose liquid formulation is the same as in the currently approved MENOPUR.

The trial is designed to compare the pharmacodynamics of MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL to the currently approved MENOPUR powder and solvent for solution for injection, 75 IU.

Notes: MENOPUR solution for injection in pre-filled pen 1200 IU/1.92 mL will in this document hereafter be referred to as MENOPUR liquid, and MENOPUR powder and solvent for solution for injection, 75 IU will hereafter be referred to as MENOPUR powder.

1.2 Scientific Justification for Conducting the Trial

The present trial is a phase 3 trial designed to demonstrate the non-inferiority of MENOPUR liquid versus MENOPUR powder with respect to number of fertilized oocytes in women undergoing controlled ovarian stimulation.

MENOPUR liquid is a new multi-dose liquid formulation of MENOPUR in a pre-filled pen developed to offer patients a more convenient administration than the current reconstitution, needle and syringe method.

1.3 Benefit / Risk Aspects

Benefits

The treatment cycle is provided to the participating subjects free of charge, as Ferring compensates the investigational sites for their expenses. Subjects participating in this trial may benefit by

achieving a pregnancy. Subjects in this trial will be closely monitored, and they will have either the same or more frequent visits to the clinic compared to routine treatment, depending on local practice. In addition, the data obtained from the treatment cycle may provide useful information for optimizing the ovarian response and for clinical planning of subsequent treatment cycles.

Risks

Participation in this clinical trial does not create additional risks for the subjects beyond those associated with ART treatment. The risks associated with ART treatment, including controlled ovarian stimulation and intracytoplasmic sperm injection (ICSI), are explained to the subjects as part of the counselling prior to starting fertility treatment.

Gonadotropins

In this trial, controlled ovarian stimulation will be performed with one of two formulations of highly purified menotropin for injection: MENOPUR liquid (new formulation) or MENOPUR powder[1] (approved formulation), and the treatment regimen applied in this trial is in line with the standard posology. MENOPUR powder is a commercially available preparation with established safety and efficacy.[1] The most common adverse reactions (≥2%) with MENOPUR in ART include: abdominal cramps; enlarged abdomen; abdominal pain; headache; injection site pain and reaction; injection site inflammation; and ovarian hyperstimulation syndrome (OHSS).

Subjects are closely monitored throughout the trial and the risks associated with the use of gonadotropin products for ovarian stimulation are well known. The most serious risk associated with gonadotropin treatment is OHSS. OHSS manifests itself with increasing degrees of severity. Moderate/severe OHSS is associated with marked ovarian enlargement, fluid accumulation and other complications. The risk of early OHSS can be minimized by withholding gonadotropins, withholding human chorionic gonadotropin (hCG) or administering gonadotropin-releasing hormone (GnRH) agonist for triggering of final follicular maturation. Very rare cases of serious allergic reactions have been reported after injection of gonadotropins. The risk of treatment-induced anti-drug-antibodies for gonadotropin products is very low and no safety or efficacy concern has been identified with regards to immunogenicity with MENOPUR.

Concomitant Fertility Medications and Trial Procedures

The concomitant fertility medication used in the trial (i.e. the oral contraceptives and GnRH agonist for downregulation and prevention of premature LH surge, the hCG for triggering of final follicular maturation and the vaginal progesterone for luteal phase support), are approved products considered generally well tolerated and are used in accordance with labelling.

Concerning the trial procedures, the double-blind double-dummy design requires that subjects have two investigational medicinal product (IMP) injections daily during the stimulation period, one with the active compound and one with placebo, instead of one as in standard clinical practice. This

may therefore cause more injection site reactions than normally observed for standard clinical practice. The blood sampling might be associated with mild discomfort, bruising and a very rare risk of infection. The transvaginal ultrasound examinations may be associated with mild discomfort and a very rare risk of infection. The oocyte retrieval procedure is associated with discomfort and very rarely infections and bleeding. The transfer procedure is associated with mild discomfort and very rarely infections and spotting / mild bleeding. Additional, but less serious, complications during controlled ovarian stimulation are mild to moderate ovarian enlargement, local reactions, discomfort and pain at the site of injection of gonadotropins and concomitant fertility medication, as well as abdominal pain.

Pregnancy-related Events

The frequency of multiple pregnancies / births and their associated neonatal health complications, is another serious concern associated with ART cycles. To minimize this risk in the present trial, single blastocyst transfer is expected to be performed in the majority of patients. Double blastocyst transfer will only be allowed in cases where there are no good-quality blastocysts available. The incidence of miscarriage is higher in women undergoing controlled ovarian stimulation than in women conceiving spontaneously. The risk of ectopic pregnancy is also higher, but mainly in patients with a history of tubal obstruction. Furthermore, the prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions; this is thought to be due to differences in parental characteristics (e.g. maternal age and sperm characteristics) and multiple pregnancies.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To demonstrate non-inferiority of MENOPUR liquid versus MENOPUR powder with respect to the number of fertilized oocytes in women undergoing controlled ovarian stimulation.

Secondary Objectives

- To evaluate the pregnancy rates after stimulation with MENOPUR liquid and MENOPUR powder.
- To evaluate the follicular development during stimulation with MENOPUR liquid and MENOPUR powder.
- To evaluate the serum endocrine profile during stimulation with MENOPUR liquid and MENOPUR powder.
- To evaluate the number of oocytes retrieved, the number and quality of embryos, and the number and quality of blastocysts, associated with MENOPUR liquid and MENOPUR powder.
- To evaluate treatment efficiency of MENOPUR liquid and MENOPUR powder.
- To evaluate the safety profile of MENOPUR liquid and MENOPUR powder, including adverse events, routine safety laboratory parameters, local tolerability and immunogenicity.

2.2 Endpoints

Primary Endpoint

- Number of fertilized (2 pronuclei [2PN]) oocytes at 19±2 hours after insemination.

Secondary Endpoints

- Positive βhCG rate (positive βhCG test 10-14 days after blastocyst transfer).
- Clinical pregnancy rate (transvaginal ultrasound showing at least 1 intrauterine gestational sac with fetal heart beat 5-6 weeks after blastocyst transfer).
- Ongoing pregnancy rate (at least one intrauterine viable fetus 8-9 weeks after blastocyst transfer).
- Early pregnancy loss (defined as a positive βhCG test but no ongoing pregnancy at 8-9 weeks after blastocyst transfer).
- Follicular development as assessed by transvaginal ultrasound on stimulation day 6 and last day of stimulation.

- Endocrine profile:
  - Serum follicle-stimulating hormone (FSH) on day 6, last day of stimulation and at oocyte retrieval, and corresponding population pharmacokinetics (PK) analysis.
  - Serum Anti-Müllerian hormone (AMH) on last day of stimulation and at end-of-trial.
  - Human chorionic gonadotropin (hCG) and luteinizing hormone (LH) on day 6 and last day of stimulation.
  - Estradiol (E2) and progesterone (P4) on day 6 and last day of stimulation.
- Number of oocytes retrieved, number of metaphase II oocytes, fertilization rate, and number and quality of blastocysts 5 days after oocyte retrieval.
- Total gonadotropin dose and number of stimulation days.
- Frequency of OHSS (early OHSS if the onset is ≤9 days after triggering of final follicular maturation and late OHSS if the onset is >9 days after triggering of final follicular maturation).
- Frequency and intensity of adverse events.
- Changes in circulating levels of clinical chemistry and hematology parameters and proportion of subjects with markedly abnormal changes.
- Frequency and intensity of injection site reactions (redness, pain, itching, swelling and bruising) assessed by the subject during the stimulation period.
- Frequency of treatment-induced anti-MENOPUR antibodies, overall as well as with neutralizing capacity.
- Technical malfunctions of the pen.

Post-trial Endpoints

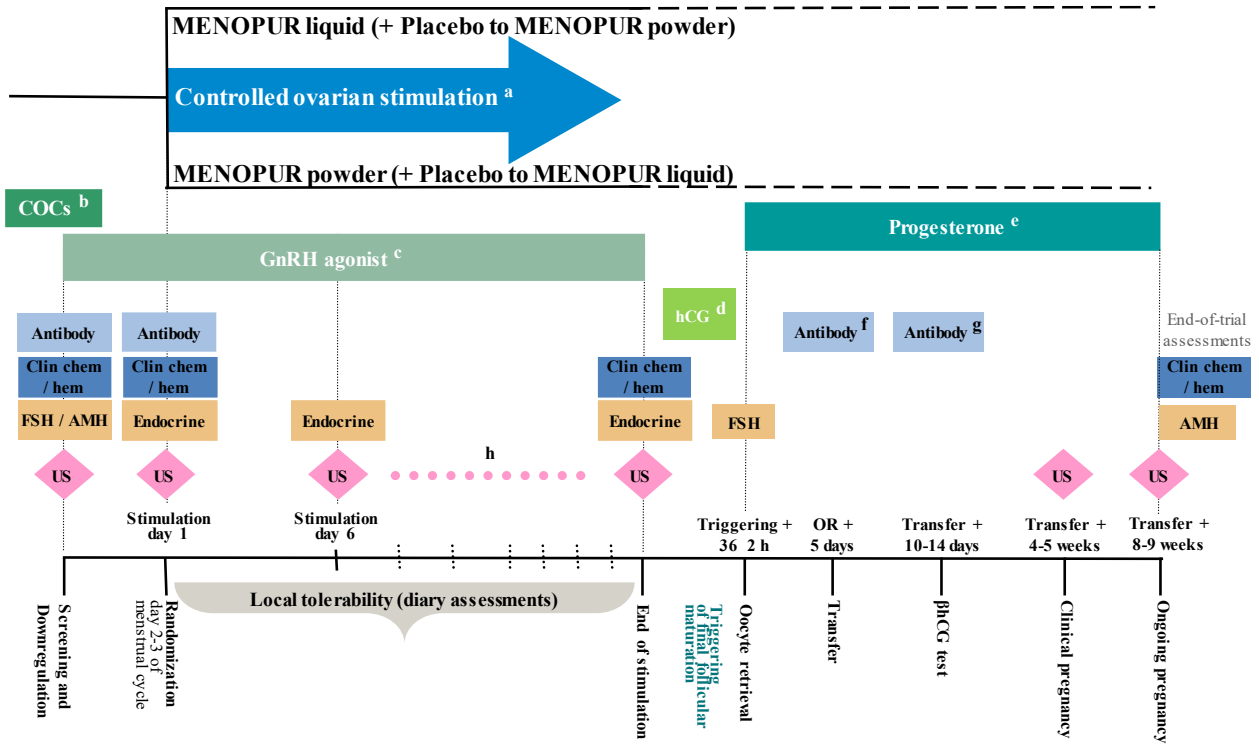
- Live birth rate.
- Late pregnancy loss rate (defined as an ongoing pregnancy but no live birth).
- Neonatal health including SAEs at birth, and SAEs at 4 weeks and minimum 6 months after birth.

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

A trial flow diagram is presented in Figure 3-1.



a 225 IU MENOPUR liquid or 225 IU MENOPUR powder for the first 5 stimulation days, followed by potential adjustments of 75 IU
b Combined oral contraceptives (CYCLAFEM) 1 tablet/day for at least 14 days but no more than 21 days
c GnRH agonist (LEUPROLIDE ACETATE) 0 1 mL (500 µg)/day with reduction of dose to 0 05 mL (250 µg)/day from stimulation day 1 until end of stimulation
d hCG (NOVAREL 2x5,000 IU)
e Progesterone (ENDOMETRIN) 3x100 mg/day
f 7-10 days after the last MENOPUR liquid or MENOPUR powder dose (may coincide with the transfer visit)
g 21-28 days after the last MENOPUR liquid or MENOPUR powder dose (may coincide with the βhCG visit)
h Stimulation day 1, 6 and thereafter at least every second day
AMH anti-Müllerian hormone, COCs combined oral contraceptives, FSH follicle-stimulating hormone, GnRH gonadotropin-releasing hormone, hCG human chorionic gonadotropin, OR oocyte retrieval, US ultrasound

Figure 3-1 Trial Flow Diagram

3.1.2 Overall Design and Control Methods

This is a phase 3, randomized, double-blind double-dummy, parallel-group, multicenter non-inferiority trial. Approximately 400 females undergoing controlled ovarian stimulation as a part of a GnRH agonist protocol at infertility centers in the US will be randomized 1:1 to receive either MENOPUR liquid (including Placebo to MENOPUR powder) or MENOPUR powder (including Placebo to MENOPUR liquid). Randomization will be stratified by trial site and age group (<35 years and ≥35 years). The primary endpoint is the number of fertilized oocytes.

Pituitary downregulation will be done following a protocol using combined oral contraceptives (NORTREL; daily for at least 14 days but no more than 21 days) and a GnRH agonist (LEUPROLIDE ACETATE) which will be initiated at a dose of 0.1 mL (500 µg)/day starting 4 days before the last day on oral contraceptives. Downregulation will be assessed starting on or after day 10 of LEUPROLIDE ACETATE administration, but no later than day 20. In the event of spontaneous menses, subject should be instructed to continue LEUPROLIDE ACETATE and be seen at the center within 3 days to assess downregulation. If downregulation is confirmed (serum E2 ≤20 pg/mL (central laboratory) and transvaginal ultrasound showing no ovarian cysts), the subject is to be randomized and gonadotropins initiated within 3 days. If an ovarian cyst is detected and the E2 level is >20 pg/mL, the subject can undergo outpatient aspiration of the ovarian cyst at the discretion of her physician with assessment of estradiol >1 day later. Subjects can be reassessed to confirm downregulation a maximum of 3 times. The GnRH agonist dose will be reduced to 0.05 mL (250 µg)/day on stimulation day 1 and administration continued until end of gonadotropin administration.

Within 3 days of downregulation confirmation, subjects will be randomized to receive either MENOPUR liquid (including Placebo to MENOPUR powder) or MENOPUR powder (including Placebo to MENOPUR liquid) initiated at 225 IU for 5 days. From stimulation day 6 onward, based on follicular response assessed by transvaginal ultrasound, dosing can be adjusted every second day as needed by 75 IU per adjustment. However, the maximum gonadotropin dose will be 450 IU/day and the minimum dose will be 75 IU/day; gonadotropin dosing can continue for a maximum of 20 days, and coasting is not allowed. Subjects will self-inject the GnRH agonist and gonadotropins (including placebo) at home after receiving instruction by a member of the clinical trial staff (e.g. a trial nurse).

Injection of 2 x 5,000 IU hCG (NOVAREL) will be administered for the triggering of final follicular maturation as soon as 3 follicles of ≥17 mm are observed on transvaginal ultrasound. In the case of excessive ovarian response (>30 follicles of ≥12 mm each and/or E2 levels ≥5000 pg/mL (local laboratory)), the cycle will be cancelled. Oocyte retrieval will take place 36±2 hours after triggering of final follicular maturation, and oocytes will be inseminated by ICSI 4±2 hours after retrieval; oocyte maturity will be recorded. Fertilization (number of pronuclei) will be assessed 19±2 hours following ICSI. Blastocyst quality will be assessed on day 5 following oocyte retrieval.

All subjects will have single blastocyst transfer if they have at least one good-quality (i.e. grade 3BB or above) blastocyst available on day 5 following oocyte retrieval. If no good-quality blastocyst is available, they may have double blastocyst transfer, if at least two blastocysts are available. Transfer of day 6 (or later) blastocyst(s) is not allowed. Remaining blastocysts may be cryopreserved by vitrification. All cryopreserved blastocysts can be used by the subject after completion of the trial in accordance with local guidelines and/or regulations.

Vaginal progesterone inserts (ENDOMETRIN), 100 mg three times daily will be administered for luteal phase support starting the day after oocyte retrieval and continuing up to menses, negative βhCG, pregnancy loss or for a maximum of 10 weeks total if pregnancy is confirmed.

Blood samples will be collected throughout the trial for the purpose of evaluating the endocrine profile, clinical chemistry and hematology parameters as well as anti-MENOPUR antibodies. Endocrine parameters (FSH, LH, hCG, E2 and P4) are assessed at baseline (E2 at confirmation of downregulation and FSH, LH, hCG and P4 on stimulation day 1), day 6, and at end-of-stimulation (day of trigger), and furthermore, FSH is also assessed at oocyte retrieval. In addition, AMH is assessed on stimulation day 1, on the last day of stimulation, and at end-of-trial. Clinical chemistry and hematology are assessed at screening, last day of stimulation, and end-of-trial. Anti-MENOPUR antibodies are assessed at four occasions. The first sample is taken at the screening visit and is exclusively used to re-establish the anti-drug antibody analytical assays. The subsequent three samples are used for analysis of anti-MENOPUR antibodies in the individual subjects in the trial, and are taken prior to dosing on stimulation day 1 and at two occasions post-dosing: 7-10 days after the last MENOPUR liquid or MENOPUR powder dose (this may coincide with the transfer visit) and 21-28 days after the last MENOPUR liquid or MENOPUR powder dose (this may coincide with the βhCG test visit). Subjects with a treatment-induced anti-MENOPUR antibody response will be followed until the response has become negative or returned to the pre-dosing level. These subjects will be called in for assessments at 2 months after the last post-dosing anti-MENOPUR antibody sampling. If required, further assessments will be made at 3, 4, 6, 9 and 12 months after the last post-dosing anti-MENOPUR antibody sampling. The assessments will be terminated when two consecutive assessments are negative or indicate that the pre-dosing level has been reached, with a maximum follow-up period of one year. The assessments will also be terminated if the subject commences a new treatment cycle with any gonadotropin preparation.

Local tolerability of MENOPUR liquid or MENOPUR powder following subcutaneous administration will be assessed by the subject three times daily: immediately, 30 minutes and 24 hours after each injection. The assessment of injection site reactions will be made throughout the stimulation period and recorded by the subject in a diary.

Concerning post-trial follow-up, all subjects with an ongoing pregnancy will be followed. Data will be gathered on delivery information (live birth and neonatal health). In addition, data on neonatal SAEs will be collected at 4 weeks and minimum 6 months after birth.

3.1.3 Trial Schedule

The estimated trial schedule is as follows:

First subject first visit (FSFV):	Q4 2019
Last subject last visit (LSLV):	Q4 2020
Last 4-weeks neonatal health follow-up:	Q1 2021
Last 6-months neonatal health follow-up:	Q3 2021

3.2 Planned Number of Trial Sites and Subjects

The trial is planned to be conducted at up to 25 infertility centers in the US. It is planned to randomize 400 subjects of whom 200 subjects will be randomized to MENOPUR liquid and 200 subjects will be randomized to MENOPUR powder. It is estimated that approximately 800 subjects should be screened to achieve 400 subjects eligible for randomization.

A blinded sample size reassessment will be done when data on the primary endpoint are available for 70% of the planned subjects or when 300 subjects are randomized, whichever comes first. The number of randomized subjects may be adjusted up to a maximum of 500 subjects, corresponding to a blinded one-sample standard deviation estimate of 5.8 and 85% power.

3.3 Interim Analysis and Administrative Review

No interim analysis intended to compare treatment groups with respect to efficacy or safety is planned.

The assumptions underlying the sample size calculations, such as the variability of the primary efficacy endpoint will be monitored in a blinded manner. This monitoring will be performed by the project statistician who will evaluate the blinded one-sample standard deviation in relation to the assumptions underlying the sample size (see sections 9.1 and 9.9).

3.4 Data Monitoring Committee

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

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The primary objective of the trial is to demonstrate non-inferiority of MENOPUR liquid compared with MENOPUR powder with respect to number of fertilized oocytes in women undergoing an ART program.

Strict criteria have been incorporated in the design of this comparative efficacy trial to properly assess the effect of the interventions on treatment outcome. In general, to minimize variation, standardization of criteria, timing of assessments, procedures and interventions have to a great extent been incorporated in the design of this trial.[2,3,4]

This is a randomized controlled double-blind double-dummy trial using an approved gonadotropin preparation as an active comparator. It is a parallel group design restricted to a single treatment cycle. The double-blind double-dummy design ensures that the subjects, investigators and other assessors such as embryologists and central laboratory personnel are blinded to individual treatment allocation throughout the trial, including the post-trial activities. Similarly, Ferring staff will also remain blinded to individual subject treatment allocation during the conduct of the trial. The trial will be a multi-center trial. This set-up ensures that the required number of subjects can be recruited within a reasonable time and also has the advantage that it should facilitate subsequent generalization of the results.

The trial is designed to demonstrate non-inferiority of MENOPUR liquid versus MENOPUR powder with respect to number of fertilized oocytes. The non-inferiority margin has been set at 1.60 which is considered suitable considering the clinical implications of this margin. A detailed justification is provided in section 9.1.

Subjects will undergo controlled ovarian stimulation with a daily starting dose of 225 IU MENOPUR liquid, or 225 IU MENOPUR powder, following a GnRH agonist protocol. The daily gonadotropin dose is fixed for the first five stimulation days after which it may be adjusted by 75 IU based on the individual response. The selection of doses is described in detail in section 3.5.4. Monitoring of ovarian response by transvaginal ultrasound and blood sampling for assessment of several endocrine parameters will be performed regularly during stimulation.

In this trial, oocytes will be inseminated using ICSI in order to have a standardized fertilization method for all participating subjects. Furthermore, it will facilitate the interpretation of the subsequent embryo quality findings, as the timing of these assessments relative to the time of insemination can be accurately determined. In clinical practice, the choice of ICSI has previously mainly been determined by the presence of male factor infertility or fertilization failure in previous in vitro fertilization (IVF) cycles, but in recent years the use of ICSI has increased steadily. ICSI is now frequently used in routine management of infertile couples, expanding beyond those with male factor infertility.

The present protocol requires single blastocyst transfer on day 5 for all women with at least one good-quality blastocyst available. Women with no good-quality blastocyst may have double blastocyst transfer (if two blastocysts are available). The scientific justification for incorporating these features is that it will ensure that the data obtained in this trial are in line with the current clinical directions taken for maintaining efficacy (i.e. ongoing pregnancy rates) and minimizing risks (i.e. multiple pregnancies).[5,6,7,8] Further, there is increasing evidence suggesting that late stages of embryo progression are better predictors of clinical pregnancy than early embryo

development parameters.[9] In subjects with good prognosis, the transfer of blastocysts yields a higher live birth rate than that achieved with transfer of the same number of cleavage stage embryos.

3.5.2 Selection of Endpoints

For the present trial, the number of fertilized oocytes at 19±2 hours after insemination has been set as the primary endpoint as per agreement with FDA.

Positive βhCG, clinical pregnancy and ongoing pregnancy are included as secondary endpoints in the trial. The secondary endpoints also cover commonly investigated pharmacodynamic parameters such as endocrine profile and ovarian response as well as standard evaluations of safety profile. Furthermore, oocyte and embryo quality will be assessed and a detailed evaluation of blastocyst quality is also included in the trial.

3.5.3 Blinding

The two investigational medicinal products (IMPs) differ in presentation as MENOPUR liquid is provided in a pre-filled injection pen, while MENOPUR powder is provided as a vial with powder and a vial with diluent. The trial design is therefore double-blind, double-dummy, ensuring unbiased evaluation by the subject, the investigator and other trial personnel such as personnel performing the ultrasound monitoring, embryologists, and central laboratory personnel.

Similarly, the Ferring clinical trial team (i.e. data manager, statistician, clinical trial manager, clinical project leader, field monitor, medical writer, pharmacovigilance physician, pharmacovigilance manager, medical monitor and medical officer) will be blinded to treatment allocation until breaking of the blind. The blind will be broken when the trial database is declared clean and released to the statistician. A more detailed description of the blinding is provided in section 5.5.1.

3.5.4 Selection of Doses in the Trial

The starting dose of 225 IU for this trial is in accordance with the labelling recommendations for MENOPUR powder in the US for women who have received a GnRH agonist for pituitary suppression.

The dose of the IMPs will be initiated at 225 IU for the first 5 days. From stimulation day 6 onward, based on the subject's follicular response assessed by transvaginal ultrasound, dosing can be adjusted every second day, as needed, by 75 IU per adjustment. However, the maximum gonadotropin dose will be 450 IU/day and the minimum dose will be 75 IU/day; gonadotropin dosing can continue for a maximum of 20 days and coasting is not allowed.

The doses and overall treatment regimens for the combined oral contraceptives (NORTREL), GnRH agonist (LEUPROLIDE ACETATE), hCG (NOVAREL) and progesterone (ENDOMETRIN) products are in line with the recommendations in the respective products' labelling for the indication of ART and/or standard clinical practice.

3.5.5 Selection of the Trial Population

This trial will include women undergoing ICSI who are aged 18-42 years and who may have had up to two previous controlled ovarian stimulation cycles. The subjects have been diagnosed with unexplained infertility, tubal infertility, endometriosis stage I-II or have partners diagnosed with male factor infertility, and are considered eligible for ICSI. Women with a history of recurrent miscarriages will not be included in the trial. The allowed BMI is 17.5-38.0 kg/m^2, thus including underweight, normal weight, overweight and obese subjects.

The exclusion criteria are aligned with the contraindications for the use of gonadotropins in the labelling for these preparations.

Altogether, the population selected for this trial would be expected to be representative of patients undergoing controlled ovarian stimulation in ICSI cycles.

3.5.6 Follow-up Procedures

Treatment Monitoring

Subjects will return to the trial site for regular scheduled clinic visits as required per protocol for measurement of hormone levels, transvaginal ultrasound, 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. Clinical pregnancy will be confirmed by transvaginal ultrasound, indicating at least 1 intrauterine gestational sac with fetal heart beat at 5-6 weeks after blastocyst transfer. Ongoing pregnancy will be confirmed by at least 1 intrauterine viable fetus at 8-9 weeks after blastocyst transfer.

Post-trial Activities

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 addition, data on neonatal SAEs will be collected at 4 weeks and minimum 6 months after birth.

Immunogenicity Follow-up

Subjects with a treatment-induced anti-MENOPUR antibody response will be followed until the response has become negative or returned to the pre-dosing level, or for a maximum of 1 year.

Access to Therapy after End-of-Trial

Concerning access to therapy after completion of the trial, MENOPUR powder is approved for controlled ovarian stimulation and is commercially available in the US, while MENOPUR liquid is currently under clinical development and cannot be offered to subjects after participation in this clinical trial.

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 consents, prior to any trial-related procedure.
2. Females between the ages of 18 and 42 years. The subjects must be at least 18 years (including the 18th birthday) when they sign the informed consent and no more than 42 years (up to the day before the 43rd birthday) at the time of randomization who desire pregnancy.
3. Body mass index (BMI) between 17.5 and 38.0 kg/m^2 (both inclusive) at screening.
4. Regular menstrual cycles of 24 to 35 days, presumed to be ovulatory.
5. Documented history of infertility for at least 12 months before randomization for women ≤ 35 years or for at least 6 months for women ≥ 36 years. Women with documented bilateral tubal occlusion or male factor infertility requiring the use of donor sperm established as a cause of infertility are eligible at diagnosis.
6. Early follicular phase (cycle day 2-4) serum FSH level between 1 and 12 IU/L (results obtained within 3 months prior to randomization).
7. Serum Anti-Müllerian hormone (AMH) level greater than 1.0 ng/mL at screening (central laboratory).
8. 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.
9. At least 1 cycle with no fertility medication immediately prior to screening.
10. Hysterosalpingography, hysteroscopy, or saline hysterosonogram documenting uterine anatomy appropriate for ART at screening or within 12 months prior to screening.
11. Transvaginal ultrasound documenting presence and adequate visualization of both ovaries, without evidence of clinically significant abnormality (e.g., endometrioma ≥3 cm, no dermoid cysts) and normal adnexa (e.g., no hydrosalpinx) at screening. Both ovaries must be accessible for oocyte retrieval.
12. 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.
13. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests at screening or within 6 months prior to screening.

14. Confirmation of downregulation prior to randomization, defined as serum E2 ≤20 pg/mL (central laboratory) and transvaginal ultrasound showing no ovarian cysts.
15. Willing and able to comply with the protocol, including scheduled clinic visits and laboratory tests, for the duration of the trial.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be eligible for trial participation:

1. More than two previous controlled ovarian stimulation cycles for IVF/ICSI
2. Known stage III-IV endometriosis (American Society for Reproductive Medicine, 2012)[10].
3. Oocyte donor or embryo recipient; gestational or surrogate carrier.
4. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy [excl. ectopic pregnancy] and before week 24 of pregnancy).
5. 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.
6. The use of hormonal preparations (except for thyroid medication) within 3 months prior to screening.
7. Use of fertility modifiers during the last menstrual cycle before start of downregulation, including dehydroepiandrosterone (DHEA) and metformin.
8. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
9. History or presence of heart disease, cardiovascular or cerebrovascular disease or disorder (e.g. coronary artery disease, hypertension).
10. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
11. Any known endocrine (total testosterone, prolactin and TSH) or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of controlled thyroid function disease.
12. Known tumors of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
13. Known moderate or severe impairment of renal or hepatic function.
14. Any abnormal finding of clinical chemistry, hematology and vital signs at screening, which is judged clinically significant by the investigator.
15. Currently breastfeeding.
16. Pregnancy (negative urine pregnancy test must be documented at screening and prior to the first IMP administration), or contraindication to pregnancy.

17. Presence of abnormal uterine bleeding of undetermined origin.
18. Known abnormal cervical cytology of clinical significance observed within three years prior to randomization (unless the clinical significance has been resolved).
19. Findings at the gynecological examination at screening that preclude gonadotropin therapy in the opinion of the investigator or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
20. History of chemotherapy (except for gestational conditions) or radiotherapy.
21. Current or recent (12 months prior to randomization) abuse of alcohol or drugs, and/or current (last month) intake of more than 14 units of alcohol per week.
22. Current or recent (3 months prior to screening) smoking more than 10 cigarettes per day (or the equivalent).
23. Hypersensitivity to any active ingredient or excipients in the medicinal products used in this trial.
24. Participation in any experimental drug trial within 30 days prior to screening, including previous participation in the present trial.
25. Known mental incapacity or language barrier precluding adequate understanding of the informed consent information and the trial activities.
26. Clinic staff member directly involved in the conduct of the trial. 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

Once downregulation is confirmed, subjects will within 3 days be randomized in a 1:1 ratio to treatment with either MENOPUR liquid (including Placebo to MENOPUR powder) or MENOPUR powder (including Placebo to MENOPUR liquid), and stimulation will be initiated. Randomization is performed centrally through the electronic case report form (e-CRF). The randomization number will be allocated to the subject together with the treatment allocation. When a subject is randomized to the trial, she will always be assigned to the lowest available randomization number. An independent statistician will prepare a computer-generated randomization list and randomization is performed in blocks. Blocks will be maintained within trial sites, i.e. the randomization will be stratified by trial site. In addition, randomization will also be stratified by age (<35 years and ≥35 years). The block size will only be revealed when the trial database is declared clean and released to the statistician. Details of subject enrolment will be recorded on a subject identification

code list for all randomized subjects kept by the investigator.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

The subjects must not have used fertility modifiers, including dehydroepiandrosterone (DHEA) and metformin, or hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomization.

Use of any medications other than the trial medication provided for this trial should be avoided from the screening period until completion of the trial. Occasional use of over the counter medications or prescription drugs may be allowed at the discretion of the investigator.

Any concomitant therapies used during the trial or within 3 months prior to screening will be recorded in the source documents and e-CRF, along with the main reason for their prescription/use.

4.3.2 Prohibited Therapy

It is prohibited to continue therapy outside the scope of this trial with medicinal products provided specifically for this trial.

4.4 Withdrawal Criteria

Withdrawal from Trial

Every subject has the right to withdraw from the trial at any time for any reason, without the need to justify their decision. A subject's participation is to terminate immediately upon her request. However, the investigator should record the reason for the subject’s withdrawal, if possible.

If, at the time of discontinuation, a dose of the IMP has already been administered, the subject must be advised to agree to follow-up safety investigations, which will include all procedures outlined for the end-of-trial visit (section 6.8).

The subject can also be withdrawn from the trial at any time at the discretion of the investigator. For any discontinuation, the investigator will obtain all the required details and document the date of the premature termination and the main reason in the e-CRF.

A subject that withdraws from the trial will not be replaced.

Withdrawal of Consent

If the subject withdraws her consent, data collected up to withdrawal will remain in the database, but no further data will be collected. Samples and recordings obtained before withdrawal may be

analyzed. This will be described in the Informed Consent Documents. The subject can request destruction of samples which would otherwise have been kept in storage.

Trial Stopping Criteria

Occurrence of the following adverse events or abnormal laboratory values may warrant consideration of trial termination:

- Life-threatening SAEs with suspected causality to the IMP, including but not limited to OHSS (section 8.3.1).
- Formation of treatment-induced neutralizing antibodies to gonadotropins.

The internal Safety Management Team at the sponsor will review each occurrence and provide a recommendation as to whether to discontinue the trial. The responsibilities and composition of the internal Safety Management Team are provided in a separate charter document, available before the first subject's first visit.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products

Subjects will be randomized to the following IMPs in a 1:1 ratio in the trial:

- MENOPUR liquid (MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL) including Placebo to MENOPUR powder (powder and solvent for solution for injection)
- MENOPUR powder (MENOPUR powder and solvent for solution for injection, 75 IU) including Placebo to MENOPUR liquid (solution for injection in pre-filled pen)

Treatment will be provided to the subjects as double-dummy treatment with the combination of a pre-filled injection pen with MENOPUR liquid and vials (powder and diluent) with Placebo to MENOPUR powder, or a pre-filled injection pen with Placebo to MENOPUR liquid and vials (powder and diluent) with MENOPUR powder. Table 5-1 provides an overview of the double-dummy treatment components

Table 5-1 Double-dummy Treatment Overview

Randomized to	Pre-filled injection pen with	Vials (powder and diluent) with
MENOPUR liquid	MENOPUR liquid	Placebo to MENOPUR powder
MENOPUR powder	Placebo to MENOPUR liquid	MENOPUR powder

In order to maintain the blinding of the trial, the pre-filled injection pens with MENOPUR liquid and Placebo to MENOPUR liquid will be identical in appearance. Likewise, the vials (powder and diluent) with MENOPUR powder and Placebo to MENOPUR powder will be identical in appearance.

MENOPUR liquid and MENOPUR powder will be initiated at dose of 225 IU for the first 5 days. From stimulation day 6 onward, dosing can be adjusted as needed every second day by 75 IU per adjustment based on the subject's follicular response. The maximum dose will be 450 IU/day and the minimum dose will be 75 IU/day; dosing can continue for a maximum of 20 days. Coasting is not allowed.

The IMPs are administered as a daily subcutaneous injection in the lower part of the abdomen. Subjects will self-inject the IMP at home after being instructed by trial staff at the site (e.g. a trial nurse) on how to administer the IMP. To minimize local injection site reactions, it is advisable to change the injection site regularly, but it should always be on the same side of the navel in order to be able to distinguish between injection site reactions related to MENOPUR liquid or Placebo to MENOPUR liquid and those related to MENOPUR powder or Placebo to MENOPUR powder.

The timing of the gonadotropin injections should be aligned with the GnRH agonist injections (see below).

For information on warnings and precautions, please refer to the Investigator's Brochure for MENOPUR liquid[11] and Prescribing Information for MENOPUR powder.[1]

5.1.2 Non-Investigational Medicinal Products

The non-investigational medicinal products (NIMPs) to be used are listed in Table 5-2.

Table 5-2 Non-investigational Medicinal Products

NIMP	Trade name	Dose
Combined oral contraceptives	NORTREL 1/35 (norethindrone [1 mg] and ethinyl estradiol [0.035 mg])	1 mg/0.035 mg (1 tablet) daily for at least 14 days but no more than 21 days during the downregulation period.
GnRH agonist	LEUPROLIDE ACETATE (leuprolide acetate)	0.1 mL (500 µg)/day administered as subcutaneous injections in the upper thigh during the downregulation period, followed by a dose of 0.05 mL (250 µg)/day from stimulation day 1 throughout the gonadotropin treatment period.
hCG	NOVAREL (chorionic gonadotropin)	1 mL (2 x 5,000 IU) administered by intramuscular injection according to label as soon as 3 follicles of ≥17 mm are observed on transvaginal ultrasound.
Progesterone	ENDOMETRIN (progesterone)	100 mg vaginal inserts three times daily, for luteal phase support continuing up to menses, negative βhCG test, pregnancy loss, or for a maximum of 10 weeks total if pregnancy is confirmed.

All NIMPs are to be used in line with the recommendations in the respective products' labelling for the indication ART and/or standard clinical practice supported by literature.

For information on warnings and precautions, please refer to the Prescribing Information for NORTREL, LEUPROLIDE ACETATE, NOVAREL, and ENDOMETRIN.

5.2 Characteristics and Source of Supply

All medicinal products are provided by Ferring and will be handled according to the principles of Good Manufacturing Practice (GMP). Table 5-3 provides an overview of the presentation of each medicinal product.

Table 5-3 Characteristics of Medicinal Products

IMP / NIMP	Presentation
MENOPUR liquid (menotrophin HP), Ferring Pharmaceuticals	MENOPUR liquid is provided as a pre-filled injection pen for multiple use (with integrated non-replaceable 3 mL cartridge). Each pen delivers 625 IU/mL of FSH activity and 625 IU/mL of LH activity
Placebo to MENOPUR liquid, Ferring Pharmaceuticals	Placebo to MENOPUR liquid is provided as a pre-filled injection pen for multiple use containing solution for injection.
MENOPUR powder (menotrophin HP), Ferring Pharmaceuticals	MENOPUR powder is provided as vials with lyophilized powder and vials with diluent. After reconstitution, each vial delivers 75 IU of FSH activity and 75 IU of LH activity.
Placebo to MENOPUR powder, Ferring Pharmaceuticals	Placebo to MENOPUR powder is provided as a vial with lyophilized powder and a vial with diluent.
NORTREL 1/35 Teva Pharmaceuticals USA, Inc.	NORTREL (norethindrone [1 mg] and ethinyl estradiol [0.035 mg]) is provided as oral tablets.
LEUPROLIDE ACETATE (GnRH agonist), Sandoz	LEUPROLIDE ACETATE (leuprolide acetate) is provided as a vial with sterile solution (14 mg/2.8 mL).
NOVAREL (hCG), Ferring Pharmaceuticals	NOVAREL (chorionic gonadotropin) is provided as vials with lyophilized powder and vials with diluent. After reconstitution, each vial delivers 5,000 IU chorionic gonadotropin.
ENDOMETRIN (progesterone), Ferring Pharmaceuticals	ENDOMETRIN (progesterone) is provided as vaginal inserts of 100 mg of progesterone.

5.3 Packaging and Labelling

Packaging and labelling of the medicinal products will be performed under the responsibility of the Clinical Trial Supply department at Ferring in accordance with GMP and U.S. regulatory requirements. Details on the packaging of each medicinal product is provided in Table 5-4.

Table 5-4 Packaging of Medicinal Products

IMP / NIMP	Presentation
MENOPUR liquid (menotrophin HP)	MENOPUR liquid is provided in boxes containing a pre-filled injection pen.
Placebo to MENOPUR liquid	Placebo to MENOPUR liquid is provided in boxes containing a pre-filled injection pen.
MENOPUR powder (menotrophin HP)	MENOPUR powder is provided in boxes containing five vials with powder and five vials with diluent.
Placebo to MENOPUR powder	Placebo to MENOPUR powder is provided in boxes containing five vials with powder and five vials with diluent.
NORTREL1/35 (combined oral contraceptive)	NORTRELis provided in boxes containing 3 blister packs each with 28 tablets.
LEUPROLIDE ACETATE (GnRH agonist)	LEUPROLIDE ACETATE is provided in boxes containing a vial.
NOVAREL (hCG)	NOVAREL is provided in boxes containing one vial with powder and one vial with diluent.
ENDOMETRIN (progesterone)	ENDOMETRIN is provided in boxes containing 21vaginal inserts and 21 disposable vaginal applicators.

All NIMPs are commercially available and will be purchased centrally. No modification from the usual commercial state of the NIMPs will be made, except for trial-specific labelling.

All products (IMPs and NIMPs) will be labelled with trial-specific labels, which contain a 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. The storage compartment shall be monitored regularly and the temperature shall be documented. Deviations in storage temperature must be reported to Ferring as instructed in the IMP/NIMP handling guideline.

Specific storage and use instructions for all IMPs and NIMPs are described in the package inserts and/or trial specific/commercial box labelling.

The IMPs will only be dispensed to subjects who meet the eligibility criteria and are randomized to a treatment group in the trial.

5.5 Blinding / Unblinding

5.5.1 Blinding

The IMP will be packaged according to a computer-generated randomization list prepared for all trial sites.

The packaged IMP kits containing the active and placebo formulation of each presentation will be indistinguishable with identical appearance, and will be labelled with random identification numbers which are linked to the treatment allocation. Once the subject is assigned a unique randomization number in the e-CRF system, the subject's treatment allocation will be transferred automatically to the Interactive Response Technology (IRT) system. Site staff will access the IRT system to obtain an identification number for the IMP kits to dispense to the subject, with both the site staff and the subject blinded to the treatment allocation. Subjects will receive two different treatment kits, one box containing a pre-filled injection pen and one box containing five vials each of powder and diluent.

The Ferring clinical trial team (i.e. data manager, statistician, clinical trial manager, clinical project leader, field monitor, medical writer, pharmacovigilance physician, pharmacovigilance manager, medical monitor and medical officer) will be blinded to treatment allocation until breaking of the blind. The blind will be broken when the trial database is declared clean and released to the statistician.

The randomization list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and locked. Likewise, the treatment allocation information in the e-CRF will not be accessible to investigators, trial staff at site or laboratory personnel during the trial.

5.5.2 Unblinding of Individual Subject Treatment

An emergency decoding possibility will be available to the investigator and designated persons at Ferring. It is the investigator's responsibility to decide whether it is medically necessary to know the investigational product the subject receives (i.e. unblinding) to ensure the subject's welfare and safety. Breaking of the blind for individual subjects in emergency situations could be required in case of suspected, unexpected serious adverse reactions (SUSARs) or in case of other important adverse events when the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and Ferring. Where the event requires immediate unblinding by the investigator, Ferring must be informed of the unblinding as soon as possible and provided with the rationale for unblinding. The investigator/person who unblinds a treatment will use the e-CRF in which he/she is required to enter a password and record the reason for unblinding before the treatment code can be broken. The e-CRF automatically records when and by whom the code is broken. The investigator must record

the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

In case of accidental unblinding, the same procedure as for emergency unblinding must be followed, i.e. the person who is accidentally unblinded will enter a password in the e-CRF and must record the reason for unblinding, while the e-CRF records when and by whom the code is broken.

If Ferring needs to unblind a subject's treatment, the e-CRF will be used for unblinding. It is required to enter a password and the reason for unblinding before the treatment code can be broken. The e-CRF records when and by whom the code was broken. The code break will occur according to corporate standard operating procedures for unplanned unblinding of trial subjects. It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the relevant health authorities and/or IRBs. In that situation, every effort will be made to maintain blinding of Ferring personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial site staff as well as staff acting on behalf of Ferring.

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

In case the e-CRF cannot be accessed by the investigator, and hence the emergency unblinding cannot be performed within the e-CRF system, the investigator should contact Ferring Pharmacovigilance using the contact details given below.

Pharmacovigilance, Ferring Pharmaceuticals
US Toll-free number: [redacted]

If Ferring Pharmacovigilance cannot access the e-CRF, a back-up procedure involving the e-CRF vendor is in place.

5.6 Treatment Compliance, Dispensing and Accountability

The IMP will only be dispensed to subjects who meet the eligibility criteria and are randomized to a treatment group in the trial. The investigator (or his/her designated staff, e.g. trial nurse) will maintain a drug-dispensing log detailing the dates and quantities of IMPs dispensed to, and used by, each subject, as well as the batch numbers, kit numbers [or other identifier used in the trial]. The monitor will verify the drug accountability during the trial.

In order to monitor compliance, the subjects are to return empty, partially used, and unused vials or pens to the investigator at each visit. The investigator (or his/her designated staff, e.g. trial nurse) 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.

5.7 Auxiliary Supplies

Ferring will provide the sites with sterile pen needles for the MENOPUR liquid pre-filled injection pens, and syringes and needles for administration of MENOPUR powder, LEUPROLIDE ACETATE, and NOVAREL.

5.8 Return and Destruction of Medicinal Products and Auxiliary Supplies

The monitor will check the supplies, the drug accountability, and inventory records. Following this check, the investigator will sign off the records.

All dispensed IMP and NIMP can be destroyed at the trial site after the drug accountability has been finalized, verified by the monitor, and signed off by the investigator. This includes residual liquid in a vial, pre-filled syringe or injection pen. Used syringes and needles should be destroyed immediately after usage according to normal procedures at each trial site. Any non-dispensed IMP/NIMP will be returned for destruction, as instructed by the Ferring Clinical Trial Supply Department, 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 Ferring.

6 TRIAL PROCEDURES

The flow of trial procedures for subjects is shown in Table 6-1.

Table 6-1 Trial Flow Chart

	Screening and Down-regulation	**Stimulation**				**Oocyte retrieval**	**Transfer**	**Pregnancy monitoring**			**End**
	Pre-stimulation period	During stimulation			End of stimula-tion	OR	Transfer	βhCG	Clinical	Ongoing	End-of-trial
Timing	<90 days before stimulation Day 1	Day 1 ≤3 days after conf. downreg.	Day 6	Day >6 to <20	End	36±2 h after hCG	5 days after OR	10-14 days after transfer	5-6 weeks after transfer	8-9 weeks after transfer	[a]
Written informed consent	X										
Inclusion/exclusion criteria	X	X[b]									
Demographics	X										
Medical history	X										
Menstrual history	X										
Reproductive history	X										
Infertility history	X										
Vital signs	X	X			X						X
Physical examination	X										X
Gynecological examination	X										X
Urine pregnancy test	X	X									
Blood collection, clin chem/hem.	X				X						X
Blood collection, antibodies[c]	X[d]	X[e]					X[f]	X[g]			X[g]
Blood collection, endocrine (central)[h]	X	X	X		X	X					X
Blood collection, endocrine (local)[i]			X	X	X						
Confirmation of downregulation[j]	X										
Randomization		X									
IMP dispensing and administration		X[k]	X	X							
Injection site reactions (diary)		X	X	X	X						
NIMP dispensing	X	X	X	X	X	X	X	X	X		
Ultrasound sonography[l]		X[b]	X	X	X		X		X	X	
Oocyte retrieval						X					
Blastocyst transfer/freezing							X				
βhCG test								X			
Drug accountability			X	X	X						X
Concomitant medication	X[m]	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
End-of-trial form											X

a) End-of-trial 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 trial.
b) Performed before randomization.
c) All subjects with a treatment-induced antibody response must be followed until the response is negative or has returned to pre-dosing level.
d) Sample exclusively used to re-establish the anti-drug antibody analytical assays.
e) Performed before the first IMP dose.
f) Blood sampling for antibody assessment must be done 7-10 days after the last IMP dose (this may coincide with the transfer visit; alternatively, a separate visit must be scheduled).
g) Blood sampling for antibody assessment must be done 21-28 days after the last IMP dose (this may coincide with the βhCG visit; alternatively, a separate visit must be scheduled).
h) Endocrine parameters for analysis by central laboratory: AMH, FSH, hCG, LH, E2 and P4. Special considerations for certain visits are as follows: Screening – AMH only, day 1 – no E2, day 6 – no AMH, oocyte retrieval – FSH only, end-of- trial – AMH only.
i) Endocrine parameters for analysis by local laboratory: E2 and P4, optional assessment; performed as per the site's standard practice.
j) Serum E2 ≤20 pg/mL (central laboratory) and transvaginal ultrasound showing no ovarian cysts.
k) The gonadotropin starting dose is 225 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. Gonadotropin is to be initiated within 3 days of confirmed downregulation.
l) Transvaginal ultrasound with exception of the transfer and ongoing pregnancy visits, where it can be either transvaginal or abdominal examination.
m) Recording of any concomitant medication within the last 3 months prior to informed consent.

6.1 Screening and Downregulation

6.1.1 Screening

Potential participants will be scheduled to come to the clinic for the screening assessments. Screening must be initiated within 90 days before stimulation day 1.

The following procedures / assessments must take place during the screening period:

- Signed and dated written informed consent must be obtained, and a copy provided to the subject, before any trial-related examinations
- Allocate a screening number
- Check the inclusion and exclusion criteria (those which are possible to check at screening)
- Demographics
- Medical history
- Menstrual history
- Reproductive history
- Infertility history
- Vital signs
- Complete physical examination (including height, weight, and BMI calculation)
- Gynecological examination
- Urine pregnancy test – must be negative
- Blood collection for central laboratory analysis of:
  - Clinical chemistry and hematology parameters
  - AMH [*note*: the results must be available prior to start of downregulation due to inclusion criterion 7]
  - Anti-MENOPUR antibodies [exclusively used to re-establish the anti-drug antibody analytical assays]
- Recording of use of any concomitant medication within the last 3 months prior to signed informed consent (except medication used in previous infertility treatment cycles which will be recorded as part of the infertility history)
- Recording of adverse events (from time of signed informed consent)

Subjects considered eligible for the trial, based on the inclusion and exclusion criteria assessed at this time point, may proceed with downregulation.

In case of positive findings of HBsAg, HCV or HIV antibody tests obtained at screening, it is the investigator's responsibility to ensure that standard reporting and referral procedures at the sites are

followed in line with local regulations.

6.1.2 Downregulation

The following procedures / assessments must be performed:

- Urine pregnancy test – must be negative
- Prepare and dispense combined oral contraceptives (NORTREL) and GnRH agonist (LEUPROLIDE ACETATE) and instruct the subject on how to administer the GnRH agonist, the subject will self-inject the GnRH agonist at home
- Start pituitary downregulation with combined oral contraceptives daily, and 4 days before the last day on oral contraceptives start GnRH agonist (LEUPROLIDE ACETATE) 0.1 mL (500 µg)/day [self-injection at home]

Combined oral contraceptives should be taken daily for at least 14 days but no more than 21 days, at the investigators judgement.

A minimum of 10 days but no more than 20 days with GnRH agonist administration should be ensured prior to confirmation of downregulation. At that time, the following assessments must be performed:

- Transvaginal ultrasound
- Blood collection for central laboratory analysis of endocrine parameters (E2 only)

Downregulation is confirmed by a serum E2 level ≤20 pg/mL and transvaginal ultrasound showing no ovarian cysts.

If an ovarian cyst is detected and the E2 level is >20 pg/mL, the subject can undergo outpatient aspiration of the ovarian cyst at the discretion of her physician with assessment of estradiol >1 day later. Subjects can be reassessed to confirm downregulation a maximum of 3 times.

Once downregulation is confirmed, the subject must proceed to the next scheduled visit within 3 days (stimulation day 1).

If downregulation is not obtained within 4 weeks of treatment with GnRH agonist, the subject is considered a screening failure and is excluded from the trial.

6.2 Stimulation

6.2.1 Stimulation Day 1

Subjects will attend the stimulation day 1 visit within 3 days of confirmed downregulation.

The following must take place prior to randomization:

- Ensure that the subject is still eligible for participation in the trial
- Check those inclusion and exclusion criteria that were not possible during screening
- Urine pregnancy test – must be negative
- Transvaginal ultrasound of uterus and ovaries (number and size of follicles)

If the subject fulfills all inclusion and no exclusion criteria, she will proceed to randomization:

- Randomization, i.e. assignment to the lowest available subject number and thereby allocation to either MENOPUR liquid (including Placebo to MENOPUR powder) or MENOPUR powder (including Placebo to MENOPUR liquid).

The following must take place after randomization but before administration of the first dose of IMP (MENOPUR liquid and Placebo to MENOPUR powder or MENOPUR powder and Placebo to MENOPUR liquid):

- Vital signs
- Blood collection for central laboratory analysis of:
  - Endocrine parameters (AMH, FSH, hCG, LH and P4)
  - Anti-MENOPUR antibodies

Once the above assessments have been completed, the following must be performed:

- Preparation and dispensing of IMP according to randomization and instruct the subject on how to administer the IMP, the subject will self-inject the IMP at home. The IMP should be injected in the lower part of the abdomen.
- Administration of IMP (MENOPUR liquid and Placebo to MENOPUR powder or MENOPUR powder and Placebo to MENOPUR liquid depending on randomization) [self-injection at home]. The starting dose of 225 IU must be maintained for 5 days.
- Hand out the diary to the subject. The subject must be instructed to assess and record injection site reactions immediately, 30 min and 24 hours after each IMP administration throughout the entire stimulation period.
- Dispensing and administration of GnRH agonist (LEUPROLIDE ACETATE) at a reduced dose of 0.05 mL (250 µg)/day [self-injection at home]
- Recording of use of any concomitant medication
- Recording of adverse events

6.2.2 Stimulation Day 6

The following must take place at stimulation day 6:

- Transvaginal ultrasound of uterus and ovaries (number and size of follicles)
- Blood collection for central laboratory analysis of:
  - Endocrine parameters (FSH, hCG, LH, E2 and P4)
- Blood collection for local laboratory analysis of [*note*: optional assessment; performed as per the site's standard practice]:
  - Endocrine parameters (E2 and P4)
- Preparation and dispensing of IMP (MENOPUR liquid and Placebo to MENOPUR powder or MENOPUR powder and Placebo to MENOPUR liquid) with potential dose adjustments: from stimulation day 6 and onwards, the daily dose may be increased by 75 IU every second day to a maximum dose of 450 IU, or decreased by 75 IU daily to a minimum dose of 75 IU, based on the individual response.
- Dispensing of GnRH agonist (LEUPROLIDE ACETATE)
- Administration of IMP and GnRH agonist [self-injection at home]
- Collection of injection site reaction data (diary pages)
- Drug accountability of IMP and GnRH agonist
- Recording of use of any concomitant medication
- Recording of adverse events

6.2.3 Stimulation Day >6 to ≤20

Visits will take place at least every second day throughout the remaining stimulation period. The maximum period of stimulation is 20 days. Coasting is not allowed.

The following must take place at all subsequent visits during the stimulation period (with the exception of the end-of-stimulation visit which is described below):

- Transvaginal ultrasound of uterus and ovaries (number and size of follicles)
- Blood collection for local laboratory analysis of [*note*: optional assessment; performed as per the site's standard practice]:
  - Endocrine parameters (E2 and P4)
- Dispensing of IMP (MENOPUR liquid and Placebo to MENOPUR powder or MENOPUR powder and Placebo to MENOPUR liquid) and GnRH agonist (LEUPROLIDE ACETATE)
- Administration of IMP and GnRH agonist [self-injection at home]
- Collection of injection site reaction data (diary pages)

- Drug accountability of IMP and GnRH agonist
- Recording of use of any concomitant medication
- Recording of adverse events

6.2.4 End-of-stimulation Visit

The end-of-stimulation visit takes place when the subject reaches the criterion for triggering of final follicular maturation or if the cycle is cancelled. Administration of hCG (NOVAREL) must take place as soon as reaching the criterion for triggering of final follicular maturation. Should the subject not reach triggering criteria after a maximum of 20 days of stimulation, the end-of-stimulation visit is to occur.

Criterion for triggering of final follicular maturation with hCG:

- 3 follicles of ≥17 mm

Criterion for cancellation of the cycle due to excessive ovarian response:

- >30 follicles of ≥12 mm each and/or E2 levels ≥5000 pg/mL (local laboratory)

The following must take place at the end-of-stimulation visit:

- Vital signs
- Transvaginal ultrasound of uterus and ovaries (number and size of follicles)
- Blood collection for central laboratory analysis of:
  - Clinical chemistry and hematology parameters
  - Endocrine parameters (AMH, FSH, hCG, LH, E2 and P4)
- Blood collection for local laboratory analysis of [*note*: optional assessment; performed as per the site's standard practice]:
  - Endocrine parameters (E2 and P4)
- Dispensing of hCG (NOVAREL) (applicable to subjects reaching criterion for triggering only)
- Collection of injection site reaction data (diary pages)
- Drug accountability of IMP and GnRH agonist
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with hCG administration, the oocyte retrieval visit must be scheduled 36±2 hours after the administration of hCG. Subjects will self-inject hCG (NOVAREL) at home.

For subjects with cycle cancellation, a visit for the first post-dosing anti-MENOPUR antibody assessment 7-10 days after the last IMP dose must be scheduled.

6.3 Oocyte Retrieval

Oocyte retrieval must take place 36±2 hours after hCG administration. All oocytes from follicles with an estimated diameter ≥12 mm should be retrieved. Oocytes will be inseminated using partner or donor sperm by ICSI 4±2 hours after retrieval.

Below are listed the procedures related to the subjects attending the oocyte retrieval visit, while procedures related to the oocytes are described in section 6.3.1.

The following must take place at the oocyte retrieval visit:

- Oocyte retrieval
- Progesterone (ENDOMETRIN) for luteal phase support dispensed [*note*: progesterone must be started the day after oocyte retrieval and continued up to menses, negative βhCG, pregnancy loss or for a maximum of 10 weeks total if pregnancy is confirmed]
- Blood collection for central laboratory analysis of endocrine parameters (FSH only)
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with oocytes retrieved following hCG administration, the next visit is the transfer visit 5 days after oocyte retrieval.

For subjects with no oocytes retrieved, the next visit is the first post-dosing anti-MENOPUR antibody assessment visit (section 6.4.2).

6.3.1 Oocyte / Embryo / Blastocyst Evaluation

The laboratory procedures regarding handling and evaluations of oocytes, embryos and blastocysts are described in detail in a trial-specific manual. This section provides an overview of the procedures and assessments to be made from oocyte retrieval until transfer at the blastocyst stage.

The flow of the trial procedures for embryos is shown in Table 6-2.

Table 6-2 Trial Flow Chart – Oocyte / Embryo / Blastocyst Procedures

	Day 0 (OR)		Day 1 after OR	Day 5 after OR
Timing	-4h (±2h)	0h	19h (±2h)	Day 5
Oocyte retrieval (OR)	X			
Assessment of maturity stage	X			
Insemination by ICSI		X		
Assessment of oocyte fertilization			X	
Assessment of embryo / blastocyst quality				X
Transfer of blastocyst(s) of the highest quality available[a]				X
Cryopreservation of blastocysts by vitrification, as applicable				X[b]

[a] In the absence of viable blastocysts, morulae can be used if deemed suitable for transfer.

[b] In case the investigator judges that a blastocyst/morula is still developing, cryopreservation on day 6 or later is allowed.

OR: Oocyte retrieval; ICSI: intracytoplasmic sperm injection

Day 0 (Oocyte Retrieval)

- Oocyte retrieval at 4±2 hours before start of the insemination procedure
- Assessment of maturity stage after oocyte retrieval and before insemination
- Insemination at 0 hours using ICSI using ejaculated sperm (fresh or frozen) from partner or donor

Day 1 after Oocyte Retrieval

- Assessment of fertilization (number of pronuclei) at 19±2 hours after insemination. Only embryos with 2 pronuclei should continue with subsequent quality assessments.

Day 5 after Oocyte Retrieval

- Assessment of embryo developmental stage / blastocyst quality
- Transfer of blastocyst(s) (section 6.4). Transfer on day 6 (or later) is not allowed.
- Cryopreservation of blastocysts by vitrification, as applicable (section 6.4). Cryopreservation on day 6 (or later) is allowed in those instances where continued culture is judged necessary/beneficial by the embryologist.

6.4 Transfer

6.4.1 Blastocyst Transfer

Transfer is performed on day 5 (blastocyst stage) after oocyte retrieval. Transfer of day 6 (or later) blastocysts is not allowed. The subject-related procedures are described below.

- Blood collection for central laboratory analysis of anti-MENOPUR antibodies (first post-dosing assessment)
- Ultrasound for image acquisition of the uterus *(applicable for a subset of trial sites)*
- Ultrasound-guided transfer of blastocyst(s) of the highest quality available according to this policy:

Subjects with at least one good-quality blastocyst (i.e. grade 3BB or above):	➢ single blastocyst transfer
Subjects with absence of a good-quality blastocyst (i.e. lower than grade 3BB):	➢ option of single blastocyst transfer ➢ option of double blastocyst transfer if at least two blastocysts are available

Note: in the absence of viable blastocysts, morulae can be used if deemed suitable for transfer.

- Cryopreservation of blastocysts by vitrification, as applicable
- Dispensing of progesterone for luteal phase support, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with blastocyst transfer, the next visit is the βhCG test visit which must be scheduled 10-14 days after transfer.

6.4.2 First Post-dosing Anti-MENOPUR Antibody Assessment (7-10 Days after Last IMP Dose)

Subjects who have been exposed to MENOPUR liquid or MENOPUR powder must have the first post-dosing anti-MENOPUR antibody assessment performed 7-10 days after the last MENOPUR liquid or MENOPUR powder dose. This may coincide with the transfer visit (section 6.4.1).

For subjects who do not attend the transfer visit, a separate visit must be scheduled, at which the following must take place:

- Blood collection for central laboratory analysis of anti-MENOPUR antibodies
- Recording of use of any concomitant medication
- Recording of adverse events

6.5 βhCG Test

6.5.1 βhCG Test

Subjects who have undergone transfer must attend a visit 10-14 days after transfer.

The following must take place:

- Blood collection for local laboratory analysis of βhCG
- Blood collection for central laboratory analysis of anti-MENOPUR antibodies (second post-dosing assessment (section 6.5.2))
- Dispensing of progesterone, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events

The blood sample for βhCG will be analyzed by the local laboratory and evaluated according to the local reference ranges. In case of doubtful / inconclusive βhCG result, a second test will be performed, preferably within 2 days. Subjects with a positive βhCG test must attend a clinical pregnancy visit 5-6 weeks after transfer (section 6.6). Subjects with a negative βhCG test must proceed to the end-of-trial assessments (section 6.8).

6.5.2 Second Post-dosing Anti-MENOPUR Antibody Assessment (21-28 Days after Last IMP Dose)

Subjects who have been exposed to MENOPUR liquid or MENOPUR powder must have the second post-dosing anti-MENOPUR antibody assessment performed 21-28 days after the last MENOPUR liquid or MENOPUR powder dose. This may coincide with the βhCG visit (section 6.5.1).

For subjects who do not attend the βhCG test visit, a separate visit must be scheduled, at which the following must take place:

- Blood collection for central laboratory analysis of anti-MENOPUR antibodies
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects who do not attend the βhCG test visit, this second post-dosing anti-MENOPUR antibody assessment may be done in connection with the end-of-trial visit (section 6.8).

6.6 Clinical Pregnancy

Subjects with a positive βhCG test must attend a visit 5-6 weeks after transfer.

The following must take place:

- Transvaginal ultrasound of uterus to assess any clinical pregnancy
- Dispensing of progesterone for luteal phase support if a vital pregnancy is confirmed
- Recording of use of any concomitant medication
- Recording of adverse events

If at least one intrauterine gestational sac with fetal heart beat is observed, vital pregnancy is confirmed. For subjects with a vital pregnancy, the next visit is the ongoing pregnancy visit (section 6.7). Subjects with no vital pregnancy must undergo end-of-trial assessments (section 6.8).

6.7 Ongoing Pregnancy

If a vital pregnancy has been documented, the subject must attend a visit 8-9 weeks after transfer.

The following procedures / assessments must take place:

- Ultrasound (transvaginal or abdominal) of uterus to assess any intrauterine viable fetus
- Recording of use of any concomitant medication
- Recording of adverse events

If at least one intrauterine viable fetus is identified, this confirms an ongoing pregnancy.

6.8 End-of-trial

If a subject attends the scheduled trial visits, the end-of-trial assessments should take place at the last scheduled trial visit.

Due to the timing of the mandatory anti-MENOPUR antibody assessments, the end-of-trial assessments can at the earliest be performed 21-28 days after the last MENOPUR liquid or MENOPUR powder dose. This may coincide with the βhCG visit for subjects with a negative βhCG test.

The following end-of-trial procedures / assessments must take place, irrespective of whether the subject discontinues the trial prematurely or completes it:

- Blood collection for central laboratory analysis of:
  - Clinical chemistry and hematology parameters
  - Endocrine parameters (AMH)

- anti-MENOPUR antibodies (second post-dosing assessment) [*note:* only applicable for subjects who have not already had a blood sample taken for the second post-dosing anti-MENOPUR antibodies assessment as described in section 6.5.2]

- Vital signs
- Physical examination (including weight)
- Gynecological examination
- Drug accountability, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events
- End-of-trial form (completion of trial or premature discontinuation, date and reason for discontinuation, if applicable)

These assessments serve to document the subject's physical health at the end of the trial.

6.9 Post-trial Activities

6.9.1 Pregnancy Outcome and Neonatal Health Follow-up

Pregnancy outcome will be gathered for all subjects with an ongoing pregnancy. Neonatal health data will also be collected. In addition, data on neonatal SAEs will be collected at 4 weeks and minimum 6 months after birth. These data will be reported separately.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Primary Endpoint

7.1.1 Number of Fertilized Oocytes

The number of fertilized oocytes will be assessed at 19±2 hours after insemination. Fertilized oocytes with 2 pronuclei will be regarded as correctly fertilized.

7.2 Assessments Related to Secondary Endpoints

7.2.1 βhCG Test

A blood serum βhCG test must be obtained 10-14 days after blastocyst transfer. If the test is positive according to the local laboratory's reference ranges, this confirms a positive βhCG. In case of doubtful / inconclusive βhCG result, a second test will be performed, preferably within 2 days, and the conclusive result recorded.

7.2.2 Clinical Pregnancy

Clinical pregnancy will be based on detection of at least 1 intrauterine gestational sac with fetal heart movement on transvaginal ultrasound at 5-6 weeks after blastocyst transfer. For clinical pregnancies, the number of intrauterine sacs and fetal heart beats will be recorded.

7.2.3 Ongoing Pregnancy

Ongoing pregnancy will be based on detection of at least 1 intrauterine viable fetus by transvaginal or abdominal ultrasound at 8-9 weeks after blastocyst transfer. For ongoing pregnancies, the number of intrauterine viable fetuses will be recorded.

7.2.4 Early Pregnancy Loss

Early pregnancy loss will be defined as a positive βhCG tests but no ongoing pregnancy at 8-9 weeks after blastocyst transfer, as described in sections 7.2.1 and 7.2.3 above.

7.2.5 Number and Size of Follicles during Stimulation

Transvaginal ultrasound will be performed at all visits during the stimulation period to count the number of follicles and measure the size of the follicles.

The 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 last day of stimulation will be recorded. Data will be recorded separately for the right and left ovary.

7.2.6 Oocytes Retrieved

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

7.2.7 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.

7.2.8 Fertilization Rate

The number of pronuclei will be counted at 19±2 hours after insemination and recorded as 0, 1, 2 or >2. Fertilized oocytes with 2 pronuclei (2PN) will be regarded as correctly fertilized. Fertilization rate is the number of 2PN oocytes divided by the number of oocytes retrieved.

7.2.9 Number and Quality of Blastocysts on Day 5

The quality evaluation of blastocysts on day 5 after oocyte retrieval will consist of assessment of three 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[12], 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.

In the event of continued culture, blastocyst grading will not be recorded after day 5.

7.2.10 Endocrine Parameters during Treatment

During treatment, the following endocrine parameters will be evaluated: AMH, FSH, LH, hCG, E2 and P4.

Baseline assessments will be made for AMH, FSH, LH, hCG and P4 on stimulation day 1 and for E2 as part of confirmation of downregulation. Blood samples for FSH, LH, hCG, E2 and P4 will also be drawn on stimulation day 6 and on the last day of stimulation, and furthermore, FSH is also assessed at oocyte retrieval. Blood samples for AMH will also be drawn on the last day of stimulation, and at end-of-trial.

Analyses of AMH, FSH, hCG, LH, E2 and P4 will be performed at a central laboratory.

7.2.11 Serum FSH Concentrations

In addition to the sampling time points mentioned in section 7.2.10, blood samples will also be drawn on day 1 and at the oocyte retrieval visit for analysis of FSH.

Based on the serum FSH concentrations obtained during the trial, a population pharmacokinetic model will be developed. The modelling results will be reported separately.

7.2.12 Ovarian Hyperstimulation Syndrome

OHSS is defined as the total of early OHSS with onset ≤9 days after triggering of final follicular maturation, and late OHSS with onset >9 days after triggering of final follicular maturation. Classification of grade is based on Golan's classification system[13] (see section 8.3 for details) and

all OHSS cases will be graded as mild, moderate or severe.

7.2.13 Adverse Events

Adverse events will be recorded from the time of signed informed consent for participation in the trial until the end-of-trial visit. For each adverse event the following parameters are recorded by the investigator on the Adverse Event Log: description of event, date and time of onset, intensity, causal relation to IMP, action taken to IMP, other actions taken, seriousness of the adverse event, date and time of outcome, and outcome. Definitions of adverse events are provided in section 8.

7.2.14 Injection Site Reactions

Every day throughout the stimulation period, the subjects will assess the local tolerability of subcutaneous injections of MENOPUR liquid or MENOPUR powder at three time points relative to the daily administration: immediately after the injection, 30 minutes after the injection and 24 hours after the injection. The subject will be informed to always inject MENOPUR liquid or Placebo to MENOPUR liquid using the pre-filled injection pen on the same side of the navel and MENOPUR powder or Placebo to MENOPUR powder using the syringe on the other side in order to be able to distinguish between injection site reactions related to MENOPUR liquid / Placebo to MENOPUR liquid and those related to MENOPUR powder / Placebo to MENOPUR powder. The following injection site reactions will be assessed: redness, pain, itching, swelling and bruising. The presence and intensity of each injection site reaction will be rated as one of the following: none, mild, moderate or severe.

The subject will record the assessments in a diary and the diary data will subsequently be transcribed to the e-CRF.

7.2.15 Anti-MENOPUR Antibodies

Blood samples for assessment of anti-MENOPUR antibodies in the individual subjects in the trial will be drawn pre-dosing and post-dosing:

- Screening [*Note*; this sample is exclusively used to re-establish the anti-drug antibody assays (e.g. screening- and confirmatory cut-points)]
- Stimulation day 1, prior to dosing (baseline; pre-dosing sample)
- 7-10 days after the last MENOPUR liquid or MENOPUR powder dose
  This may coincide with the transfer visit. Subjects not reaching transfer must be called in for this extra visit.
- 21-28 days after the last MENOPUR liquid or MENOPUR powder dose
  This may coincide with the βhCG visit. In case of discontinuation before the βhCG visit, this assessment should be done at the end-of-trial visit scheduled 21-28 days after the last

MENOPUR liquid or MENOPUR powder dose.

Ferring has developed the following assays for evaluating the immunogenicity of MENOPUR liquid or MENOPUR powder:

Assay 1) A screening immunoassay, using labelled MENOPUR as capturing component, assessing the presence in serum of anti-MENOPUR antibodies, using a parametric cut-point approach with a 5% false positive rate.

Assay 2) A confirmatory immunoassay, using unlabeled MENOPUR for quenching of signal, confirming or disconfirming the specificity of any positive results in assay 1), using a parametric cut-point approach with a 1% false positive rate.

Assay 3) A titer immunoassay determining the antibody response titer of any anti-MENOPUR antibodies confirmed in assay 2).

Assay 4) A characterization step where any confirmed anti-MENOPUR antibodies will be tested for cross-reactivity towards FSH, hCG, LH and the structurally related TSH using the parametric cut-point with 1% false positive rate determined for assay 2).

Assay 5) Neutralizing capacity of the antibodies confirmed positive in assay 2) and characterized for cross-reactivity in assay 4) will be assessed with three individual cell-based neutralizing antibody (NAb) assays (NAb FSH, NAb hCG and NAb LH) using a parametric cut-point approach with a 1% false positive rate. Samples that show cross-reactivity only to individual drug components (i.e. either to FSH, to hCG or to LH) will be tested only in the corresponding NAb assay. In case a confirmed positive sample show cross-reactivity to all drug components, it will be tested in all three NAb assays.

In subjects with a negative pre-dosing sample, a treatment-induced anti-MENOPUR antibody response will be defined as any post-dosing sample being positive in the confirmatory assay (i.e. assay 2).

In subjects with a positive pre-dosing sample, a treatment-induced anti-MENOPUR antibody response will be defined as a statistically determined fold increase in titers from the pre-dosing assessment to a post-dosing assessment.[a]

A subject is defined to have treatment-induced anti-MENOPUR antibodies with neutralizing capacity, if the subject has any post-dosing sample being positive in assay 5) and the pre-dosing sample was negative in assay 5) [this also includes the scenario of pre-dosing sample negative in assays 1) or 2) and therefore not tested in assay 5)].

[a] The fold increase in titres will be determined by minimum significant ratio (MSR) experiments during assay validation and will be stated in the validation report and the clinical trial report.

Subjects with a treatment-induced anti-MENOUPUR antibody response (both with and without neutralizing capacity) will be followed until the response becomes negative or has returned to pre-dosing level. These subjects will be called in for assessments at 2 months after the last post-dosing anti-MENOPUR antibody sampling. If required, further assessments will be made at 3, 4, 6, 9 and 12 months after the last post-dosing anti-MENOPUR antibody sampling. The assessments will be terminated when two consecutive assessments are negative or indicate that the pre-dosing level has been reached, with a maximum follow-up period of one year. The assessments will also be terminated if the subject commences a new treatment cycle with any gonadotropin preparation.

7.3 Other Assessments

7.3.1 Demographics

Demographic information will be obtained during the screening period, including the following: date of birth, ethnicity (Hispanic or Latino, Not Hispanic or Latino) and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White).

7.3.2 Medical History

Any relevant medical history will be recorded during the screening period. This includes diagnosis / symptoms, and start and end dates (or marked ongoing in case it has not been resolved).

7.3.3 Menstrual History

Information about the menstrual history (average cycle length) will be obtained during the screening period.

7.3.4 Reproductive History

Information about the reproductive history will be obtained during the screening period. This will include number of clinical pregnancies, number of fetuses and outcome. Information on primary versus secondary infertility will be derived.

7.3.5 Infertility History

Information about the causes of infertility and duration of infertility will be obtained during the screening period. This will also cover information about any previous treatment for infertility, including type of treatment and gonadotropin preparations used.

7.3.6 Confirmation of Downregulation

Pituitary downregulation should be confirmed after minimum 10 days but no more than 20 days of GnRH agonist administration during the screening / downregulation period.

Downregulation is confirmed by a serum E2 level ≤20 pg/mL and transvaginal ultrasound showing no ovarian cysts.

7.3.7 Vital Signs

Systolic and diastolic blood pressure, pulse, and temperature will be measured at screening, on day 1, on the last day of stimulation and at end-of-trial. Assessments of blood pressure and heart rate are to be measured while the subject is seated after resting for 3 minutes. All blood pressure measurements should be made using the same arm and prior to any scheduled blood draws.

7.3.8 Physical Examinations

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

In addition, height and weight, will be measured at screening for calculation of BMI, and body weight will be measured as part of the end-of-trial assessments.

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

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

7.3.9 Gynecological Examinations

A complete gynecological examination will be performed at screening and at end-of-trial. Information will be recorded for breast, external genitalia, vagina, cervix, uterus, ovaries and fallopian tubes.

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

7.3.10 Clinical Laboratory Variables

Central Laboratory Tests

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

- Screening, last day of stimulation and end-of-trial visit: serum chemistry: non-fasting glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase.
- Screening, last day of stimulation and end-of-trial visit: hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count.
- Screening, day 1, last day of stimulation and end-of-trial visit: AMH. An AMH level greater than 1.0 ng/mL should be documented at screening.
- Downregulation, day 6, and last day of stimulation: E2. An E2 level of ≤20 pg/mL should be documented to confirm downregulation prior to randomization.
- Day 1, day 6, last day of stimulation and oocyte retrieval: FSH.
- Day 1, day 6, and last day of stimulation: hCG, LH and P4.

The samples for AMH, FSH, LH, hCG and P4 on stimulation day 1 (baseline) will be collected prior to the first dose of MENOPUR liquid or MENOPUR powder. For E2, the sample confirming downregulation will be used as baseline. Samples drawn on stimulation day 6 and on the last day of stimulation will be collected at least 8 hours after the previous MENOPUR liquid, MENOPUR powder or GnRH agonist administration.

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.

Local Laboratory Tests

The following laboratory tests prior to randomization will be performed at each site's local or reference laboratory per standard practice if results are not already available in the subject's chart. Furthermore, analysis of hormones after randomization may also be performed locally. Results will be reviewed by the investigator and documented in the subject's chart and e-CRF (if applicable).

- Hormones prior to randomization: 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. In addition, the early follicular phase (cycle day 2-4) serum FSH level should be between 1-12 IU/L within 3 months prior to randomization.

- Other laboratory assessments prior to randomization: serum hepatitis B surface antigen, hepatitis C antibody, HIV antibody, and rapid plasma reagin tests are to be done at screening, if not done within 6 months prior to screening, and documented to be negative.
- Hormones after randomization: E2 and P4 may be analyzed at various time points during stimulation (optional), and serum βhCG is to be analyzed for pregnancy monitoring.

7.3.11 Blastocyst Transfer Procedure

Any difficulty or eventuality during the transfer procedure will be noted.

7.3.12 Malfunction of Pen

In case of technical malfunction of a pen, that results in a replacement of the pen, all relevant details (including time, date, a description of the malfunction and whether dosing was affected) of the incidence should be reported in a blinded manner in the e-CRF, the pen should be replaced and the treatment continued. Human errors such as misunderstanding of instructions or incorrect handling of the pen should not be regarded as technical malfunctions.

In case of adverse events caused by malfunction of the pen, these will be identified and described.

7.3.13 Concomitant Medication

The use of any concomitant medication within the last 3 months prior to informed consent for participation in the trial (except medication used in previous infertility treatment cycles which will be recorded as part of the infertility history) and throughout the trial will be recorded. Recording of concomitant medication will be performed at all visits. Any changes in concomitant medications or treatments must be recorded at each visit.

7.3.14 Ultrasound for Image Acquisition of the Uterus

At a subset of trial sites, ultrasound for image acquisition of the uterus will be carried out at the transfer visit. Details on equipment and procedures related to this exploratory assessment will be provided in a trial-specific manual.

Resultant images may be analyzed to identify features that correlate with subject response to treatment and/or clinical outcomes, such as ongoing pregnancy. These data will be reported separately.

7.4 Assessments Related to Post-trial Information

7.4.1 Pregnancy Outcome and Neonatal Health Follow-up

All subjects with an ongoing pregnancy will be followed as part of the post-trial follow-up. Live birth rate and neonatal health data at birth covering gestational age, gender, birth weight and length, and Apgar scores after 1, 5 and 10 minutes will be collected. In addition, data on neonatal SAEs will be collected at 4 weeks and minimum 6 months after birth (see section 8.5.1). These data will be reported separately.

7.4.2 Late Pregnancy Loss

The occurrence of late pregnancy losses defined as an ongoing pregnancy (i.e. at least 1 intrauterine viable fetus at 8-9 weeks after blastocyst transfer), but no live birth will be evaluated as part of the post-trial follow-up. These data will be reported separately.

7.5 Handling of Biological Samples and Other Material

A trial-specific laboratory manual will be provided to the participating sites, describing in detail how to handle, store and transport the biological samples (blood) in this trial. All biological samples will be analyzed at central laboratories and will be maintained in storage after the end of the trial. Destruction will take place within 2 years after reporting of the trial or when methods / results have been adequately validated. An exception are the blood samples analyzed by a local laboratory at the trial clinic / hospital and subsequently destroyed. For all biological samples collected in the trial, it applies that analyses beyond those described in the protocol can only be performed after obtaining the required approvals. The processes related to handling of biological samples will be described in the informed consent documents, and biobank / data protection legislation including local legislation will be adhered to.

With respect to the image recordings of the uterus, a trial-specific manual will be provided to the subset of sites participating in this exploratory assessment, describing in detail the equipment and procedures. All recordings will be stored. Data protection legislation including local legislation will be adhered to.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

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

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign or finding from physical or gynecological examination assessed as clinically significant by the investigator [*note*: pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events, but are recorded as medical history].
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.

All adverse events will be coded by Ferring Global Pharmacovigilance using the Medical Dictionary for Regulatory Activities (MedDRA) (the version effective at trial start).

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

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

The sources of adverse events cover:

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

8.2.2 Recording of Adverse Events

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

- Adverse event
- Date and time of onset
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome
- Outcome
- Seriousness.

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

Adverse Event

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

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

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

Date and Time of Onset

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

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

Intensity

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

Mild:	Awareness of signs or symptoms, but no disruption of usual activity.
Moderate:	Event sufficient to affect usual activity (disturbing).
Severe:	Inability to work or perform usual activities (unacceptable).

Causal Relationship to IMP

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

Reasonable possibility:

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

Examples:

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

No reasonable possibility:

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

Examples:

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

Action Taken to IMP

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

- No change (medication schedule maintained or no action taken)
- Discontinued
- 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 adverse event, this medication should be entered in the Concomitant Medication Log.

Date and Time of Outcome

The date and time the subject recovered or died.

Outcome

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

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

8.3 Adverse Events of Special Interest

8.3.1 Ovarian Hyperstimulation Syndrome

Symptoms and Classification

OHSS is an adverse event of special interest during controlled ovarian stimulation. Investigators will record OHSS symptoms using a classification system based on Golan's classification system[13] as shown in Table 8-1 to grade (1, 2, 3. 4 or 5) each OHSS case.

Table 8-1 Classification of Mild, Moderate and Severe OHSS (Golan's Classification System)

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

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

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

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

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

e) Hospitalization is defined as admission exceeding 24 hours.

All cases of OHSS must be reported as adverse events and followed until the adverse event has an outcome of recovered. Any case of OHSS that requires hospitalization or surgical/medical intervention should be considered severe. All cases of severe OHSS should be reported as a SAE.

Please note, that the classification of 'mild OHSS', 'moderate OHSS' and 'severe OHSS' does not refer to the classification of an adverse event's intensity (also rated mild, moderate, or severe), but to the grades in Golan's Classification System described above.

Subject narratives will be prepared for all OHSS cases.

Concerning timing, early OHSS will be defined as OHSS with onset ≤9 days after triggering of final follicular maturation and late OHSS will be defined as OHSS with onset >9 days after triggering of final follicular maturation.

Preventive Interventions of Early OHSS

Preventive interventions of early OHSS include the following:

- Cycle cancellation due to excessive ovarian response
- Administration of dopamine agonist (only in subjects with ≥20 follicles of ≥12 mm)
- Investigator requested reduction in gonadotropin dose to prevent OHSS

Investigations in case of OHSS

The investigator should report signs, symptoms and laboratory assessments used to diagnose and classify all cases of OHSS in the e-CRF. The following investigations must be conducted when OHSS symptoms are first observed and repeated when there are clinically relevant changes in the OHSS presentation:

- Body weight and maximum abdominal circumference
- Ultrasound of ovarian size and if applicable, measurement of pelvic/abdominal/thoracic fluid
- Vital signs
- Blood sample for central lab analysis of the following:
  - Progesterone and estradiol
  - Red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count and differential count
  - Alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, creatinine, gamma-glutamyl transferase, non-fasting glucose, potassium and sodium
  - Coagulation parameters (prothrombin time, activated partial thrombin time)

Any treatments of OHSS, e.g. intravenous administration of volume expanders, paracentesis, use of low-molecular-weight heparin and intravenous administration of albumin, must be recorded as concomitant medication.

8.4 Other Events of Special Interest

8.4.1 Injection Site Reactions

Injection site reactions after administration of IMP (MENOPUR liquid including Placebo to MENOPUR powder and MENOPUR powder including Placebo to MENOPUR liquid) are only to be reported as adverse events if they require active management, i.e. discontinuation of IMP, additional investigations or treatment of the injection site reaction. Local tolerability of IMP constitutes a secondary endpoint and will be evaluated in detail based on the subjects' recordings in the diary.

Local tolerability reactions after administration of NIMP are to be reported as adverse events if they fulfil the definition of an adverse event.

8.4.2 Treatment-induced Anti-MENOPUR Antibodies

Presence of treatment-induced anti-MENOPUR antibodies is not to be reported as an adverse event. These data will be described as part of the secondary endpoints.

8.4.3 Menstrual Bleeding

Menstrual bleeding is only to be reported as an adverse event in case it is excessive, painful, delayed or in any other way deviating from the subject's normal menstruation. Menstrual bleeding associated with lack of pregnancy will be reported as part of the efficacy evaluation.

8.4.4 Pregnancy Losses

The following terminology should be used for reporting of pregnancy losses during the trial:

Biochemical pregnancy:	Positive βhCG test but no gestational sac is observed on later transvaginal ultrasound, or menstruation is reported
Spontaneous abortion:	Positive βhCG test but all intrauterine gestational sacs are without fetal heart beat as documented by ultrasound, or there are no viable fetuses observed by ultrasound
Vanishing twin:	Spontaneous disappearance of at least one intrauterine gestational sac with or without heart beat in a pregnancy where one viable fetus remains as documented by ultrasound

Ectopic pregnancy:	Extrauterine gestational sac with or without fetal heart beat as documented by ultrasound or surgery

Concerning timing, a pregnancy loss occurring before ongoing pregnancy (i.e. a positive βhCG tests but no ongoing pregnancy at 8-9 weeks after blastocyst transfer) will be defined as an early pregnancy loss, while a pregnancy loss occurring after ongoing pregnancy (i.e. at least 1 intrauterine viable fetus at 8-9 weeks after blastocyst transfer but no live birth) during the post-trial follow-up will be defined as a late pregnancy loss.

8.4.5 Multiple Pregnancies

Multi-fetal gestations are not to be reported as adverse events.

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event (SAE) if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **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. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgement must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfils the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
is an **important medical event**	Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Elective Termination in the Time between Clinical and Ongoing Pregnancy

In connection with elective termination due to a congenital anomaly observed at or after the clinical pregnancy visit (i.e. 5-6 weeks after transfer), but before ongoing pregnancy has been established (i.e. 8-9 weeks after transfer), the congenital anomaly of the fetus should be reported as a SAE.

The congenital anomaly leading to elective termination will be coded using both MedDRA and ICD-10 and classified as minor or major.[c]

Serious Adverse Events during Post-trial Activities

Pregnancy outcome and neonatal health data (i.e. gestational age, gender, birth weight and length, and Apgar scores after 1, 5 and 10 minutes) will be gathered for all subjects with an ongoing pregnancy. These data will be collected at birth. In addition, data on neonatal SAEs will be collected at 4 weeks and minimum 6 months after birth. These data will be reported separately.

The following untoward medical occurrences reported as part of this post-trial follow-up information will be recorded as SAEs:

- Death of mother in connection with pregnancy or labor
- Death of neonate / infant
- Stillbirth[d]
- Neonate admitted to the neonatal intensive care unit (NICU) regardless of duration, or neonate / infant admitted to the neonatal care unit (NCU) / pediatric care unit (PCU) for more than 2 hours
- Congenital anomaly / birth defect
- Medically important event

In case of admission to NICU or NCU / PCU, the reason for admission must be reported as an SAE, rather than just the act of hospitalization.

Congenital anomalies will be coded by Ferring using both MedDRA and ICD-10 and classified as minor or major.

[c] Major abnormalities: a life threatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment.
Minor anomalies: relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.

[d] Stillbirth: ≥ gestational age 24 weeks + 0 days, calculated from the day of transfer + 19 days

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to Ferring Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

SAE Report Form

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

Ferring Pharmacovigilance
E-mail: [redacted]
US Fax: [redacted]

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

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

Overdose and medication errors of IMP with and without clinical consequences will be tracked in the e-CRF and reviewed by Ferring Pharmacovigilance on an ongoing basis.

Ferring will report SAEs according to local regulations.

8.6 Follow-up of Adverse Events and Serious Adverse Events

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

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

After the subject's last visit, the investigator must follow-up on any adverse event classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. Follow-up should continue until the outcome of recovered, recovered with sequelae or fatal, has been reached. Further, if the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.6.2 Follow-up of Serious Adverse Events with Onset during the Post-Trial

For post-trial SAEs in neonates, where the neonate has not recovered at the 6 month follow-up assessment, the investigator must follow up until the SAE has resolved. If the SAE is a chronic condition or the medical condition of the neonate is stable, the investigator and Ferring may agree that further follow-up is not required.

8.6.3 Collection of Serious Adverse Events with Onset after End-of-trial

If an investigator becomes aware of an SAE after the subject's last visit in the trial, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring Pharmacovigilance, 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 analysis plan for 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 (SAP). The SAP will be available before breaking the blind. A separate SAP will be prepared to cover the post-trial information.

9.1 Determination of Sample Size

The present trial is a pharmacodynamic comparison of a marketed product to a new formulation of the same. With 188 subjects per treatment group, the trial has at least 85% power to demonstrate the non-inferiority of MENOPUR liquid to MENOPUR powder in the number of fertilized oocytes at the 1-sided significance level of 0.025. This is based on the results for MENOPUR powder from the COMBINE trial conducted in a similar setting (GnRH agonist protocol, MENOPUR starting dose of 225 IU for the first five days, insemination by ICSI etc.) and in a similar population (infertile women between 18 and 42 years). The mean (SD) of the number of fertilized oocytes were 7.88 (5.15) with similar results in the two age groups (7.92 in the <35 years age group vs. 7.80 in the ≥35 years age group). The non-inferiority margin of -1.60 will retain 80% of the expected comparator effect.

After adjusting for 5% missing data, approximately 400 subjects will be randomized (1:1) into this trial, stratified by trial site and age (<35years and ≥35years).

A blinded sample size reassessment will be done when data on the primary endpoint are available for 70% of the planned subjects or when 300 subjects are randomized, whichever comes first. The sample size reassessment will be done without breaking the blind and without inflating the type I error of the trial, in line with current regulatory guidelines. The expected maximum number of subjects to be randomized is 500 (250 subjects per treatment group), corresponding to a blinded one-sample (both groups pooled) standard deviation estimate of 5.8 and 85% power.

9.2 Subject Disposition

The number and percentage of subjects within each analysis set, randomized subjects treated with IMP (MENOPUR liquid including Placebo to MENOPUR powder or MENOPUR powder including Placebo to MENOPUR liquid), and subjects prematurely discontinued from the trial will be summarized. All post-baseline discontinuations will be summarized by reason for discontinuation. The number of subjects screened and not randomized will be presented.

9.3 Protocol Deviations

The rating of protocol deviations as ‘minor’ and ‘major’, as well as the criteria for major protocol deviations with the implication of exclusions from the per-protocol analysis set will be decided by

the Ferring clinical team on the basis of a blinded review of data before declaration of clean file and lock of database.

The list of major protocol deviations will be detailed and documented in the clean file document prior to database release. Major protocol deviations will be summarized and listed by subject.

9.4 Analysis Sets

9.4.1 Intention-to-Treat Analysis Set

The intention-to-treat (ITT) analysis set comprises all randomized (as planned) subjects.

9.4.2 Modified Intention-to-Treat Analysis Set

The modified intention-to-treat (mITT) analysis set comprises all randomized (as planned) subjects who received at least 1 dose of IMP (MENOPUR liquid including Placebo to MENOPUR powder or MENOPUR powder including Placebo to MENOPUR liquid).

9.4.3 Per Protocol Analysis Set

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

9.4.4 Safety Analysis Set

The safety analysis set comprises all treated subjects and is analyzed according to the actual treatment received.

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 Population Characteristics

All medical history will be coded using MedDRA. The version of MedDRA will be documented. Medical history will be listed by subject and summarized for each medical item.

Concomitant medications will be coded using the World Health Organization Drug Reference List. 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).

Infertility history, menstrual history and reproductive history will be listed by subject and presented in summary tables.

9.6 Efficacy Endpoint Assessments

9.6.1 General Considerations

All primary and secondary efficacy analyses will be conducted for the mITT analysis set. Furthermore, sensitivity analyses will be conducted for the PP and ITT analysis sets as appropriate.

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 Endpoint

The primary objective of the trial is to demonstrate the non-inferiority of MENOPUR liquid versus MENOPUR powder with respect to the number of fertilized oocytes in women undergoing controlled ovarian stimulation powder. The non-inferiority limit for the difference between treatments (MENOPUR liquid minus MENOPUR powder) is set as -1.60. The non-inferiority hypothesis to be tested for the primary endpoint will be:

$$H_0: \mu_{\text{MENOPUR liquid}} - \mu_{\text{MENOPUR powder}} \leq -1.60$$

against the alternative

$$H_1: \mu_{\text{MENOPUR liquid}} - \mu_{\text{MENOPUR powder}} > -1.60$$

where $\mu_{\text{MENOPUR liquid}}$ and $\mu_{\text{MENOPUR powder}}$ denote the mean numbers of fertilized oocytes in subjects treated with MENOPUR liquid and MENOPUR powder, respectively.

The null hypothesis (H_0) will be tested against the alternative by constructing a 2-sided 95% confidence interval for the difference in the least squares mean number of fertilized oocytes between the two treatment groups. If the lower-limit of the 95% confidence interval is greater than the non-inferiority limit (-1.60), the null hypothesis will be rejected and it will be claimed that MENOPUR liquid is non-inferior to MENOPUR powder with respect to the number of fertilized oocytes.

Due to the expected large sample size, the primary endpoint will be analyzed using a mixed effects two-way analysis of variance (ANOVA) model, based on the asymptotic normal approximation. The model will include the treatment group and the age group as fixed factors, as well as the trial site as a random effect. The least squares mean estimate of the treatment difference in the number of fertilized oocytes and the associated 95% confidence interval will be derived through an

LSMEANS statement in the SAS PROC GLM procedure. For subjects who do not have any oocytes retrieved, or do not have fertilization assessment due to early withdrawal, or any other reason, the number of fertilized oocytes will be considered as zero.

If the 95% confidence interval for the treatment difference not only lies above the non-inferiority limit (-1.60) 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.

The primary efficacy analysis will be conducted for the mITT population. 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 efficacy endpoints will be summarized using tables and figures, as appropriate. Additional details will be specified in the Statistical Analysis Plan. The secondary efficacy endpoints include:

- Positive βhCG rate, clinical pregnancy rate and ongoing pregnancy rate will be presented by descriptive statistics by treatment group.
- Early pregnancy loss will be presented by descriptive statistics 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 ≤9 mm, 10-11 mm, 12-14 mm, 15-16 mm, and ≥17 mm) and subject level (largest follicle size 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. The analyses will be based on the central laboratory values.
- The number of oocytes retrieved, the number of metaphase II oocytes, and the number of oocytes undergoing ICSI 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 number and quality of blastocysts 5 days after oocyte retrieval will be summarized by frequency distribution and by descriptive statistics for each treatment group.

Based on the serum FSH concentrations, a population pharmacokinetic model will be developed. The modelling will be detailed in a modelling analysis plan and reported separately.

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

Analyses for the safety analysis set will be conducted according to the actual treatment received.

Missing values will be treated as missing, except for causality, intensity, seriousness, and outcome of adverse events. A worst-case approach will be used: if causality is missing, the adverse event will be regarded as related to the IMP; if the intensity of an adverse event is missing, the adverse event will be regarded as severe; if seriousness is missing, the adverse event 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 adverse event is defined as an adverse event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state. Only treatment-emergent adverse events will be presented in summary tables.

All data will be listed per subject and adverse event.

Written narratives will be issued for all SAEs and adverse events leading to discontinuation.

Adverse events judged by the investigator as being reasonably possibly related to IMP will be termed adverse drug reactions.

Overview of Treatment Emergent Adverse Events

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

- All adverse event.
- Severe adverse events.
- Adverse drug reactions.
- Adverse events leading to discontinuation.
- SAEs.
- Deaths.

Incidence of Adverse Events

Treatment-emergent adverse events 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 adverse event, the percentage of subjects with an adverse event, 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 adverse event tables described below.

Incidence of Adverse Events by Relationship to IMP

Treatment-emergent adverse events for each treatment group will be tabulated by SOC, preferred term, and relationship to IMP.

Incidence of Adverse Events by Intensity

Treatment-emergent adverse events for each treatment group will be tabulated by SOC, preferred term, and intensity.

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 adverse events.

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

SAEs 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, if any.

Furthermore, treatment-emergent adverse events occurring in ≥5% in any treatment group will be tabulated by SOC and preferred term.

9.8.3 OHSS

Frequency of OHSS is a secondary endpoint. 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.

9.8.4 Injection Site Reactions

Frequency and intensity of injection site reactions is a secondary endpoint. For each injection site reaction (redness, pain, itching, swelling and bruising), the number of events and number of subjects experiencing those events will be tabulated by time (immediately, 30 minutes, 24 hours),

reaction and intensity (none, mild, moderate and severe).

9.8.5 Anti-MENOPUR Antibodies

Frequency of anti-MENOPUR antibodies is a secondary endpoint. The proportion of subjects with treatment-induced anti-MENOPUR antibodies as well as the proportion of subjects with treatment-induced anti-MENOPUR antibodies with neutralizing capacity will be tabulated.

9.8.6 Technical Malfunctions of the Pen

Technical malfunctions of the pen is a secondary endpoint. The frequency of technical malfunctions of the pen will be tabulated.

9.8.7 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.

9.8.8 Physical Examination

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

9.8.9 Gynecological Examination

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

9.8.10 Safety Laboratory Variables

Baseline, last day of stimulation and end-of-trial safety 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 last day of stimulation and from baseline to end-of-trial will be summarized by treatment group using descriptive statistics.

9.8.11 Additional 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:

- Live birth rate

- Late pregnancy loss rate (defined as an ongoing pregnancy but no live birth).
- Neonatal health including SAEs at birth, and SAEs at 4 weeks and minimum 6 months after birth.

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

9.9 Interim Analyses and Administrative Review

No interim analysis is planned.

A sample size reassessment (see section 9.1) will be performed without breaking the blind and without inflating the type I error of the trial, in line with the current regulatory guidelines for non-inferiority trials by FDA. This monitoring will be performed by the project statistician who will evaluate the one-sample standard deviation of the primary efficacy endpoint in a blinded manner in relation to the assumptions underlying the sample size calculation.

A restricted recalculation rule for the sample size reassessment will be used. Accordingly, 400 subjects should be randomized to achieve sufficient power if the blinded one-sample standard deviation estimate of the primary efficacy endpoint is 5.15. If the estimated standard deviation is above the assumed value of 5.15, the sample size can be adjusted up to a maximum of 500 subjects (250 subjects per treatment group), corresponding to a standard deviation of 5.80. If the blinded one-sample standard deviation estimate is below the expected 5.15, the sample size will not be decreased below the planned 400 subjects.

Blinded monitoring of the assumptions underlying the sample size is recommended specifically for non-inferiority trials by FDA[14] and in general by EMA.[15]

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

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

Source Documents - ICH Definition

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

Trial-specific Source Data Requirements – Ferring

Source documents need to be preserved for the maximum period of time permitted by local requirements. For each subject enrolled, the investigator will indicate in the source documents that the subject participates in this trial, and will record at least the following information, if applicable:

- Existence of subject (initials, date of birth)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent (date and time of obtaining written informed consent)
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical history, infertility history, menstrual history and reproductive history
- Body weight measurements
- Visit dates
- Dates of administration of IMP
- Dates and daily doses of NIMP
- Dates and daily doses of concomitant medication
- Date of oocyte retrieval and number of oocytes retrieved
- Date of transfer and number and quality of blastocysts transferred
- Number and quality of blastocysts cryopreserved

- Results of βhCG test and ultrasound at clinical and ongoing pregnancy visits
- Pregnancy outcome, i.e. live birth or pregnancy loss, and neonatal health at birth
- Injection site reactions after IMP administration – diary
- Adverse events (description as well as start/stop date and time)
- OHSS symptoms, preventive interventions, investigations and treatments
- Follow-up on treatment-induced anti-MENOPUR antibody response
- Reason for discontinuation
- Event of unblinding, including the reason for unblinding

No specific protocol data can be recorded directly in the e-CRF without prior written or electronic record.

If the trial sites use electronic patient record systems, the sponsor will decide if the electronic patient records qualify for the trial and document the decision. If the electronic patient records system does not qualify for the trial, it may be considered to utilize paper data sheets for source data as an exception.

The source data for the endocrine parameters, clinical chemistry and hematology parameters as well as anti-MENOPUR antibodies will be available at the central laboratory. Laboratory reports will be available at the sites for endocrine parameters, clinical chemistry and hematology parameters.

10.2 e-CRF/Electronic Case Report Form

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

Trial data should be entered into the e-CRF in a timely manner. The time-frame will be specified in the investigator agreement.

The investigator will approve/authorize the e-CRF entries for each subject, with the exception of the treatment allocation module which is un-accessible to the investigator to maintain the assessor-blinding, with an electronic signature which is equivalent to a handwritten signature.

The e-CRF 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 in an electronic format and will be provided to the investigator before access to the e-CRF is revoked.

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

10.3 Data Management

A data management plan will be created under the responsibility of the Global Biometrics Department, Ferring. 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 also include information about the intended use of computerised systems, a description of the security measures employed to protect the data and a description of the electronic data flow.

10.4 Provision of Additional Information

On request, the investigator will provide Ferring with additional data relating to the trial, duly anonymized and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Council for Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of e-CRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions.

The investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The investigator will cooperate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits. When the first subject is randomized at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits per site will be determined by the enrolment rate.

The source data verification process and definition of key variables to be monitored and the monitoring strategy will be described in detail in the Monitoring Plan for the trial.

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 evaluate trial conduct and compliance with the trial protocol, ICH-GCP, the applicable regulatory requirements, and standard operating procedures.

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 regulatory authorities or IRB.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the e-CRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g. the confidential subject identification code

and the signed Informed Consent 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 IRBs approval or favorable opinion.

12.2 Deviations from the Protocol

Deviations from the protocol should not occur. If deviations occur, the investigator must inform the sponsor, and the implications of the deviation must be reviewed and discussed. All deviations must be documented, and a record of protocol deviations should be retained by the investigator and sponsor.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and 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. Furthermore, the data and information collected during the post-trial follow-up activities will be reported in clinical trial report addendums, including live birth, neonatal health at birth, and neonatal SAEs at 4 weeks and minimum 6 months after birth.

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, one 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 (ICMJE) 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 comments prior to submission. Comments will be given within four 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

ICMJE 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 public registry, i.e. www.ClinicalTrials.gov; a website maintained by the National Library of Medicine at the US National Institutes of Health. Trial registration may occur in other registries in accordance with local regulatory requirements. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

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 Approval

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

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

The end of the trial is defined as the date of LSLV, i.e. when the last subject completes the end-of-trial visit. Post-trial activities will cover the period until collection of the last pregnancy outcome and neonatal health data at birth, and safety follow-up data on neonates for a minimum of 6 months after birth.

In the case of early termination, Ferring must notify the end of the trial to the relevant regulatory authorities and the concerned IRBs as soon as possible, clearly explain the reasons, and describe follow-up measures, if any, taken for safety reasons.

Within one year of the end of the trial, Ferring shall send the final Clinical Trial Report to the relevant regulatory authorities.

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

Informed Consent Documents regarding Participation in the Trial – Subject

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, sources of funding, any possible conflicts of interest, anticipated benefits, potential risks of the trial and the discomfort it may entail, post-trial provisions 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, or the person delegated by 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. Subjects must be given the option of being informed about the general outcome and the results of the trial.

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 and dated Informed Consent Form before any trial-related procedure.

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.

Informed Consent Documents regarding Data Collection on the Neonate – Parental Consent

A separate information and informed consent form is required to collect pregnancy outcome data on the neonate and the investigator will obtain a freely given written consent from the child-custody holders, i.e. the subject and the subject's partner in case of joint custody. The child-custody holders must be given ample time before the consent is obtained. The Informed Consent Documents must be signed and dated by the child-custody holders and the investigator who has provided information to the child-custody holders. Written consent by the child-custody holders regarding collection of pregnancy outcome data on the neonate must be obtained before the subject is randomized and preferably at the time of obtaining written consent by the subject regarding participation in the trial.

The investigator will explain that the child-custody holders are completely free to refuse to consent to this data collection or to withdraw consent at any time, without any consequences and without the need to justify their decision.

The child-custody holders will receive a copy of the Subject Information and their signed and dated Informed Consent Form before any data collection on the neonate.

The child-custody holders will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, ethics committee representatives or FDA inspector(s), in accordance with applicable regulatory requirements, may review the neonate's source records and data. Data protection will be handled in compliance with national / local regulations.

14.6 Subject Participation Card

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

- That she is participating in a clinical trial.
- That she is treated with menotropins for assisted reproductive technologies.
- The name and phone number of the investigator.
- The name, address and phone number of Ferring contact (as required by local regulations).

The subjects will be asked to keep the Subject Participation Card in their possession at all times during the trial.

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

14.7 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP, and other national law(s) in the US 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 are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the trial takes place. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

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

16 ARCHIVING

16.1 Investigator File

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

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

No trial site document may be destroyed without prior written agreement between the investigator and Ferring. Should the investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. If the investigator retires and the documents can no longer be archived by the site, Ferring can arrange having the Investigator File archived at an external archive.

16.2 Trial Master File

Ferring will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

17 REFERENCES

1. MENOPUR – menotropins for injection. Ferring Pharmaceuticals. Prescribing Information, Version: February 2014.
2. Vail A, Gardener E. Common statistical errors in the design and analysis of subfertility trials. Hum Reprod 2003; 18: 1000-1004.
3. Daya S. Pitfalls in the design and analysis of efficacy trials in subfertility. Hum Reprod 2003; 18: 1005-1009.
4. Arce J-C, Nyboe Andersen A, Collins J. Resolving methodological and clinical issues in the design of efficacy trials in assisted reproductive technologies: a mini-review. Hum Reprod 2005; 20: 1757-1771.
5. Csokmay JM, Hill MJ, Chason RJ, Hennessy S, James AN, Cohen J, DeCherney AH, Segars JH, Payson MD. Experience with a patient-friendly, mandatory, single-blastocyst transfer policy: the power of one. Fertil Steril 2011; 96: 580-584.
6. Kresowik JD, Stegmann BJ, Sparks AE, Ryan GL, van Voorhis BJ. Five-years of a mandatory single-embryo transfer (mSET) policy dramatically reduces twinning rate without lowering pregnancy rates. Fertil Steril 2011; 96: 1367-1369.
7. Practice Committee of Society for Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine. Elective single-embryo transfer. Fertil Steril 2012; 97: 835-842.
8. Practice Committee of the Society for Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine. Criteria for number of embryos to transfer: a committee opinion. Fertil Steril 2013; 99: 44-46.
9. Rehman KS, Bukulmez O, Langley M, Carr BR, Nackley AC, Doody KM, Doody KJ. Late stages of embryo progression are a much better predictor of clinical pregnancy than early cleavage in intracytoplasmic sperm injection and in vitro fertilisation cycles with blastocyst-stage transfer. Fertil Steril 2007; 87: 1041-1052.
10. Practice Committee of the Society for Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. Fertil Steril 2012; 98:591-8.
11. Menopur (FE 999906) Investigator's Brochure, Ferring Pharmaceuticals, Edition 5, August 2017.
12. 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 fertilisation and human reproductive genetics. The Parthenon Publishing Group. 1999. Pp 378-388.

13. Golan A, Ron-El R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Survey 1989; 44: 430-440.

14. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Draft guidance November 2016, Non-inferiority Clinical Trials to Establish Effectiveness.

15. The European Agency for the Evaluation of Medicinal Products (EMEA), Committee for Proprietary Medicinal Products (CPMP). Points to consider on switching between superiority and non-inferiority. CPMP/EWP/482/99.

CLINICAL TRIAL PROTOCOL
SUMMARY OF CHANGES

A randomized, double-blind double-dummy trial comparing MENOPUR solution for injection in a pre-filled pen and MENOPUR powder and solvent for solution for injection (menotropins for injection) in a GnRH agonist cycle in women aged 18-42 years undergoing an assisted reproductive technology program

Trial 000303

CLARA
(Comparison of MENOPUR Liquid and Powder in Women Undergoing ART)

IND Number:	053954
Investigational Medicinal Product:	MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL MENOPUR powder and solvent for solution for injection, 75 IU
Indication:	Development of multiple follicles and pregnancy in ovulatory women undergoing controlled ovarian stimulation as part of an assisted reproductive technology (ART) cycle
Phase:	3
Name and Address of Sponsor:	Ferring Pharmaceuticals, Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: [redacted]
GCP Statement:	This trial will be performed in compliance with GCP.

RATIONALE FOR CHANGES:

This present document describes the changes made to the clinical trial protocol, version 3.0, dated 28 March 2018.

The following aspects have been changed:

- Addition of image acquisition of the uterus at the blastocyst transfer visit, which will be performed at a subset of trial sites
- Update of trial timelines
- Correction of an inconsistency related to the blood sampling schedule
- Correction of typos in a sentence related to the sample size considerations
- Clarification of trial-specific source data requirements

IMPLICATIONS OF CHANGE:

This protocol update has implications for the informed consent form, and the revised text is included in the present document.

There are no immediate implications to the trial as recruitment has not started.

The changes do not affect the safety of subjects, scope of investigation, or scientific rigor of the trial. The present summary of changes as well as an updated protocol (version 4.0) will be submitted to IRBs and approval will be obtained prior to the respective sites starting the trial.

AMENDED TEXT:

Superseded wording is marked as ~~strike through~~, and new wording is shown in *italics*.

1 SYNOPSIS – PLANNED TRIAL PERIOD

Superseded Prior Wording

First subject first visit (FSFV): ~~Q3 2018~~
Last subject last visit (LSLV): ~~Q3 2019~~

New Protocol Wording

First subject first visit (FSFV): *Q3 2019*
Last subject last visit (LSLV): *Q3 2020*

2 SYNOPSIS – METHODOLOGY

Superseded Prior Wording

Blood samples… Clinical chemistry and hematology are assessed at screening and ~~at~~ end-of-trial …

New Protocol Wording

Blood samples… Clinical chemistry and hematology are assessed at screening, *last day of stimulation,* and end-of-trial …

3 SYNOPSIS – STATISTICAL METHODS

Superseded Prior Wording

… This is based on the results for MENOPUR powder from the COMBINE trial in a similar setting …

New Protocol Wording

… This is based on the results for MENOPUR powder from the COMBINE trial *conducted* in a similar setting …

4 SECTION 3.1.3 – METHODOLOGY

Superseded Prior Wording

Blood samples… Clinical chemistry and hematology are assessed at screening and ~~at~~ end-of-trial …

New Protocol Wording

Blood samples… Clinical chemistry and hematology are assessed at screening, *last day of stimulation,* and end-of-trial …

5 SECTION 3.1.3 – TRIAL SCHEDULE

Superseded Prior Wording

First subject first visit (FSFV) is planned to ~~Q3 2018~~

Last subject last visit (LSLV) is planned to ~~Q3 2019~~

New Protocol Wording

First subject first visit (FSFV) is planned to *Q3 2019*

Last subject last visit (LSLV) is planned to *Q3 2020*

6 TABLE 6-1 – TRIAL FLOW CHART

Superseded Prior Wording

	Screening and Down-regulation	**Stimulation**				**Oocyte retrieval**	**Transfer**	**Pregnancy monitoring**			**End**
	Pre-stimulation period	During stimulation			End of stimula-tion	OR	Transfer	βhCG	Clinical	Ongoing	End-of-trial
Timing	…	…	…	…	…	…	…	…	…	…	…
…											
Ultrasound sonography[p]	X	X[b]	X	X	X				X	X	
…											

p) Transvaginal ultrasound with exception of the ongoing pregnancy visit, where it can be either transvaginal or abdominal examination

New Protocol Wording

	Screening and Down-regulation	**Stimulation**				**Oocyte retrieval**	**Transfer**	**Pregnancy monitoring**			**End**
	Pre-stimulation period	During stimulation			End of stimula-tion	OR	Transfer	βhCG	Clinical	Ongoing	End-of-trial
Timing	…	...	…	…	…	…	…	…	…	…	...
…											
Ultrasound sonography[p]	X	X[b]	X	X	X		*X*		X	X	
…											

p) Transvaginal ultrasound with exception of the *transfer and* ongoing pregnancy visit*s*, where it can be either transvaginal or abdominal examination.

7 SECTION 6.4.1 – BLASTOCYST TRANSFER

Superseded Prior Wording

Transfer is performed on day 5 (blastocyst stage) after oocyte retrieval. Transfer of day 6 (or later) blastocysts is not allowed. The subject-related procedures are described below.

- Blood collection for central laboratory analysis of anti-MENOPUR antibodies (first post-dosing assessment)
- Transfer of blastocyst(s) of the highest quality available according to this policy: …

New Protocol Wording

Transfer is performed on day 5 (blastocyst stage) after oocyte retrieval. Transfer of day 6 (or later) blastocysts is not allowed. The subject-related procedures are described below.

- Blood collection for central laboratory analysis of anti-MENOPUR antibodies (first post-dosing assessment)
- *Ultrasound for image acquisition of the uterus (applicable for a subset of trial sites)*
- *Ultrasound-guided* transfer of blastocyst(s) of the highest quality available according to this policy: …

8 SECTION 7.3.10 – CLINICAL LABORATORY VALUES

Superseded Prior Wording

- Screening and end-of-trial visit: serum chemistry: non-fasting glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase.
- Screening and end-of-trial visit: hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count.

New Protocol Wording

- Screening*, last day of stimulation* and end-of-trial visit: serum chemistry: non-fasting glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase.
- Screening*, last day of stimulation* and end-of-trial visit: hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count.

9 SECTION 7.3.14 – ULTRASOUND FOR IMAGE ACQUISITION OF THE UTERUS

New Protocol Wording

7.3.14 Ultrasound for Image Acquisition of the Uterus

At a subset of trial sites, ultrasound for image acquisition of the uterus will be carried out at the transfer visit. Details on equipment and procedures related to this exploratory assessment will be provided in a trial-specific manual.

Resultant images may be analyzed to identify features that correlate with subject response to treatment and/or clinical outcomes, such as ongoing pregnancy. These data will be reported separately.

10 SECTION 7.5 – HANDLING OF BIOLOGICAL SAMPLES

Superseded Prior Wording

7.5 Handling of Biological Samples

A trial-specific laboratory manual will be provided to the participating sites, describing in detail how to handle, store and transport the biological samples (blood) in this trial. ... The processes related to handling of biological samples will be described in the informed consent documents, and biobank / data protection legislation including local legislation will be adhered to.

New Protocol Wording

7.5 Handling of Biological Samples *and Other Material*

A trial-specific laboratory manual will be provided to the participating sites, describing in detail how to handle, store and transport the biological samples (blood) in this trial. ... The processes related to handling of biological samples will be described in the informed consent documents, and biobank / data protection legislation including local legislation will be adhered to.

With respect to the image recordings of the uterus, a trial-specific manual will be provided to the subset of sites participating in this exploratory assessment, describing in detail the equipment and procedures. All recordings will be stored. Data protection legislation including local legislation will be adhered to.

11 SECTION 9.1 – DETERMINATION OF SAMPLE SIZE

Superseded Prior Wording

… This is based on the results for MENOPUR powder from the COMBINE trial ~~in a similar~~ conducted in a similar setting …

New Protocol Wording

… This is based on the results for MENOPUR powder from the COMBINE trial conducted in a similar setting …

12 SECTION 9.8.10 – SAFETY LABORATORY VALUES

Superseded Prior Wording

Baseline and end-of-trial safety 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 end-of-trial will be summarized by treatment group using descriptive statistics.

New Protocol Wording

Baseline*, last day of stimulation* and end-of-trial safety 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 last day of stimulation and* from baseline to end-of-trial will be summarized by treatment group using descriptive statistics.

13 SECTION 10.1 – SOURCE DATA AND SOURCE DOCUMENTS

Superseded Prior Wording

Trial-specific Source Data Requirements – Ferring

…

- Informed consent (~~date and time of oral information, date and time of handing out Informed Consent Documents,~~ date and time of obtaining written informed consent)

…

New Protocol Wording

…

- Informed consent (date and time of obtaining written informed consent)

…

14 MASTER INFORMED CONSENT DOCUMENTS – BLASTOCYST TRANSFER VISIT

Superseded Prior Wording

... During this visit, you will have the following tests and procedures performed:

- have a transvaginal ultrasound as part of the blastocyst transfer process and
- ...

New Informed Consent Wording

... During this visit, you will have the following tests and procedures performed:

- have a transvaginal *or abdominal* ultrasound as part of the blastocyst transfer process *(and might include collection of ultrasound images of the uterus)* and
- ...

15 MASTER INFORMED CONSENT DOCUMENTS – RETENTION OF SAMPLES

Superseded Prior Wording

Blood samples ...

The samples will be labeled with your study subject ID (not your name), and your identity will remain confidential. When all the needed information from the study has been gathered, the samples will be destroyed. Destruction for all blood samples will take place within 2 years after reporting of the study results, except blood samples analyzed by the local laboratory which are destroyed sooner.

...

New Informed Consent Wording

Blood samples ...

The samples will be labeled with your study subject ID (not your name), and your identity will remain confidential. When all the needed information from the study has been gathered, the samples will be destroyed. Destruction for all blood samples will take place within 2 years after reporting of the study results *or when methods / results have been adequately validated*, except blood samples analyzed by the local laboratory which are destroyed sooner.

...

If images of your uterus are collected, these recordings will be labeled with your study subject ID (not your name), and your identity will remain confidential.

CLINICAL TRIAL PROTOCOL
SUMMARY OF CHANGES #02

A randomized, double-blind double-dummy trial comparing MENOPUR solution for injection in a pre-filled pen and MENOPUR powder and solvent for solution for injection (menotropins for injection) in a GnRH agonist cycle in women aged 18-42 years undergoing an assisted reproductive technology program

Trial 000303

CLARA
(Comparison of MENOPUR Liquid and Powder in Women Undergoing ART)

IND Number:	053954
Investigational Medicinal Product:	MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL MENOPUR powder and solvent for solution for injection, 75 IU
Indication:	Development of multiple follicles and pregnancy in ovulatory women undergoing controlled ovarian stimulation as part of an assisted reproductive technology (ART) cycle
Phase:	3
Name and Address of Sponsor:	Ferring Pharmaceuticals, Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: [redacted]
GCP Statement:	This trial will be performed in compliance with GCP.

DOCUMENT INFORMATION:

This present document describes the changes made to the clinical trial protocol, version 4.0, and the master informed consent form, version 2.0; both dated 01 March 2019.

IMPLICATIONS OF CHANGE:

There are no immediate implications to the trial as recruitment has not started.

The changes do not affect the safety of subjects, scope of investigation, or scientific rigor of the trial. The present summary of changes as well as an updated protocol (version 5.0) will be submitted to IRBs and approval will be obtained prior to the respective sites starting the trial. Moreover, an updated master informed consent form (version 3.0) will be issued.

SUMMARY OF MAIN CHANGES TO CLINICAL TRIAL PROTOCOL:

- The combined oral contraceptive used as part of the pituitary downregulation protocol has been changed from CYCLAFEM 1/35 to NORTREL 1/35 due to lack of availability. Both products contain 1 mg norethindrone and 0.035 mg ethinyl estradiol per tablet.
- The previous inclusion criterion on serum AMH and FSH levels has been split into two separate criteria. The AMH sample can be taken at any time during the cycle and will be analyzed by the central laboratory. The FSH sample must be taken at cycle days 2-4 and will be analyzed by the local laboratory.
- The previous inclusion criterion on normal Pap smear has been replaced by a new exclusion criterion on known abnormal cervical cytology with the purpose of consistency across ongoing Ferring trials. The original criterion was aligned to the Ferring 000293 protocol under the assumption that the present trial would be started during the conduct of that trial, but has been changed to match the Ferring 000001 and 000002 trials which will be ongoing when the present trial starts. This change should make it simpler for sites participating in multiple Ferring trials at the same time.
- Eligibility criteria that may be assessed based on information in the subject's chart have been omitted as individual assessments at the screening visit.
- The blood sampling schedule on stimulation day 1 has been simplified. Serum E2 is analyzed by the central laboratory as part of the confirmation of downregulation, which occurs within 3 days before stimulation day 1. Serum E2 will therefore not be analyzed again on stimulation day 1. Furthermore, the optional local analysis of serum E2 and P4 on stimulation day 1 has been left out.
- A typo in the flow chart regarding the timing of stimulation day 1 has been corrected.
- The timing of the oocyte maturity stage assessment has been expanded.
- The data collection on follicle size has been simplified leading to omission of average follicle size and average size of the 3 largest follicles from the display of follicular development.
- The general term 'administration device' has been replaced with the specific term 'pen'.
- Neonatal SAEs will be assessed also at 4 weeks after birth.
- Trial timelines have been updated.

The affected sections, tables, and figures have been revised in accordance with the above changes and have been implemented in version 5.0 of the clinical trial protocol.

SUMMARY OF MAIN CHANGES TO MASTER INFORMED CONSENT FORM:

The protocol changes summarized on the previous page have been applied in the master informed consent form as applicable. In addition, the following revision has been made:

- Text added to mention that the blood samples taken in connection with anti-MENOPUR antibodies may also be used to qualify the antibody assays.

The changes have been implemented in version 3.0 of the master informed consent form.

CLINICAL TRIAL PROTOCOL
SUMMARY OF CHANGES #03

A randomized, double-blind double-dummy trial comparing MENOPUR solution for injection in a pre-filled pen and MENOPUR powder and solvent for solution for injection (menotropins for injection) in a GnRH agonist cycle in women aged 18-42 years undergoing an assisted reproductive technology program

Trial 000303

CLARA
(Comparison of MENOPUR Liquid and Powder in Women Undergoing ART)

IND Number:	053954
Investigational Medicinal Product:	MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL MENOPUR powder and solvent for solution for injection, 75 IU
Indication:	Development of multiple follicles and pregnancy in ovulatory women undergoing controlled ovarian stimulation as part of an assisted reproductive technology (ART) cycle
Phase:	3
Name and Address of Sponsor:	Ferring Pharmaceuticals, Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: [redacted]
GCP Statement:	This trial will be performed in compliance with GCP.

DOCUMENT INFORMATION:

This present document describes the changes made to the clinical trial protocol, version 5.0, dated 03 June 2019.

IMPLICATIONS OF CHANGE:

There are no immediate implications to the trial as recruitment has not started.

The changes do not affect the safety of subjects, scope of investigation, or scientific rigor of the trial. The present summary of changes as well as an updated protocol (version 6.0) will be submitted to IRBs and approval will be obtained prior to the respective sites starting the trial. The revisions are considered administrative changes.

This protocol update does not have implications for the informed consent form.

SUMMARY OF MAIN CHANGES TO CLINICAL TRIAL PROTOCOL:

- It has been clarified that the reduction in GnRH agonist (LEUPROLIDE ACETATE) dose from 0.1 mL (500 µg)/day to 0.05 mL (250 µg)/day should occur on stimulation day 1. The previous wording "once downregulation has been confirmed" has been considered too unspecific and therefore changed to "stimulation day 1".
- The template statement on how to record instances of accidental unblinding has been customized by removing "(e.g. the subject tells the investigator)" as this scenario is not applicable for the present trial with a double-blind, double-dummy design.
- The request for subjects to return the Subject Participation Card at the end-of-trial visit has been omitted in line with revisions made to Ferring's clinical trial protocol template.
- The explanation of IMP/NIMP destruction has been deleted, as this process is described in a manual outside the protocol.
- The description of the functions included in the Ferring clinical trial team has been expanded to include the field monitors, as monitoring of this trial will be conducted by Ferring employees and not a Contract Research Organization.
- Exclusion criterion 12 has been corrected from UK English spelling ("gonadotrophin") to US English spelling ("gonadotropin").
- A typo has been rectified; "MENOPUR powder (including Placebo to MENOPUR powder)" has been corrected to "MENOPUR powder (including Placebo to MENOPUR liquid)".

The affected sections and figures have been revised in accordance with the above changes and have been implemented in version 6.0 of the clinical trial protocol.

CLINICAL TRIAL PROTOCOL
SUMMARY OF CHANGES #04

A randomized, double-blind double-dummy trial comparing MENOPUR solution for injection in a pre-filled pen and MENOPUR powder and solvent for solution for injection (menotropins for injection) in a GnRH agonist cycle in women aged 18-42 years undergoing an assisted reproductive technology program

Trial 000303

CLARA
(Comparison of MENOPUR Liquid and Powder in Women Undergoing ART)

IND Number:	053954
Investigational Medicinal Product:	MENOPUR solution for injection in pre-filled pen, 1200 IU/1.92 mL MENOPUR powder and solvent for solution for injection, 75 IU
Indication:	Development of multiple follicles and pregnancy in ovulatory women undergoing controlled ovarian stimulation as part of an assisted reproductive technology (ART) cycle
Phase:	3
Name and Address of Sponsor:	Ferring Pharmaceuticals, Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: [redacted]
Amendment Number:	04
Sites where Effective:	All trial sites
Date of Protocol:	Original: 18 Dec 2017 / Current: 14 Oct 2019

This Protocol Amendment
- temporary halt of recruitment and implications for continued trial conduct -
is issued as urgent safety measures due to COVID-19 required to protect subjects against immediate hazard to their health and safety and is implemented immediately

DOCUMENT INFORMATION:

Protocol change intended to eliminate an apparent immediate hazard to subjects.

REASON FOR CHANGE TO THE CLINICAL TRIAL PROTOCOL:

- The COVID-19 pandemic has caused extensive restrictions on the movement of local populations in countries worldwide and recommendations to focus health care resources on essential activities only. Subsequently, clinical trial participants are experiencing increased difficulty in attending scheduled visits and trial sites are operating at reduced capacity.

- On 17 March 2020, the American Society for Reproductive Medicine (ASRM) issued a guidance on patient management and clinical recommendations, including: *"Suspend initiation of new treatment cycles…. Strongly consider cancellation of all embryo transfers whether fresh or frozen… Continue to care for patients who are currently "in-cycle""*.

- On 18 March 2020, the Food and Drug Administration (FDA) issued a guidance on conduct of clinical trials of medicinal products during the COVID-19 pandemic, including general considerations for how to ensure the safety of trial participants, maintain compliance with GCP and minimize risks to trial integrity.

Ferring has conducted a risk assessment, which led to this change to the clinical trial protocol. This document outlines the deliberations and decisions.

SUMMARY OF MAIN CHANGES TO CLINICAL TRIAL PROTOCOL:

Ferring is issuing a temporary halt of recruitment, i.e. a pause of screening and randomization. Ferring is issuing guidance for continued trial conduct and management of subjects already included in the trial. The table below provides guidance for how to manage the subjects according to stage in the trial.

Temporary halt of recruitment	**Continued trial conduct for management of subjects already included in the trial**
• Pause screening • Pause randomization	• Screened subjects (not yet initiated downregulation): downregulation will not be initiated; the screening period will be extended by the approximate duration of this COVID-19 related temporary recruitment halt • Subjects in downregulation (not yet randomized): stop downregulation and do not proceed to randomization; these subjects will be allowed to initiate a new downregulation phase when this COVID-19 related temporary recruitment halt is lifted • Randomized subjects: continue per protocol and document any deviations

In case subjects are prevented from attending scheduled visits, the investigator (or designee) will attempt to contact the subject by phone or other ways to inquire about potential adverse events and changes to concomitant medication.

IMPLICATIONS OF CHANGE:

The implications of these changes to the protocol are summarized below. The actions are considered urgent safety measures due to COVID-19 required to protect subjects against immediate hazard to their health and safety and are therefore implemented immediately.

- Trial sites, regulatory authorities and independent research boards will be informed.
- Subjects will be verbally informed by the investigator of potential changes to the course of action, as applicable for the individual subject. This will be documented in the subject's medical records.

- Protocol deviations (including deviations to the aspects described in this 'change to protocol') should be avoided whenever possible except where necessary to eliminate an immediate hazard to the subject. If deviations occur they will be documented as per standard practice, with additional specification whether they were related to the COVID-19 situation.

- Ferring will continuously monitor the situation and will lift the temporary halt of recruitment (screening and randomization) and resume the trial activities as per protocol when it is judged that the situation allows for this. Ferring will notify sites, regulatory authorities and independent research boards accordingly.