CLINICAL TRIAL PROTOCOL

A randomised, controlled, assessor-blind, parallel groups, multicentre trial comparing the efficacy and safety of highly purified human chorionic gonadotropin (HP-hCG) and recombinant human chorionic gonadotropin (rhCG) for triggering of final follicular maturation in women undergoing controlled ovarian stimulation

FASHION
(Efficacy and safety of HP-hCG and rhCG for triggering of final follicular maturation)

Trial 000191

Investigational Medicinal Product:	FE 999086, HP-hCG (CHORAPUR)
Indication:	For Assisted Reproductive Technology (ART) programme such as in vitro fertilisation: triggering of final follicular maturation and luteinisation after stimulation of follicle growth
Phase:	III
Name and Address of Sponsor:	Laboratórios Ferring Ltda Praça São Marcos 624 Alto de Pinheiros 05455-050 São Paulo Brazil Tel: (+55) 11 3024 7500
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A randomised, controlled, assessor-blind, parallel groups, multicentre trial comparing the efficacy and safety of highly purified human chorionic gonadotropin (HP-hCG) and recombinant human chorionic gonadotropin (rhCG) for triggering of final follicular maturation in women undergoing controlled ovarian stimulation

SIGNATORY INVESTIGATOR

[redacted] University of Sao Paulo, Ribeirão Preto, Brazil

TRIAL SITES

5 sites in Brazil

PLANNED TRIAL PERIOD	CLINICAL PHASE
Estimated FPFV: Q4 2015 Estimated LPLV / end-of-trial: Q4 2016	III

OBJECTIVES

Primary

- To demonstrate non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg for triggering of final follicular maturation with respect to number of oocytes retrieved in women undergoing controlled ovarian stimulation

Secondary

- To evaluate HP-hCG and rhCG with respect to oocyte fertilisation
- To evaluate HP-hCG and rhCG with respect to pregnancy
- To compare HP-hCG with rhCG with respect to endocrine profile
- To compare HP-hCG with rhCG with respect to safety profile

ENDPOINTS

Primary

- Number of oocytes retrieved

Secondary

- Number of metaphase II oocytes (only applicable for insemination using ICSI)
- Number of fertilised (2PN) oocytes
- Fertilisation rate (the rate of fertilised oocytes to oocytes retrieved for subjects with oocytes retrieved and also the rate of fertilised oocytes to metaphase II oocytes for subjects with oocytes inseminated using ICSI)

- Positive βhCG rate (positive serum βhCG test 13-15 days after transfer)
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)
- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer)
- Circulating concentrations of estradiol, progesterone and hCG at transfer and 13-15 days after transfer
- Frequency and intensity of adverse events
- Early and late OHSS rates
- Frequency and intensity of injection site reactions (redness, pain, itching, swelling and bruising) assessed by the subject after hCG administration

Post-trial Information

- Live birth rate and neonatal health at birth for subjects who have achieved a vital pregnancy

METHODOLOGY

This is a randomised, assessor-blind, parallel groups, multicentre trial comparing the efficacy and safety of highly purified human chorionic gonadotropin (HP-hCG, CHORAPUR, Ferring Pharmaceuticals) and recombinant human chorionic gonadotropin (rhCG, OVIDREL, Merck Serono) for triggering of final follicular maturation in women undergoing controlled ovarian stimulation. The trial procedures are in line with routine clinical practice, i.e. controlled ovarian stimulation following a GnRH antagonist protocol, triggering of final follicular maturation, oocyte retrieval, embryo / blastocyst transfer and pregnancy monitoring.

On day 2-3 of the menstrual cycle, subjects will start controlled ovarian stimulation with highly purified menotrophin (HP-hMG, MENOPUR, Ferring Pharmaceuticals). The initial daily dose of HP-hMG is 150 IU SC, followed by potential dose adjustments based on the subject's response as observed on transvaginal ultrasound, depending on the centre's practice and the investigator's judgement. During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation day 1, 6 and hereafter at least every other day until the end of stimulation. Coasting is prohibited. GnRH antagonist (cetrorelix acetate, CETROTIDE, Merck Serono) will be initiated on stimulation day 6 at a daily dose of 0.25 mg and continued throughout the controlled ovarian stimulation.

The criterion for triggering of final follicular maturation is ≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm observed on transvaginal ultrasound. Randomisation and administration of hCG will take place on the day of reaching the criterion for triggering of final follicular maturation. Subjects will be randomised in a 1:1:1 ratio to either HP-hCG 5,000 IU IM, HP-hCG 5,000 IU SC, or rhCG 250 μg SC. Randomisation will be stratified by the number of follicles ≥12 mm at the end of stimulation (two strata: <10 follicles and ≥10 follicles). Subjects who do not meet the criterion for triggering of final follicular maturation will not proceed to randomisation and are considered screening failures.

Oocyte retrieval will take place 36h (±2h) after hCG administration. All oocytes from follicles with an estimated diameter ≥12 mm should be retrieved. Oocytes will be inseminated within 6h after retrieval using IVF or ICSI. In case of ICSI, maturity stage should be assessed. On day 1 after

oocyte retrieval, fertilisation will be assessed, and the correct fertilisation will be defined as oocytes with 2 pronuclei (2PN). On day 3 after oocyte retrieval, the number of embryos and good-quality embryos (≥6 blastomeres and ≤20% fragmentation) will be assessed. In case of continued culture, the number of blastocysts and good-quality blastocysts (grade 3BB or above) will be assessed on day 5 after oocyte retrieval. Subjects will undergo transfer of 1-2 embryos or blastocysts on day 3 or day 5 after oocyte retrieval.

Vaginal progesterone capsules (UTROGESTAN, Besins Healthcare) 3 × 200 mg/day will be provided for luteal phase support starting the day of or the day after oocyte retrieval, depending on the centre's practice, and continuing until the clinical pregnancy visit (can be discontinued earlier in case of no embryo / blastocyst transfer, a negative βhCG test or pregnancy loss).

Pregnancy monitoring consists of a visit 13-15 days after transfer where a serum βhCG test will be taken and a visit 5-6 weeks after transfer assessing clinical and vital pregnancy via transvaginal ultrasound.

Blood samples will be collected at the end of stimulation, the embryo / blastocyst transfer visit and the βhCG visit for analysis of endocrine profile (estradiol, progesterone and hCG) and potential analysis of anti-hCG antibodies.

Local tolerability of the hCG preparations will be assessed by the subject three times after the hCG administration: immediately, 30 minutes and 24 hours after.

Post-trial Activities
All subjects with a vital pregnancy will be followed till delivery to gather information on pregnancy outcome, e.g. live birth. Furthermore, data will be gathered on neonatal health at birth, including minor/major congenital anomalies.

NUMBER OF SUBJECTS

It is planned to randomise 258 subjects from 5 sites in Brazil. It is estimated that up to 300 subjects should be screened to achieve 258 subjects eligible for randomisation.

The assumptions underlying the sample size estimation will be evaluated by the Data Monitoring Committee (DMC) in a blinded manner and the number of randomised subjects may be adjusted up to a maximum of 348 subjects.

CRITERIA FOR INCLUSION / EXCLUSION

This trial will include women aged 18-39 years, diagnosed with infertility and considered eligible for IVF/ICSI treatment. Women with more than 3 previous controlled ovarian stimulation cycles, with poor response in a previous cycle at a gonadotropin starting dose of 150 IU/day or higher, or with excessive response in a previous cycle at a gonadotropin starting dose of 150 IU/day or lower are excluded from participation.

The complete list of inclusion and exclusion criteria is provided below.

Inclusion criteria

1. Informed Consent Form signed prior to screening evaluations.

2. Willing and able to comply with the protocol for the duration of the trial.
3. In good physical and mental health.
4. Pre-menopausal females between the ages of 18 and 39 years. The subjects must be at least 18 years (including the 18th birthday) when they sign the informed consent and no more than 39 years (up to the day before the 40th birthday) at the time of randomisation.
5. Documented history of infertility (e.g. unable to conceive for at least 1 year for subjects <35 years of age; or unable to conceive for at least 6 months for subjects ≥35 years of age, subjects with bilateral tubal occlusion or absence of fallopian tubes, or subjects who require donor sperm).
6. Use of fresh or frozen ejaculated sperm from male partner or donor. If partner sperm will be used, male partner should have a semen analysis that is at least adequate for ICSI based on analysis within 6 months prior to randomisation.
7. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 3 cm or enlarged ovaries which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) at screening. Both ovaries must be accessible for oocyte retrieval.
8. Hysterosalpingography, hysteroscopy, saline infusion sonography, or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g. no evidence of clinically interfering uterine fibroids defined as submucous or intramural fibroids larger than 3 cm in diameter, no endometrial or endocervical polyps and no congenital structural abnormalities which are associated with a reduced chance of pregnancy) within 1 year prior to randomisation.
9. Regular menstrual cycles of 24-35 days (both inclusive), presumed to be ovulatory.
10. Body mass index (BMI) between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
11. Follicular development with ≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm observed on transvaginal ultrasound at the end of stimulation in the trial cycle.
12. Early follicular phase (cycle day 2-4) serum levels of FSH between 1 and 12 IU/L (results obtained within 6 months prior to randomisation).
13. Negative urine pregnancy test at screening and negative urine pregnancy test on the day of stimulation day 1 prior to administration of gonadotropin for controlled ovarian stimulation.
14. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), syphilis, Human T-Cell Lymphotropic Virus (HTLV) 1 and 2 antibody tests within 2 years prior to randomisation.
15. Willing to accept transfer of 1-2 embryos / blastocysts.

Exclusion Criteria

1. Known mental incapacity or language barrier precluding adequate understanding of the informed consent information and the trial activities.

2. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
3. Known endometriosis stage III and IV according to the revised classification of the American Society for Reproductive Medicine (ASRM).
4. Known polycystic ovarian syndrome (PCOS) according to the revised Rotterdam consensus.
5. History of more than three previous controlled ovarian stimulation cycles.
6. Poor response in a previous controlled ovarian stimulation cycle using a gonadotropin starting dose of 150 IU/day or higher. Poor response is defined as <4 oocytes retrieved, or cycle cancellation prior to oocyte retrieval due to inadequate follicular development.
7. Excessive response in a previous controlled ovarian stimulation cycle using a gonadotropin starting dose of 150 IU/day or lower. Excessive response is defined as ≥20 oocytes retrieved or cycle cancellation prior to oocyte retrieval due to excessive follicular development, including risk of ovarian hyperstimulation syndrome (OHSS).
8. OHSS leading to hospitalisation in a previous controlled ovarian stimulation cycle.
9. At risk of developing moderate / severe OHSS in the current controlled ovarian stimulation cycle, as judged by the investigator at the end of stimulation (i.e. on the day of randomisation).
10. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy and before week 24 of pregnancy, excluding ectopic pregnancy).
11. Known surgical or medical condition that may interfere with absorption, distribution, metabolism, or excretion of the drugs to be used.
12. Undiagnosed vaginal bleeding.
13. Currently breast-feeding.
14. Known abnormal karyotype of subject or of her partner / sperm donor, as applicable, depending on source of sperm used for insemination in this trial. In case partner sperm will be used and the sperm production is severely impaired (concentration <1 million/mL), normal karyotype, including no Y-chromosome microdeletion, must be documented.
15. Use of epididymis and testicular sperm from partner or donor.
16. Known inherited or acquired thrombophilia disease.
17. Known active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
18. Known porphyria.
19. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of controlled thyroid function disease.
20. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
21. Known moderate or severe impairment of renal or hepatic function.
22. Findings at the gynaecological examination at screening which preclude gonadotropin

stimulation or are associated with a reduced chance of pregnancy, e.g. retained intrauterine device.

23. Known current active pelvic inflammatory disease.
24. Known abnormal cervical cytology of clinical significance observed within three years prior to randomisation (unless the clinical significance has been resolved).
25. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
26. Use of fertility modifiers during the last menstrual cycle before start of controlled ovarian stimulation, including oral contraceptives, clomiphene citrate, gonadotropins, dehydroepiandrosterone (DHEA) or insulin sensitisers.
27. Any concomitant medications that would interfere with evaluation of trial medications. Specifically, any non-trial hormonal therapy (except for thyroid medication and non-systemic steroids) or continuous use of prostaglandin inhibitors (non-steroid anti-inflammatory drugs (NSAIDs), including aspirin) within 4 weeks prior to start of controlled ovarian stimulation.
28. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
29. Hypersensitivity to any drug substance or excipients in a GnRH or any GnRH analogue / derivative.
30. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.
31. Addictive substance abuse, defined as current or past (1 year prior to randomisation) abuse of alcohol or drugs, and/or current (1 month prior to randomisation) intake of more than 14 units of alcohol per week, and/or current or past (3 months prior to randomisation) smoking habit of more than 20 cigarettes per day.
32. Previous participation in the trial.

MEDICINAL PRODUCTS

Investigational Medicinal Products (IMPs)

IMP	Trade name	Dose
HP-hCG	CHORAPUR	A single 5,000 IU IM or SC injection on the day of reaching the criterion for triggering of final follicular maturation.
rhCG	OVIDREL	A single 250 µg SC injection on the day of reaching the criterion for triggering of final follicular maturation.

Concomitant Therapy / Non-investigational Medicinal Products (NIMPs)

NIMP	Trade name	Dose
HP-hMG	MENOPUR	150 IU SC injection once daily as starting dose on day 2-3 of the menstrual cycle. Potential dose adjustments based on the subject's response as observed on transvaginal ultrasound, depending on the centre's practice and the investigator's judgement.
GnRH antagonist (cetrorelix acetate)	CETROTIDE	0.25 mg SC injection once daily, starting on stimulation day 6 and continued throughout the stimulation period.
Progesterone	UTROGESTAN	3 × 200 mg daily as vaginal capsules, starting on the day of or the day after oocyte retrieval, depending on the centre's practice, and continued until the clinical pregnancy visit. Progesterone support can be terminated earlier in case of no transfer, a negative βhCG test or pregnancy loss.

DURATION OF TREATMENT

IMP will be administered as a single injection.

STATISTICAL METHODS

The non-inferiority margin for the difference between treatments (HP-hCG 5,000 IU versus rhCG 250 µg) is set to -3.0 oocytes. Non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg will be established by doing the comparisons in sequential order as follows:

1) HP-hCG 5,000 IU IM vs. rhCG 250 µg SC

2) HP-hCG 5,000 IU SC vs. rhCG 250 µg SC
This will only be evaluated if the first comparison establishes non-inferiority

It is assumed that the three treatments are equivalent with respect to number of oocytes retrieved. The number of oocytes retrieved is assumed to follow a normal distribution with a mean of 10-12

and a standard deviation of 6.0. Under these assumptions, a sample size of 258 subjects (86 subjects per group) will result in approximately 90% power to establish non-inferiority for the first comparison and approximately 80% power to establish non-inferiority for both comparisons. The number of subjects with major protocol deviations affecting the primary endpoint is assumed to be negligible. Therefore the sample size has not been adjusted to account for major protocol deviations affecting the primary endpoint.

Sample Size Monitoring
The standard deviation of the number of oocytes retrieved will be evaluated in a blinded manner. If the standard deviation is larger than 6.0, the sample size may be increased to a maximum of 348 subjects (116 subjects per group) corresponding to a standard deviation of 7.0.

Primary Endpoint
The non-inferiority hypothesis to be tested for the primary endpoint is

$$H_0: OR_{HP\text{-}hCG} - OR_{rhCG} \leq -3.0 \text{ against the alternative } H_A: OR_{HP\text{-}hCG} - OR_{rhCG} > -3.0$$

where $OR_{HP\text{-}hCG}$ and OR_{rhCG} denotes the number of oocytes retrieved with HP-hCG 5,000 IU (IM or SC) and rhCG 250 µg SC, respectively.

For each comparison, the null hypothesis (H_0) will be tested against the alternative (H_A) by constructing a two-sided 95% confidence interval for the difference in number of oocytes retrieved. The confidence interval will be based on analysis of variance (ANOVA) model including treatment, randomisation stratum and trial site as factors. The primary endpoint will be analysed for the intention-to-treat (ITT) and the per-protocol (PP) analysis sets. Since this is a non-inferiority trial, the ITT and the PP analysis sets will have equal importance and should lead to similar conclusions for a robust interpretation.

Evaluation of the Primary Objective
If the 95% confidence interval for the treatment difference not only lies above the non-inferiority limit but also above zero, there is evidence of superiority in terms of statistical significance at the two-sided 5% level. In this case, the p-value from the test for superiority will be reported. There is no need for a multiplicity adjustment, since it is a simple closed test procedure. This interpretation is in line with European Medicines Agency (EMA) “Points to consider on switching between superiority and non-inferiority”.

The result of the analysis of the primary endpoint (number of oocytes retrieved) is essential for the non-inferiority claim. The number of metaphase II oocytes (only applicable for insemination using ICSI) and the number of fertilised oocytes are considered the key secondary endpoints supportive of the primary endpoint. The analyses of the remaining secondary endpoints are intended to provide additional characterisation of the treatment effect.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical Classification System
ART	assisted reproductive technology
ASRM	American Society for Reproductive Medicine
AUC	area under curve
βhCG	beta unit of human chorionic gonadotropin
BMI	body mass index
COS	controlled ovarian stimulation
DHEA	dehydroepiandrosterone
DMC	Data Monitoring Committee
EC	ethics commitee
e-CRF	electronic Case Report Form
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FPFV	first patient first visit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
h	hour(s)
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HP-hCG	highly purified human chorionic gonadotropin
HP-hMG	highly purified menotrophin
HTLV	human T-cell lymphotropic virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICH	International Conference on Harmonisation
ICMART	International Committee Monitoring Assisted Reproductive Technologies
ICMJE	International Committee of Medical Journal Editors
ICSI	intracytoplasmic sperm injection
IM	intramuscular(ly)
IMP	investigational medicinal product
ITT	intention-to-treat
IU	international units
IVF	in vitro fertilisation
L	litre
LH	luteinising hormone
LLOQ	lower limit of quantification
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MII	metaphase II

mL	millilitre
NCU	neonatal care unit
NICU	neonatal intensive care unit
NIMP	non-investigational medicinal product
nmol	nanomol
NSAID	non-steroidal anti-inflammatory drug
OHSS	ovarian hyperstimulation syndrome
OR	oocyte retrieval
PCOS	polycystic ovarian syndrome
pmol	picomol
2PN	2 pronuclei
PP	per-protocol
PT	preferred term
rhCG	recombinant hCG
SAE	serious adverse event
SC	subcutaneous(ly)
SOC	system organ class
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TVU	transvaginal ultrasound
µg	microgram
ULOQ	upper limit of quantification
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Human chorionic gonadotropin (hCG) belongs to the gonadotropins, Anatomical Therapeutic Chemical (ATC) code G03GA01, and is a glycoprotein hormone produced by the human placenta. It is comprised of an alpha subunit that is common to luteinising hormone (LH) and follicle-stimulating hormone (FSH), and a beta subunit that is unique to hCG. The action of hCG is qualitatively the same as that of the pituitary gonadotropin LH. However, hCG has a significantly longer half-life and thus has a greater effect compared to LH.[1]

Exogenous human chorionic gonadotropin (hCG) has been used for treatment of female and male infertility for many years. In females, hCG mimics LH surge and thereby is used to induce ovulation in anovulatory or oligo-ovulatory women or to trigger final follicular maturation in women undergoing assisted reproductive technology (ART) programmes.[1]

CHORAPUR is a highly purified hCG (HP-hCG) obtained from the urine of pregnant women. An identical product to CHORAPUR is currently marketed by Ferring in some countries under the trade name BREVACTID. Additionally, for nearly 20 years Ferring has marketed another urine-derived hCG product CHORAGON, which used to be available in Brazil. Both CHORAPUR and CHORAGON have a dosage form of 5000 IU for intramuscular (IM) administration, but have different drug substance suppliers. Due to the cease of drug substance supply for CHORAGON, Ferring intends to replace CHORAGON with CHORAPUR worldwide. CHORAPUR (BREVACTID) 5,000 IU has been demonstrated to be bioequivalent with CHORAGON 5,000 IU in terms of pharmacokinetic and pharmacodynamic properties after IM administration in healthy volunteers in a phase I trial.[1] In addition, comparability studies of hCG drug substances from the two suppliers have shown that the drug substance of CHORAPUR has higher purity than that of CHORAGON,[1] and therefore CHORAPUR as a more purified product may be suitable also for subcutaneous (SC) administration.

Choriogonadotropin alfa (OVIDREL, Merck Serono) is a recombinant hCG (rhCG) expressed by a Chinese hamster ovarian cell line.[2] It is commercially available as a pre-filled pen containing 250 µg hCG to be administered SC for triggering of final follicular maturation in an ART setting.

To support the registration of CHORAPUR, the present phase III trial is conducted with the primary objective of documenting the non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg for triggering of final follicular maturation with respect to number of oocytes retrieved in women undergoing controlled ovarian stimulation.

1.2 Scientific Justification for Conducting the Trial

A number of studies[2,3,4,5] have compared the efficacy and safety of urine-derived hCG administered IM and rhCG administered SC for triggering of final follicular maturation in women undergoing ART. All concluded that there were no statistically significant differences between the two preparations in clinical outcomes including the number of oocytes retrieved and the clinical pregnancy rate. A recent trial compared another HP-hCG product against rhCG and demonstrated that the two products were equally efficient and safe for triggering of final follicular maturation when administered SC.[6]

The present trial intends to complement and expand the prior comparison of HP-hCG and rhCG by having a three-arm design to compare rhCG 250 µg SC to both HP-hCG (CHORAPUR) 5,000 IU IM and HP-hCG (CHORAPUR) 5,000 IU SC. CHORAPUR is approved for the intended indication in several countries based on the available data, but for registration purpose in other countries (including Brazil), there is a need to document in a phase III trial with adequate power that HP-hCG 5,000 IU IM is not inferior to rhCG 250 µg SC with respect to number of oocytes retrieved in women undergoing controlled ovarian stimulation.

With improved purification, HP-hCG is now possible to be administered SC in addition to the approved IM route of administration. The SC route of administration for another, less purified urine-derived hCG product 10,000 IU was demonstrated to be bioequivalent to the IM route with respect to hCG exposure as assessed by the area under the curve (AUC); meanwhile, it was shown to be well tolerated in healthy pituitary-suppressed women.[7] Supported by all the evidence above, this trial will also examine the efficacy and safety of HP-hCG 5,000 IU SC versus rhCG 250 µg SC.

1.3 Benefit / Risk Aspects

Benefits
The treatment cycle is provided to the participating subjects free of charge, as Ferring compensates the investigational clinics for their expenses. Subjects participating in this trial may benefit by achieving a pregnancy. In addition, the data obtained from the treatment cycle may provide useful information for optimising the ovarian response and for clinical planning of subsequent treatment cycles.

Risks
Participating in the trial does not imply extra risks for the subjects in comparison to routine practice for triggering of final follicular maturation. The risks associated with ART treatment, including the risk of controlled ovarian stimulation and clinical and laboratory procedures, are explained to the subjects as part of the counselling prior to starting treatment.

CHORAPUR and OVIDREL are both approved products (although CHORAPUR is approved in other countries than Brazil) and the treatment regimen applied in this trial is in line with the standard posology. Based on the available data, the most frequently reported adverse events in relation to CHORAPUR include headache and injection site reactions (both reported to occur in more than 10% of patients), nausea, abdominal pain, vomiting, mild or moderate ovarian hyperstimulation syndrome (OHSS) and breast swelling (all reported to occur in 1-10% of patients).[8] The most common adverse events in relation to use of OVIDREL are headache, injection site reactions, tiredness, nausea, abdominal pain, vomiting and mild or moderate OHSS (all reported to occur in 1-10% of patients).[9]

As part of the ART treatment in this trial, subjects will receive concomitant fertility medications including gonadotropin, GnRH antagonist and progesterone. The concomitant fertility medications are approved products and are considered generally well tolerated. The most frequently reported adverse events with these concomitant medication products are similar to those reported for hCG preparations, such as headache, injection site reactions, abdominal pain, nausea and mild or

moderate OHSS. Furthermore, the vaginal progesterone has been associated with local intolerance (burning, pruritus or fatty discharge) but incidences are very low.

Most commonly observed adverse events in ART treatment are related to overstimulation of the ovaries, e.g. OHSS. They are mainly dose dependent and dependent on the individual subject's response to the treatment. OHSS manifests itself with increasing degree of severity. Moderate / severe OHSS is associated with marked ovarian enlargement, fluid accumulation and other complications. Subjects are closely monitored throughout the trial and the risk of developing early OHSS can be prevented by withholding gonadotropins and withholding hCG. Very rare cases of serious allergic reactions to hormone preparations have been reported.

The number of embryos / blastocysts transferred will for each subject depend on the availability of embryos / blastocysts of good morphological quality, local regulations and clinical practice. Transfer of 2 embryos / blastocysts is associated with increased risk of multiple pregnancies / births and the related neonatal health problems, compared to transfer of a single embryo / blastocyst. Participation in this trial does not imply transfer of more embryos / blastocysts than what is judged appropriate by the subject, the investigator and local regulations. The incidence of miscarriage is higher in women undergoing controlled ovarian stimulation than in women conceiving spontaneously, and also the risk of ectopic pregnancy is higher but mainly in patients with a history of tubal obstruction.

Subjects will also undergo standard ART treatment procedures, e.g. transvaginal ultrasound, blood sampling, oocyte retrieval and transfer. The transvaginal ultrasound examinations may be associated with mild discomfort and a very rare risk of infection. The blood sampling might be associated with mild discomfort, bruising 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 mild bleeding.

Benefits / Risks

Participation in this trial is not expected to have a negative influence on the subject's likelihood of conceiving compared to normal clinical practice. Furthermore, participation does not imply extra risks for the subjects in comparison to routine IVF/ICSI treatment. In conclusion, the evaluation of benefits and risks indicates that participation in this trial is associated with a favourable benefit-risk ratio.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To demonstrate non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg for triggering of final follicular maturation with respect to number of oocytes retrieved in women undergoing controlled ovarian stimulation

Secondary Objectives

- To evaluate HP-hCG and rhCG with respect to oocyte fertilisation
- To evaluate HP-hCG and rhCG with respect to pregnancy
- To compare HP-hCG with rhCG with respect to endocrine profile
- To compare HP-hCG with rhCG with respect to safety profile

2.2 Endpoints

Primary Endpoint

- Number of oocytes retrieved

Secondary Endpoints

- Number of metaphase II oocytes (only applicable for insemination using ICSI)
- Number of fertilised (2PN) oocytes
- Fertilisation rate (the rate of fertilised oocytes to oocytes retrieved for subjects with oocytes retrieved and also the rate of fertilised oocytes to metaphase II oocytes for subjects with oocytes insemination using ICSI)
- Positive βhCG rate (positive serum βhCG test 13-15 days after transfer)
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)
- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer)
- Circulating concentrations of estradiol, progesterone and hCG at transfer and 13-15 days after transfer
- Frequency and intensity of adverse events
- Early and late OHSS rates
- Frequency and intensity of injection site reactions (redness, pain, itching, swelling and bruising) assessed by the subject after hCG administration

Post-trial Information

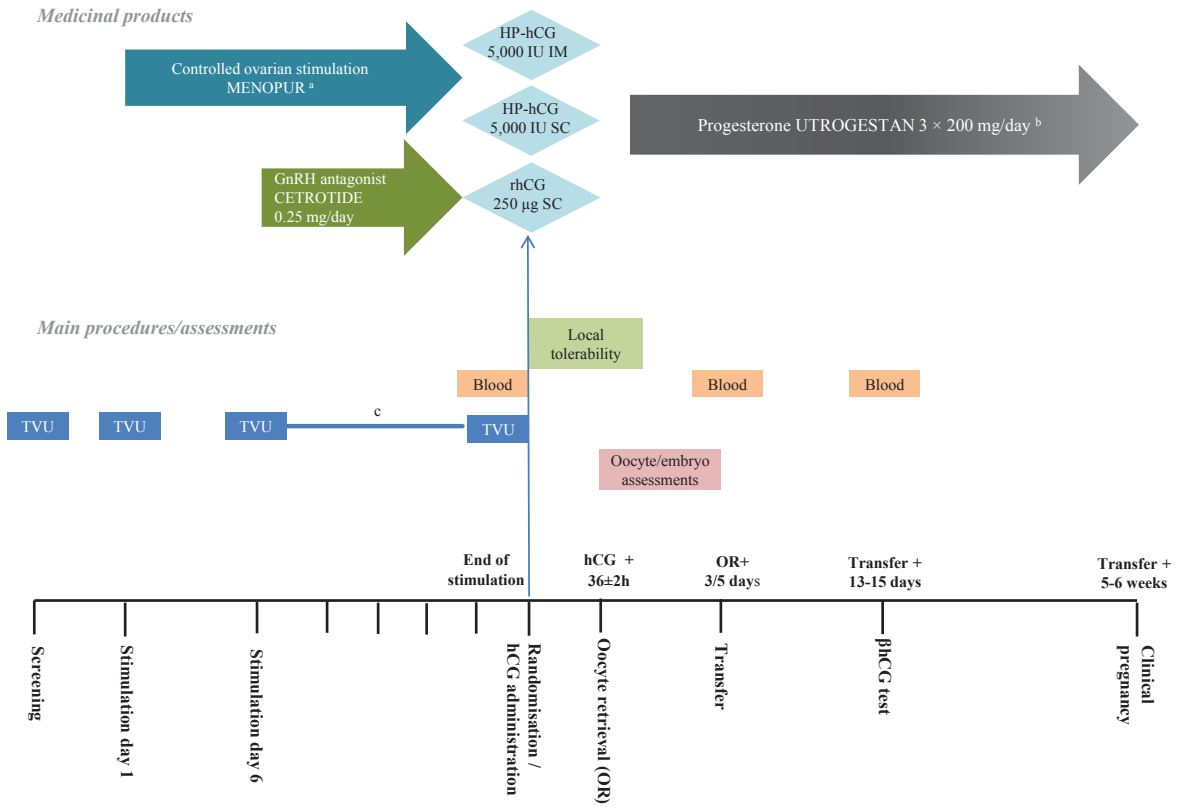
- Live birth rate and neonatal health at birth for subjects who have achieved a vital pregnancy

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

A diagram illustrating the trial period is shown in Figure **3-1**.



[a] Starting dose of 150 IU/day SC; followed by potential dose adjustments according to individual response.
[b] Progesterone can start on the day of or the day after oocyte retrieval and should continue until clinical pregnancy visit (can be discontinued earlier in case of no embryo / blastocyst transfer, a negative βhCG test or pregnancy loss).
[c] Stimulation day 1, 6 and hereafter at least every other day until the end of stimulation.
Abbreviations: GnRH=gonadotropin-releasing hormone, hCG=human chorionic gonadotropin, HP-hCG=highly purified hCG, IM=intramuscular(ly), OR=oocyte retrieval, rhCG=recombinant hCG, SC=subcutaneous(ly), TVU=transvaginal ultrasound.

Figure 3-1 Trial Diagram

3.1.2 Overall Design and Control Methods

Trial Design

This is a randomised, assessor-blind, parallel groups, multicentre trial comparing the efficacy and safety of HP-hCG (CHORAPUR, Ferring Pharmaceuticals) and rhCG (OVIDREL, Merck Serono) for triggering of final follicular maturation in women undergoing controlled ovarian stimulation. The trial procedures are in line with routine clinical practice, i.e. controlled ovarian stimulation following a GnRH antagonist protocol, triggering of final follicular maturation, oocyte retrieval, embryo / blastocyst transfer and pregnancy monitoring.

On day 2-3 of the menstrual cycle, subjects will start controlled ovarian stimulation with highly purified menotrophin (HP-hMG, MENOPUR, Ferring Pharmaceuticals). The initial daily dose of HP-hMG is 150 IU SC, followed by potential dose adjustments based on the subject's response as observed on transvaginal ultrasound, depending on the centre's practice and the investigator's judgement. During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation day 1, 6 and hereafter at least every other day until the end of stimulation. Coasting is prohibited. GnRH antagonist (cetrorelix acetate, CETROTIDE, Merck Serono) will be initiated on stimulation day 6 at a daily dose of 0.25 mg and continued throughout the controlled ovarian stimulation.

The criterion for triggering of final follicular maturation is ≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm observed on transvaginal ultrasound. Randomisation and administration of hCG will take place on the day of reaching the criterion for triggering of final follicular maturation. Subjects will be randomised in a 1:1:1 ratio to either HP-hCG 5,000 IU IM, HP-hCG 5,000 IU SC, or rhCG 250 μg SC. Randomisation will be stratified by the number of follicles ≥12 mm at the end of stimulation (two strata: <10 follicles and ≥10 follicles). Subjects who do not meet the criterion for triggering of final follicular maturation will not proceed to randomisation and are considered screening failures.

Oocyte retrieval will take place 36h (±2h) after hCG administration. All oocytes from follicles with an estimated diameter ≥12 mm should be retrieved. Oocytes will be inseminated within 6h after retrieval using IVF or ICSI. In case of ICSI, maturity stage should be assessed. On day 1 after oocyte retrieval, fertilisation will be assessed, and the correct fertilisation will be defined as oocytes with 2 pronuclei (2PN). On day 3 after oocyte retrieval, the number of embryos and good-quality embryos (≥6 blastomeres and ≤20% fragmentation) will be assessed. In case of continued culture, the number of blastocysts and good-quality blastocysts (grade 3BB or above) will be assessed on day 5 after oocyte retrieval. Subjects will undergo transfer of 1-2 embryos or blastocysts on day 3 or day 5 after oocyte retrieval.

Vaginal progesterone capsules (UTROGESTAN, Besins Healthcare) 3 × 200 mg/day will be provided for luteal phase support starting the day of or the day after oocyte retrieval, depending on the centre's practice, and continuing until the clinical pregnancy visit (can be discontinued earlier in case of no embryo / blastocyst transfer, a negative βhCG test or pregnancy loss).

Pregnancy monitoring consists of a visit 13-15 days after transfer where a serum βhCG test will be taken and a visit 5-6 weeks after transfer assessing clinical pregnancy via transvaginal ultrasound.

Blood samples will be collected at the end of stimulation, the embryo / blastocyst transfer visit and the βhCG visit for analysis of endocrine profile (estradiol, progesterone and hCG) and potential analysis of anti-hCG antibodies.

Local tolerability of the hCG preparations will be assessed by the subject three times after the hCG administration: immediately, 30 minutes and 24 hours after.

Post-trial Activities
All subjects with a vital pregnancy will be followed till delivery to gather information on pregnancy outcome, e.g. live birth. Furthermore, data will be gathered on neonatal health at birth, including minor/major congenital anomalies.

3.1.3 Trial Schedule

Estimated First patient first visit (FPFV):	Q4 2015
Estimated Last patient last visit (LPLV) / end-of-trial:	Q4 2016

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomise 258 subjects from 5 sites in Brazil. It is estimated that up to 300 subjects should be screened to achieve 258 subjects (86 subjects per group) eligible for randomisation.

The assumptions underlying the sample size estimation will be evaluated by the Data Monitoring Committee (DMC) in a blinded manner and the number of randomised subjects may be adjusted up to a maximum of 348 subjects.

3.3 Interim Analysis

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

3.4 Data Monitoring Committee (DMC)

An internal DMC consisting of the sponsor's Medical Officer at Ferring Global Clinical R&D, the sponsor's Medical Officer in Brazil and the project-responsible statistician at Ferring Global Biometrics will be established.

The assumptions underlying the sample size estimation will be evaluated by the DMC in a blinded manner and the number of randomised subjects may be adjusted up to a maximum of 348 subjects. The charter of the DMC will specify the relevant details.

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 the non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg for triggering of final follicular maturation with respect to number of oocytes retrieved in women undergoing controlled ovarian stimulation.

This is a randomised controlled trial using an approved hCG product as an active comparator. It is a parallel group design restricted to a single treatment cycle. The trial will be assessor-blind, as a

double-blind design is not considered feasible for the present trial for various practical reasons, which are described in detail in section 3.5.3. The assessor-blinding will ensure unbiased evaluation by the investigators, embryologists and central laboratory personnel. Similarly, Ferring staff will also remain blinded to individual subject treatment allocation during the conduct of the trial. The trial will be a multicentre 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 generalisation of the results.

The trial is designed with adequate power to demonstrate non-inferiority of HP-hCG IM versus rhCG SC with respect to number of oocytes retrieved. The non-inferiority margin for this primary endpoint has been set at -3.0. A non-inferiority margin of -3.0 has been recommended by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) and follows regulatory precedence for the approval of infertility indications with the number of oocytes retrieved as primary endpoint. [10,11,12,13] The margin has also been used in previous clinical trials comparing the efficacy and safety of different hCG products.[2,3,4] The number of oocytes retrieved is assumed to follow a normal distribution with a mean of 10-12 and a standard deviation of 6.0. With a sample size of 86 subjects per group, it is expected that the difference in the number of oocytes retrieved between the HP-hCG groups and the rhCG group has to be less than 1.2 in order to meet the non-inferiority margin of -3.0. As an example, if the average number of oocytes retrieved in the rhCG group is 12.0, the average number of oocytes retrieved in the HP-hCG groups has to be at least 10.8 in order to establish non-inferiority.

Strict criteria have been incorporated in the design of this comparative efficacy trial to properly assess the effect of different hCG products on treatment outcome. In general, treatment and procedures before hCG administration have been standardised to minimise variation of follicular development. After screening, eligible subjects will undergo a standardised controlled ovarian stimulation by receiving the same gonadotropin at the same starting dose. All subjects will follow the GnRH antagonist protocol by using the same GnRH antagonist at the same dose and starting at the same time. In addition, transvaginal ultrasound will be performed regularly to monitor the follicular development and only subjects with adequate follicular development can be randomised and proceed to receive hCG for triggering of final follicular maturation. To further control for the confounding of follicular development, randomisation is stratified by the number of follicles ≥12 mm at the end of stimulation (two strata: <10 follicles and ≥10 follicles).

The retrieval of all oocytes from follicles with an estimated diameter ≥12 mm and the following insemination of oocytes by either IVF or ICSI reflect the procedures used in the target population for the proposed indication. To account for the different transfer policies across clinics and across individuals in the same clinic, the present protocol allows transfer on day 3 or day 5 after oocyte retrieval. A maximum of 2 embryos / blastocysts can be transferred, as this is in line with the current clinical practices taken for maintaining efficacy (i.e. pregnancy) and minimising risks (i.e. multiple pregnancies) of the controlled ovarian stimulation cycle. Meanwhile, some flexibility has been given regarding the choice of single or double transfer of embryos / blastocysts, as the transfer takes place after assessment of the primary endpoint.

Subjects who achieve a vital pregnancy will be followed up till delivery to collect information on pregnancy outcome. In addition, neonatal health data will be gathered at birth.

3.5.2 Selection of Endpoints

The primary endpoint of this trial, the number of oocytes retrieved, is an objective and measurable parameter. The number of oocytes retrieved is a direct measure of the main pharmacological action of hCG preparations, as it integrates a cascade of intrafollicular events necessary for oocyte release from the follicle.[2] The number of oocytes retrieved has also been used as the primary endpoint in other trials comparing the efficacy and safety of hCG products of different origins.[2,3,4,6]

Secondary endpoints will explore the qualitative and quantitative impact of HP-hCG and rhCG with regard to oocyte maturity, fertilisation rate and pregnancy. To investigate the pharmacodynamic effect, endocrine profile represented by estradiol and progesterone will be evaluated at the end of stimulation, the embryo / blastocyst transfer visit and the βhCG visit. Safety endpoints cover adverse events, early and late OHSS rates, and injection site reactions. Pre-defined injection site reactions, i.e. redness, pain, itching, swelling and bruising, will be assessed by the subjects at three occasions spanning from immediately after injection to 24 hours after.

Post-trial activities cover follow-up of subjects who have achieved a vital pregnancy to collect data on pregnancy outcome and neonatal health at birth.

In conclusion, the primary and secondary endpoints are appropriate for this trial.

3.5.3 Blinding

The investigational medicinal products (IMPs) in this trial differ in presentation, as HP-hCG is provided as a pair of powder vial and solvent ampoule to be administered either SC or IM after reconstitution, whereas rhCG is provided as a pre-filled pen to be administered SC only. Furthermore, rhCG is manufactured by Merck Serono and bought commercially for use in this trial. Therefore, a double-blind, double-dummy design is not feasible.

Previous trials comparing the efficacy and safety of rhCG and urine-derived hCG have been open-label studies with no blinding of investigators, other assessors or sponsor.[2,6] This trial is assessor-blind, however, ensuring unbiased evaluation by the investigators, embryologists and laboratory personnel. The trial staff dispensing and/or administering IMP, the trial coordinator (person entering data into the electronic case report form (e-CRF); can be the same person who dispense and/or administer IMP), the in-field monitors and the participating subjects will know the treatment allocation once the subjects are randomised. Precaution will be taken to ensure that the treatment allocations are not available to the investigators or other assessors throughout the trial. Subjects will be clearly instructed not to discuss their treatment allocation with the investigator.

The Ferring clinical trial team (except IMP Department members) will be blinded to individual and group treatment allocation until breaking of the blind.

3.5.4 Selection of Doses in the Trial

Each subject meeting the criterion for triggering of final follicular maturation will receive a single dose of 5,000 IU HP-hCG IM, 5,000 IU HP-hCG SC or 250 µg rhCG SC.

The doses are selected to be consistent with the posology of the respective products for the indication of triggering of final follicular maturation in women undergoing ART.[8,9] The approved rhCG (OVIDREL) dose is 250 µg, which has been suggested to be equivalent to approximately

6,500 IU.[12] Standard dose of urine-derived hCG for triggering of final follicular maturation is either 5,000 or 10,000 IU. The lowest effective dose of 5,000 IU is selected for HP-hCG in this trial, as this would be a reasonable approach in clinical practice.

OVIDREL (rhCG) has been approved for SC administration, while CHORAPUR (HP-hCG) is approved for IM administration only. With improved purification, HP-hCG is now possible to be administered SC in addition to the approved IM route of administration. The SC route of administration for another, less purified urine-derived hCG product 10,000 IU was demonstrated to be bioequivalent to the IM route with respect to hCG exposure as assessed by AUC and was shown to be well tolerated in healthy pituitary-suppressed women.[7] Supported by all the evidence above, this trial will also examine the efficacy and safety of HP-hCG 5,000 IU SC.

The treatment regimen in this trial for HP-hMG (MENOPUR), the GnRH antagonist (CETROTIDE) and progesterone (UTROGESTAN) is according to the respective products' labelling for the indication of ART and/or standard clinical practice supported by literature.

3.5.5 Selection and Timing of Dose for Each Subject

Administration of hCG will take place when there is adequate follicular development for triggering of final follicular maturation, i.e. when ≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm are observed on transvaginal ultrasound. While the follicular development criterion may vary slightly across clinics and individual situation, a standardised criterion must be established for the purpose of the trial. Subjects having <3 follicles with a diameter ≥17 mm at the end of stimulation are at risk of having no available embryos / blastocysts for transfer, whereas subjects having ≥25 follicles with a diameter ≥12 mm are at risk of developing early moderate / severe OHSS.

3.5.6 Selection of the Trial Population

The trial population is representative of patients undergoing IVF/ICSI treatment. The subjects are women with documented history of infertility, including tubal infertility, unexplained infertility, infertility related to endometriosis stage I/II according to the revised classification of the American Society for Reproductive Medicine (ASRM)[14] or infertility due to male factor, eligible for IVF and/or ICSI treatment. Patients with polycystic ovary syndrome (PCOS) by the revised Rotterdam consensus[15] or patients with endometriosis stage III-IV by the revised ASRM classification[14] are excluded from participation. Women having contraindications to controlled ovarian stimulation with gonadotropins will be excluded from participation in this trial.

For the purpose of this trial, considerations have been given to ensure the trial population is suitable for triggering of final follicular maturation and that the trial population is relatively homogeneous in relation to ovarian response. To minimise the number of potential poor and excessive responders in the trial, eligibility for participation is based on ovarian response defined by the number and size of follicles in this controlled ovarian stimulation cycle and in previous cycles.

This trial includes women within the age group of 18-39 years, as increasing female age is associated with fewer oocytes and a reduction in oocyte or embryo quality. The allowed body mass index (BMI) is 17.5-32.0 kg/m^2, thus covering underweight, normal weight, overweight and obese patients.

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

3.5.7 Follow-up Procedures

Post-Trial Activities
Post-trial activities cover follow-up of pregnancy outcome and neonatal health at birth for subjects who have achieved a vital pregnancy.

Access to Therapy after End-of-Trial
HP-hCG is for single use in one treatment cycle. Concerning access to therapy after completion of the trial, HP-hCG is not currently approved in Brazil and cannot be offered to patients for future treatment cycles. However, the comparator rhCG is approved for triggering of final follicular maturation and is commercially available in Brazil.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

Subjects must meet all of the criteria listed below to be eligible for participation in the trial.

1. Informed Consent Form signed prior to screening evaluations.
2. Willing and able to comply with the protocol for the duration of the trial.
3. In good physical and mental health.
4. Pre-menopausal females between the ages of 18 and 39 years. The subjects must be at least 18 years (including the 18th birthday) when they sign the informed consent and no more than 39 years (up to the day before the 40th birthday) at the time of randomisation.
5. Documented history of infertility (e.g. unable to conceive for at least 1 year for subjects <35 years of age; or unable to conceive for at least 6 months for subjects ≥35 years of age, subjects with bilateral tubal occlusion or absence of fallopian tubes, or subjects who require donor sperm).
6. Use of fresh or frozen ejaculated sperm from male partner or donor. If partner sperm will be used, male partner should have a semen analysis that is at least adequate for ICSI based on analysis within 6 months prior to randomisation.
7. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 3 cm or enlarged ovaries which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) at screening. Both ovaries must be accessible for oocyte retrieval.
8. Hysterosalpingography, hysteroscopy, saline infusion sonography, or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g. no evidence of clinically interfering uterine fibroids defined as submucous or intramural fibroids larger than 3 cm in diameter, no endometrial or endocervical polyps and no congenital structural abnormalities which are associated with a reduced chance of pregnancy) within 1 year prior to randomisation.
9. Regular menstrual cycles of 24-35 days (both inclusive), presumed to be ovulatory.
10. Body mass index (BMI) between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
11. Follicular development with ≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm observed on transvaginal ultrasound at the end of stimulation in the trial cycle.
12. Early follicular phase (cycle day 2-4) serum levels of FSH between 1 and 12 IU/L (results obtained within 6 months prior to randomisation).
13. Negative urine pregnancy test at screening and negative urine pregnancy test on the day of stimulation day 1 prior to administration of gonadotropin for controlled ovarian stimulation.

14. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), syphilis, Human T-Cell Lymphotropic Virus (HTLV) 1 and 2 antibody tests within 2 years prior to randomisation.
15. Willing to accept transfer of 1-2 embryos / blastocysts.

4.1.2 Exclusion Criteria

Subjects meeting any of the criteria listed below will **not** be eligible for participation in the trial.

1. Known mental incapacity or language barrier precluding adequate understanding of the informed consent information and the trial activities.
2. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
3. Known endometriosis stage III and IV according to the revised classification of the American Society for Reproductive Medicine (ASRM).[14]
4. Known polycystic ovarian syndrome (PCOS) according to the revised Rotterdam consensus.[15]
5. History of more than three previous controlled ovarian stimulation cycles.
6. Poor response in a previous controlled ovarian stimulation cycle using a gonadotropin starting dose of 150 IU/day or higher. Poor response is defined as <4 oocytes retrieved, or cycle cancellation prior to oocyte retrieval due to inadequate follicular development.
7. Excessive response in a previous controlled ovarian stimulation cycle using a gonadotropin starting dose of 150 IU/day or lower. Excessive response is defined as ≥20 oocytes retrieved or cycle cancellation prior to oocyte retrieval due to excessive follicular development, including risk of OHSS.
8. OHSS leading to hospitalisation in a previous controlled ovarian stimulation cycle.
9. At risk of developing moderate / severe OHSS in the current controlled ovarian stimulation cycle, as judged by the investigator at the end of stimulation (i.e. on the day of randomisation).
10. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy and before week 24 of pregnancy, excluding ectopic pregnancy).
11. Known surgical or medical condition that may interfere with absorption, distribution, metabolism, or excretion of the drugs to be used.
12. Undiagnosed vaginal bleeding.
13. Currently breast-feeding.
14. Known abnormal karyotype of subject or of her partner / sperm donor, as applicable, depending on source of sperm used for insemination in this trial. In case partner sperm will be used and the sperm production is severely impaired (concentration <1 million/mL), normal karyotype, including no Y-chromosome microdeletion, must be documented.
15. Use of epididymis and testicular sperm from partner or donor.
16. Known inherited or acquired thrombophilia disease.

17. Known active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
18. Known porphyria.
19. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of controlled thyroid function disease.
20. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
21. Known moderate or severe impairment of renal or hepatic function.
22. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. retained intrauterine device.
23. Known current active pelvic inflammatory disease.
24. Known abnormal cervical cytology of clinical significance observed within three years prior to randomisation (unless the clinical significance has been resolved).
25. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
26. Use of fertility modifiers during the last menstrual cycle before start of controlled ovarian stimulation, including oral contraceptives, clomiphene citrate, gonadotropins, dehydroepiandrosterone (DHEA) or insulin sensitisers.
27. Any concomitant medications that would interfere with evaluation of trial medications. Specifically, any non-trial hormonal therapy (except for thyroid medication and non-systemic steroids) or continuous use of prostaglandin inhibitors (non-steroid anti-inflammatory drugs (NSAIDs), including aspirin) within 4 weeks prior to start of controlled ovarian stimulation.
28. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
29. Hypersensitivity to any drug substance or excipients in a GnRH or any GnRH analogue / derivative.
30. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.
31. Addictive substance abuse, defined as current or past (1 year prior to randomisation) abuse of alcohol or drugs, and/or current (1 month prior to randomisation) intake of more than 14 units of alcohol per week, and/or current or past (3 months prior to randomisation) smoking habit of more than 20 cigarettes per day.
32. Previous participation in the trial.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The participating subjects will be recruited among the patients attending the clinics included in the trial. Advertisements may be used if approved by Brazil's National Ethics Committees (ECs) and regulatory authorities, as applicable, according to local regulations and the clinic's practices.

A screening number is allocated to each subject who has given written informed consent to participate in the trial. A subject must always be assigned to the lowest available screening number at each site. A subject screening / enrolment log for all screened subjects must be maintained by the investigator.

4.2.2 Randomisation

Subjects who meet the criterion for triggering of final follicular maturation will be randomised in a 1:1:1 ratio to treatment with either HP-hCG 5,000 IU IM, HP-hCG 5,000 IU SC, or rhCG 250 µg SC. Randomisation is performed centrally through the e-CRF and will be stratified by the number of follicles ≥12 mm on the last day of stimulation (two strata: <10 follicles and ≥10 follicles). The randomisation number will be allocated to the subject together with the treatment allocation. When a subject is randomised to the trial, she will always be assigned to the lowest available randomisation number. An independent statistician at the Ferring Global Biometrics Department will prepare a computer-generated randomisation list and randomisation is performed in blocks. Blocks will be maintained within trial sites, i.e. the randomisation will be stratified by trial site. The block size will only be revealed when the trial database is declared clean and locked. An overview of recruitment will be recorded on a subject identification code list for all randomised subjects kept by the investigator.

4.3 Restrictions

4.3.1 Prohibited Therapy

Prohibited Therapy before and during the Trial

Subjects must not use any fertility modifiers during the last menstrual cycle before start of controlled ovarian stimulation, including oral contraceptives, clomiphene citrate, gonadotropins, DHEA or insulin sensitisers.

Subjects must not use any concomitant medications that would interfere with evaluation of trial medications within 4 weeks before start of controlled ovarian stimulation. These prohibited concomitant medications include any non-trial hormonal therapy (except for thyroid medication and non-systemic steroids) and continuous use of prostaglandin inhibitors (NSAIDs, including aspirin).

It is prohibited to administer other hCG preparations than HP-hCG/rhCG or to administer other concomitant fertility medications than those provided throughout the trial.

Prohibited Therapy after the Trial
It is prohibited to continue therapy outside the scope of the trial with medicinal products provided specifically for the trial.

4.3.2 Other Restrictions

Subjects participating in the trial are not allowed to have any of the following addictive substance abuse as listed below:

- Any current or past (1 year prior to randomisation) abuse of alcohol or drugs
- Any current or past (3 months prior to randomisation) smoking habit of more than 20 cigarettes per day
- Any current (1 month prior to randomisation) intake of more than 14 units of alcohol per week

4.4 Withdrawal Criteria

Withdrawal from Trial
The subjects have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the investigator should record the reason for the subject's withdrawal, if possible. The investigator also has the right to withdraw subjects. 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.

Withdrawal of Consent
If the subject withdraws her consent, no further data will be obtained. However, already obtained samples may be analysed. This will be described in the informed consent. The subject can request destruction of samples which would otherwise have been kept in storage.

4.5 Subject Replacement

A subject can only be assigned one screening number and one randomisation number. Subjects who discontinue prematurely from the trial after randomisation are not to be replaced, i.e. randomisation numbers are uniquely linked to each subject and cannot be re-used.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products (IMPs)

Subjects who meet the criterion for triggering of final follicular maturation will be randomised in a 1:1:1 ratio to either HP-hCG 5,000 IU IM, HP-hCG 5,000 IU SC, or rhCG 250 µg SC (Table 5-1). Administration of hCG will take place on the day of reaching the criterion for triggering of final follicular maturation (≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm).

Table 5-1 Investigational Medicinal Products (IMPs)

IMP	Trade name	Dose
HP-hCG	CHORAPUR	A single 5,000 IU IM or SC injection on the day of reaching the criterion for triggering of final follicular maturation.
rhCG	OVIDREL/ OVITRELLE [a)]	A single 250 µg SC injection on the day of reaching the criterion for triggering of final follicular maturation.

[a)] OVIDREL is the trade name in Brazil and OVITRELLE is the trade name in Europe.

5.1.2 Non-Investigational Medicinal Products (NIMPs)

As concomitant therapy in the controlled ovarian stimulation cycle, subjects will use the following non-investigational medicinal products (NIMPs) as illustrated in Table 5-2.

Table 5-2 Non-Investigation Medicinal Products (NIMPs)

NIMP	Trade name	Dose
HP-hMG	MENOPUR	150 IU SC injection once daily as starting dose on day 2-3 of the menstrual cycle. Potential dose adjustments based on the subject's response as observed on transvaginal ultrasound, depending on the centre's practice and the investigator's judgement.
GnRH antagonist (cetrorelix acetate)	CETROTIDE	0.25 mg SC injection once daily, starting on stimulation day 6 and continued throughout the stimulation period.
Progesterone	UTROGESTAN	3 × 200 mg daily as vaginal capsules, starting on the day of or the day after oocyte retrieval, depending on the centre's practice, and continued until the clinical pregnancy visit. Progesterone support can be terminated earlier in case of no transfer or a negative βhCG test or pregnancy loss.

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

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 and manufacturer of each medicinal product.

Table 5-3 Characteristics and Source of Supply of Medicinal Products

IMP / NIMP	Presentation	Manufacturer
CHORAPUR (HP-hCG)	CHORAPUR is provided as 1 vial with white lyophilised powder and 1 ampoule with 1 mL solvent. After reconstitution, 1 mL solvent contains 5,000 IU hCG.	Ferring Pharmaceuticals
OVIDREL/ OVITRELLE [a)] (rhCG)	OVIDREL/OVITRELLE [a)] (choriogonadotropin alfa) is provided as a pre-filled pen (0.5 mL) for single use delivering 250 µg choriogonadotropin alfa.	Merck Serono
MENOPUR (HP-hMG)	MENOPUR is provided in 1 vial with white lyophilised powder and 1 ampoule with 1 mL solvent containing 0.9% sodium chloride. After reconstitution, 1 mL solvent contains 75 IU of FSH activity and 75 IU of LH activity.	Ferring Pharmaceuticals
CETROTIDE (GnRH antagonist)	CETROTIDE (cetrorelix acetate) is provided as powder and solvent for solution for injection. After reconstitution, 1 mL solvent contains 0.25 mg cetrorelix.	Merck Serono
UTROGESTAN (progesterone)	UTROGESTAN is provided as vaginal capsules, each containing 200 mg of progesterone.	Besins Healthcare

[a)] OVIDREL is the trade name in Brazil and OVITRELLE is the trade name in Europe.

5.3 Packaging and Labelling

Packaging and labelling of the medicinal products will be performed under the responsibility of the IMP Department at Ferring in accordance with GMP and national regulatory requirements. Details on the packaging of each medicinal product are provided in Table 5-4.

Table 5-4 Packaging of Medicinal Products

IMP / NIMP	Packaging
CHORAPUR (HP-hCG)	CHORAPUR is provided in boxes containing 1 vial with white lyophilised powder and 1 ampoule with solvent for single use. The dry substance must be reconstituted with the solvent prior to use.
OVIDREL/ OVITRELLE [a)] (rhCG)	OVIDREL/OVITRELLE [a)] is provided in commercial boxes containing 1 pre-filled pen and 1 needle for single use.
MENOPUR (HP-hMG)	MENOPUR is provided in commercial boxes containing 5 vials with white lyophilised powder and 5 ampoules with 1 mL solvent each.
CETROTIDE (GnRH antagonist)	CETROTIDE is provided in commercial boxes containing 1 vial with powder, 1 pre-filled syringe with 1 mL solvent, 1 mixing needle and 1 injection needle for single use.
UTROGESTAN (progesterone)	UTROGESTAN is provided in commercial boxes containing 21 capsules; each capsule contains 200 mg micronized progesterone.

[a)] OVIDREL is the trade name in Brazil and OVITRELLE is the trade name in Europe.

All IMPs and NIMPs will be labelled with trial-specific labels, which contain a self-adhesive tear-off portion to be affixed to the Drug Accountability Form maintained at the trial site.

The content of the labels will be in accordance with Annex 13, EudraLex, volume 4 and national requirements.

5.4 Conditions for Storage and Use

A trial medication delegate, typically a trial nurse, will be identified at each site for handling trial medication related issues, including dispensing and/or administering IMP. The trial medication delegate 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 without delay and the medicinal products must not be used until further instructions from Ferring are received.

Conditions for storage of the medicinal products before and after dispensing to the subjects are listed in Table 5-5.

Table 5-5 Conditions for Storage of Medicinal Products

IMP / NIMP	Before dispensing to subject	After dispensing to subject
CHORAPUR (HP-hCG)	Do not store above 25°C. Do not freeze. Store in original package to protect from light.	Do not store above 25°C. Do not freeze. Store in original package to protect from light.
OVIDREL/ OVITRELLE [a)] (hCG)	Store in refrigerator at 2-8ºC. Do not freeze. Store in original package to protect from light.	Store in refrigerator at 2-8ºC. Do not freeze. Store in original package to protect from light.
MENOPUR (HP-hMG)	Do not store above 25°C. Do not freeze. Store in original package to protect from light.	Do not store above 25°C. Do not freeze. Store in original package to protect from light.
CETROTIDE (GnRH antagonist)	Do not store above 25°C. Do not freeze. Store in original package to protect from light.	Do not store above 25°C. Do not freeze. Store in original package to protect from light.
UTROGESTAN (progesterone)	Do not freeze. Store in original package. No other special storage conditions required.	Do not freeze. Store in original package. No other special storage conditions required.

[a)] OVIDREL is the trade name in Brazil and OVITRELLE is the trade name in Europe.

Depending on the storage facilities at the clinic, more restrictive temperature requirements (e.g. storage in refrigerator at 2-8ºC) than those listed in Table 5-5 may be implemented.

For information on warnings, precautions and treatment of overdose, please refer to the Investigator's Brochure for CHORAPUR and the Summary of Product Characteristics (SPC) for OVIDREL, MENOPUR, CETROTIDE and UTROGESTAN.

5.5 Blinding / Unblinding

5.5.1 Blinding

The trial is assessor-blind, and all investigators, embryologists and laboratory personnel will be blinded to treatment allocation throughout the trial. The trial staff dispensing and/or administering IMP, the trial coordinators, the in-field monitors and the participating subjects will know the treatment allocation once the subjects are randomised. Precaution must be taken to ensure that the treatment allocations are not available to the investigators or other assessors throughout the trial. Subjects must be clearly instructed to only discuss their treatment allocation with the trial staff dispensing and/or administering IMP and not to mention it to the investigator.

The randomisation 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 on the e-CRF will not be accessible to assessors or the Ferring clinical trial team or laboratory personnel during the trial.

The Ferring clinical trial team (except IMP Department members) will be blinded to treatment allocation until breaking of the blind. The blind will be broken when the trial database is declared clean and locked.

5.5.2 Unblinding of Individual Subject Treatment

Emergency decoding envelopes will be available to the investigator and designated persons at Ferring. Breaking of the blind for individual subjects in emergency situations is only permitted in case of a suspected unexpected serious adverse reaction (SUSAR) or in case of an important adverse event where the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and Ferring. The person who opens a code envelope must record on it the reason and the date of opening, and then sign and date the opened envelope. It should be recorded in the e-CRF that the code is broken, why, when and by whom. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding.

In case of accidental unblinding (e.g. the subject tells the investigator), the same documentation as for emergency unblinding must be obtained, i.e. the code envelope must be opened and why, when and by whom must be noted both on the code envelope and in the e-CRF, and the event must also be recorded in the subject's medical record.

It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities and/or EC. 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 must be collected before the database is declared clean and locked.

5.6 Dispensing and Accountability, Return and Destruction

To maintain blinding, the investigator will not be involved in any handling of medicinal products (neither IMP nor NIMP). The trial medication delegate will maintain subject dispensing logs, detailing the dates, quantities and batch numbers of dispensed and returned IMP and NIMP for each subject. The trial medication delegate will also manage the overall drug accountability at the site.

The monitor will verify drug accountability of IMP and NIMP throughout the trial and will document any discrepancies.

Concerning destruction, the trial medication delegate at the site must ensure destruction of used IMPs and NIMPs in accordance with local legislation after drug accountability has been verified by the monitor and signed off by the trial medication delegate, while un-used IMPs and NIMPs will be returned for destruction as instructed by the IMP Department of Ferring.

5.7 Auxiliary Supplies

Ferring will supply safety containers for the collection of used pens, syringes, vials and needles under request from the clinics.

6 TRIAL PROCEDURES

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

Table 6-1 Trial Flow Chart

	Screening	Pre-treatment	Treatment	Post-treatment				End
	Eligibility	COS	Triggering Randomisation/ hCG administration [a]	Oocyte retrieval (OR)	Trans-fer	Pregnancy monitoring		End-of-trial
						βhCG	Clinical	
Timing	<90 days before randomisation		The day of reaching the triggering criterion	36h ±2h after triggering	Day 3/5 after OR	13-15 days after transfer	5-6 weeks after transfer	[b]
Written informed consent	X							
Inclusion/exclusion criteria	X	X [c]	X [d]					
Demographics	X							
Medical history	X							
Infertility history	X							
Menstrual history	X							
Reproductive history	X							
Body measurements	X							X
Physical examination	X							X
Gynaecological examination	X							X
Urinary pregnancy test	X	X [c]						
Transvaginal ultrasound	X	X [e]	X [d]				X	
Blood collection (endocrine and anti-hCG antibodies)			X [d]		X [f]	X [f]		
HP-hMG for COS		X						
GnRH antagonist		X [g]						
Randomisation			X					
IMP administration			X					
Local tolerability			X					
Oocyte retrieval				X				
Progesterone for luteal phase support [h]				X	X	X	X	
Embryo / blastocyst transfer					X			
βhCG test						X		
Drug accountability		X		X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
End-of-trial form								X

[a] Randomisation and administration of hCG take place on the day of reaching the criterion for triggering of final follicular maturation, i.e. ≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm observed on transvaginal ultrasound.
[b] End-of-trial form must be completed at the subject's last scheduled visit or within 2 weeks after last scheduled visit in case of premature discontinuation. All subjects with a vital pregnancy will be followed up after the end of trial.
[c] Performed before start of stimulation.
[d] Performed at the end of stimulation visit before randomisation.
[e] Performed on stimulation day 1, 6 and hereafter at least every other day until the end of stimulation.
[f] Blood collection for anti-hCG antibodies is only performed for subjects who have attended the transfer and βhCG visits.
[g] GnRH antagonist will be initiated on stimulation day 6 and continued throughout stimulation.
[h] Progesterone can start on the day of or the day after oocyte retrieval and should continue until clinical pregnancy visit (can be discontinued earlier in case of no embryo / blastocyst transfer, a negative βhCG test or pregnancy loss).

Abbreviations: COS=controlled ovarian stimulation, h=hour(s), hCG=human chorionic gonadotropin, HP-hMG=highly purified menotropin, IMP=investigational medicinal product, OR=oocyte retrieval

6.1 At All Visits

The following will be done at all visits throughout the trial:

- Drug accountability, if applicable
- Recording of use of any concomitant medication (for screening visit: within the last 3 months prior to signing informed consent for participation in the trial)
- Recording of adverse events (for screening visit: from the date of signed informed consent for participation in the trial)

6.2 Screening

Potential participants will be scheduled to come to the clinic for the screening assessments. Screening must be initiated within 90 days before randomisation (corresponding to around 75 days before stimulation day 1).

The following must take place during the screening period:

- Signed and dated written informed consent, obtained prior to any trial-related procedures
- Allocation of a screening number
- Check of inclusion and exclusion criteria (those which are possible to check at screening)
- Demographics (age, ethnicity, race)
- Collection of the following data:
  - Medical history
  - Infertility history
  - Menstrual history
  - Reproductive history
- Body measurements (body weight, height) [*note*: these are used for calculation of BMI]
- Physical examination
- Gynaecological examination and transvaginal ultrasound
- Urinary pregnancy test – must be negative

Subjects considered eligible for the trial based on the inclusion and exclusion criteria assessed at this time point may proceed to the next visit, scheduled on day 2-3 of the menstrual cycle.

6.3 Controlled Ovarian Stimulation

On day 2-3 of the menstrual cycle, subjects will attend the stimulation day 1 visit. GnRH antagonist must be started on stimulation day 6. The other visits during the stimulation period will be scheduled according to individual's response, the investigator's judgement and the clinic's practice; however, transvaginal ultrasound must be performed on stimulation day 1, 6 and hereafter at least every other day until the end of stimulation.

The following must take place:

At stimulation day 1 visit

Prior to start of HP-hMG administration

- Ensure that the subject is still eligible for participation in the trial
- Check those inclusion and exclusion criteria that were not possible during screening
- Urinary pregnancy test – must be negative
- Transvaginal ultrasound of ovaries (number and size of follicles; in case one of more follicles ≥10 mm are observed on the transvaginal ultrasound, these functional cysts may be punctured prior to start of HP-hMG, or the start of controlled ovarian stimulation may be delayed to the next cycle)

After confirmation of eligibility for HP-hMG administration

- Dispense and/or administer HP-hMG (starting from stimulation day 1; the starting dose of HP-hMG is 150 IU once daily, followed by potential dose adjustments according to individual response; the first administration of HP-hMG takes place at the clinic and can be done by the trial medication delegate, another qualified trial staff, or by the subject herself under supervision of the aforementioned person)

At stimulation day 6 visit and visits hereafter until the end of stimulation

- Dispense and/or administer GnRH antagonist (starting from stimulation day 6; the first administration of GnRH antagonist takes place at the clinic and can be done by the trial medication delegate, another qualified trial staff or by the subject herself under supervision of the aforementioned person)
- Transvaginal ultrasound must be performed on stimulation day 6 and hereafter at least every other day until the end of stimulation

6.4 Randomisation / hCG Administration

Randomisation occurs at the end of stimulation visit when the subject reaches the following criterion (hCG criterion) for triggering of final follicular maturation as observed on transvaginal ultrasound:

- ≥3 follicles with a diameter ≥17 mm **and**
- <25 follicles with a diameter ≥12 mm

Subjects who do not meet the hCG criterion are considered screening failures and will not proceed to randomisation.

Subjects who meet the hCG criterion will have the following procedures / assessments prior to randomisation:

- Ensure that the subject is still eligible for participation in the trial
- Check the inclusion and exclusion criteria that were not possible during stimulation

- Blood collection for analysis of endocrine profile (estradiol, progesterone and hCG) and potential analysis of anti-hCG antibodies

If the subject fulfils all inclusion and exclusion criteria, she will proceed to randomisation:

- Randomisation, i.e. assignment to the lowest available subject number within stratum and thereby allocation to either 5,000 IU HP-hCG IM, 5,000 IU HP-hCG SC or 250 µg rhCG SC
- Dispense IMP according to randomisation
- Hand out the diary to the subject for local tolerability assessment

The IM administration of IMP should be done by the trial medication delegate or another qualified trial staff, while the SC administration of IMP can also be done by the subject under supervision of the trial medication delegate or another qualified trial staff. In either administration route, the subject should be under observation by the trial medication delegate or another qualified trial staff in the immediate period after the administration. Care must be taken to ensure blinding of the investigator and other assessors.

After the administration of IMP, the subject must do the following:

- Assessment of local tolerability (recorded in a diary) – the first evaluation of injection site reactions (redness, pain, itching, swelling and bruising) is done immediately after the injection of IMP, followed by the second evaluation 30 minutes after injection of IMP and the third evaluation 24 hours after injection of IMP

The next visit is the oocyte retrieval visit, which must be scheduled 36h (±2h) after the hCG administration.

6.5 Oocyte Retrieval

Oocyte retrieval must take place 36h (±2h) after hCG administration. All oocytes from follicles with an estimated diameter ≥12 mm should be retrieved.

The following must take place at the oocyte retrieval visit:

- Oocyte retrieval. Oocytes must be cultured individually in separate dishes / droplets.
- Assessment of maturity stage (applicable for oocytes undergoing ICSI)
- Insemination within 6h after retrieval using IVF or ICSI using ejaculated sperm (fresh or frozen) from partner or donor
- Dispensing of progesterone for luteal support – should be started on the day of or the day after oocyte retrieval, depending on the clinic's practice, and continued until the clinical pregnancy visit (can be discontinued earlier in case of no embryo / blastocyst transfer, a negative βhCG test or pregnancy loss)
- Collection of diary pages

For subjects with no oocytes retrieved, the next visit is the end-of-trial visit (section 6.9).

Day 1 after Oocyte Retrieval

Fertilisation of oocytes will be assessed on day 1 after oocyte retrieval by counting the number of pronuclei in oocytes. Correct fertilisation is defined as oocytes with 2PN. For subjects with oocytes retrieved, the next visit is the transfer visit 3 or 5 days after oocyte retrieval (section 6.6).

6.6 Day of Transfer (Day 3 or 5 after Oocyte Retrieval)

Transfer can be performed on day 3 (embryo stage) or on day 5 (blastocyst stage) after oocyte retrieval, depending on the investigator's judgement and local clinical practice. On day 3 after oocyte retrieval, the total number of embryos and the number of good-quality embryos defined as ≥6 blastomeres and ≤20% fragmentation will be assessed. In case of continued oocyte culture, the total number of blastocysts and the number of good-quality blastocysts defined as at least 3BB[a] according to the classification system by Gardner and Schoolcraft[16] will be assessed on day 5 after oocyte retrieval.

The subject-related procedures are described below:

- Blood collection for analysis of endocrine profile (estradiol, progesterone and hCG) and potential analysis of anti-hCG antibodies
- Transfer of 1-2 embryos on day 3 or transfer of 1-2 blastocysts on day 5
- Dispensing of progesterone for luteal phase support – should be continued until the clinical pregnancy visit (can be discontinued earlier in case of no embryo / blastocyst transfer, a negative βhCG test or pregnancy loss)

Assisted hatching is prohibited.

The actual number of embryos / blastocysts transferred for each subject depends on the availability of embryos / blastocysts, local regulations and clinical practice for the subject's age. Any surplus embryos / blastocysts can be managed according to local practices.

For subjects with embryo or blastocyst transfer, the next visit is the βhCG test visit which must be scheduled 13-15 days after transfer (section 6.7).

For subjects with no embryo or blastocyst transfer, the next visit is the end-of-trial visit (section 6.9).

6.7 βhCG Test

Subjects who have undergone transfer must attend a visit 13-15 days after transfer.

The following must take place:

- Blood collection for local laboratory analysis of βhCG
- Blood collection for analysis of endocrine profile (estradiol, progesterone and hCG) and potential analysis of anti-hCG antibodies

[a] At least 3BB: Blastocyst expansion and hatching status 4, 5, 6 (independent of inner cell mass and trophectoderm) and blastocyst expansion and hatching status 3 with inner cell mass and tropectoderm gradings of A or B.

- Dispensing of progesterone for luteal phase support – should be continued until the clinical pregnancy visit (can be discontinued earlier in case of no embryo / blastocyst transfer, a negative βhCG test or pregnancy loss)

The blood sample for βhCG will be analysed by the local laboratory and evaluated according to the local reference ranges. In case of a doubtful βhCG result, the test may be repeated. Subjects with a positive βhCG test must attend a clinical pregnancy visit 5-6 weeks after transfer (section 6.8). Subjects with a negative βhCG test must proceed to the end-of-trial assessments (section 6.9).

6.8 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

If at least one gestational sac (either intrauterine or ectopic) is observed, this confirms a clinical pregnancy. If at least one intrauterine gestational sac with fetal heart beat is observed, this confirms a vital pregnancy. All subjects, irrespective of the result of the pregnancy monitoring, will proceed to the end-of-trial assessments (section 6.9). In addition, subjects with a vital pregnancy will be followed up (section 6.10).

6.9 End-of-trial

If a subject attends the scheduled trial visits, the end-of-trial assessments should take place at the subject's last scheduled trial visit or within 2 weeks after last scheduled visit in case of premature discontinuation.

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

- Body measurements (body weight)
- Physical examination
- Gynaecological examination
- Completion of end-of-trial form

6.10 Post-trial Activities

All subjects with a vital pregnancy will be followed up until delivery for pregnancy outcome data. Furthermore, data will be gathered on neonatal health at birth. These data will be reported separately.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Primary Endpoint

7.1.1 Number of Oocytes Retrieved

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

7.2 Assessments Related to Secondary Endpoints

7.2.1 Number of Metaphase II Oocytes

Maturity stage will be assessed prior to insemination for oocytes that will undergo ICSI. Maturity stage will be categorised as germinal vesicle, metaphase I, metaphase II (MII), degenerated or other.

7.2.2 Number of Fertilised Oocytes

On day 1 after oocyte retrieval, fertilisation will be assessed by counting the number of pronuclei, which will be recorded as 0, 1, 2 or >2. Correct fertilisation is defined as oocytes with 2PN.

7.2.3 Fertilisation Rate

Fertilisation rate is calculated as the rate of fertilised oocytes to oocytes retrieved for subjects with oocytes retrieved and the rate of fertilised oocytes to MII oocytes for subjects with ICSI insemination.

7.2.4 Positive βhCG Rate

A blood βhCG test must be obtained 13-15 days after transfer. If the test is positive according to the local laboratory's reference ranges, this confirms a positive βhCG.

7.2.5 Clinical Pregnancy Rate

A transvaginal ultrasound of the uterus will be performed 5-6 weeks after transfer. Clinical pregnancy will be defined as at least one gestational sac, either intrauterine or ectopic. The inclusion of ectopic pregnancies and the lack of specification of heart beat in the definition of clinical pregnancy is in line with the current International Committee Monitoring Assisted Reproductive Technologies (ICMART) and World Health Organization (WHO) glossary on ART terminology.[b,17] For intrauterine and ectopic pregnancies, the number of gestational sacs with fetal heart beat as well as without fetal heart beat will be recorded.

[b] ICMART and WHO glossary on ART terminology: Clinical pregnancy – a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancy.

7.2.6 Vital Pregnancy Rate

A transvaginal ultrasound of the uterus will be performed 5-6 weeks after transfer. Vital pregnancy will be defined as at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer.

7.2.7 Circulating Levels of Endocrine Parameters

A blood sample will be collected at the end-of-stimulation visit prior to randomisation, at transfer and at the βhCG visit for analysis of endocrine profile (estradiol, progesterone and hCG). These samples will be analysed at a central laboratory. The investigator will review and evaluate the laboratory results. The laboratory report will be signed and dated by the investigator.

7.2.8 Number and Quality of Embryos on Day 3

On day 3 after oocyte retrieval, the total number of embryos and the number of good-quality embryos will be assessed and recorded.

The quality evaluation of embryos will consist of the following morphological parameters:

- number of blastomeres (1, 2, 3, 4, 5, 6, 7, 8…)
- degree of fragmentation (≤20%, >20%)

A good-quality embryo is defined as ≥6 blastomeres and ≤20% fragmentation.

For the transferred embryos, the two quality parameters above (number of blastomeres and degree of fragmentation) must be recorded.

7.2.9 Number and Quality of Blastocysts on Day 5

On day 5 after oocyte retrieval, the total number of blastocysts and the number of good-quality blastocysts will be assessed and recorded.

The quality evaluation of blastocysts will consist of the following morphological 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.[16]

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

A. Tightly packed, many cells
B. Loosely grouped, several cells
C. Very few cells

Trophectoderm grading will be assessed as one of the following:

A. Many cells forming a cohesive epithelium
B. Few cells forming a loose epithelium
C. Very few, large cells

Blastocysts with expansion and hatching status 3-6 will have a score combining the three 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.

A good-quality blastocyst is defined as at least 3BB: blastocyst expansion and hatching status 4, 5, 6 (independent of inner cell mass and trophectoderm gradings) and blastocyst expansion and hatching status 3 with inner cell mass and trophectoderm gradings of A or B.

For the transferred blastocysts, the three quality parameters above (blastocyst expansion and hatching status, inner cell mass and trophectoderm) must be recorded.

7.2.10 Frequency and Intensity of Adverse Events

Adverse events (see definition in section 8.1) will be recorded from signing the 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. Furthermore, the pattern (e.g. the frequency, time of onset, intensity, seriousness and outcome) of the most frequent / relevant adverse events will be tabulated (see section 9.8.2).

7.2.11 Early and Late OHSS Rates

Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation and late OHSS as OHSS with onset >9 days after triggering of final follicular maturation. Classification of grade is according to Golan's classification system[18] (see section 8.3.1 for details) and all OHSS cases will be graded as mild, moderate or severe (*note*: the classification "mild OHSS", "moderate OHSS" and "severe OHSS" does not refer to the classification of an adverse event's intensity that is also rated mild, moderate, or severe).

7.2.12 Frequency and Intensity of Injection Site Reactions

The subjects will assess the local tolerability of the injections of IMP at three time points relative to the administration: immediately after the injection, 30 minutes after the injection and 24 hours after the injection. 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.

7.3 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 at screening. This includes diagnoses / symptoms and whether it is a past or ongoing occurrence.

7.3.3 Infertility History

Information about the reasons 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.

7.3.4 Menstrual History

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

7.3.5 Reproductive History

Information about the reproductive history regarding natural conception 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.

7.3.6 Body Measurements

Body measurements will be made at screening and end-of-trial. Body weight will be measured at both visits, and will be done without shoes and overcoat and using a calibrated scale. Height will

only be measured at screening and will be used to calculate BMI.

7.3.7 Physical Examination

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.

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.

7.3.8 Gynaecological Examination

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

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 Number and Size of Follicles during Stimulation

Transvaginal ultrasound will be performed during the stimulation period to count the number of follicles and measure the size of follicles. Data on the number and size of follicles will be collected prior to start of stimulation on stimulation day 1, stimulation day 6 and at the end of stimulation. Data will be recorded separately for the right and left ovary.

7.3.10 Anti-hCG Antibodies

Blood samples for potential analysis of anti-hCG antibodies will be collected at the end-of-stimulation visit prior to randomisation, the transfer visit and the βhCG visit. Samples are taken only for subjects who have attended the transfer and βhCG visits.

7.3.11 Concomitant Medication

The use of any concomitant medication within the last 3 months prior to signing the informed consent for participation in the trial (except medication used in previous infertility treatment cycles) 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.

7.3.12 Drug Dispensing and Accountability

For all medicinal products, dates of administration and dose administered will be recorded. Furthermore, time of administration will also be recorded for IMP, HP-hMG and GnRH antagonist. Details on drug dispensing and accountability are provided in section 5.6.

7.3.13 End-of-Trial Form

An end-of-trial form must be filled in at the subject's last visit, irrespective of whether the subject completes the trial or not. Completion / discontinuation status will be recorded, as well as date and reason for discontinuation in case the subject did not complete the trial.

7.4 Assessments Related to Post-trial Information

All subjects with a vital pregnancy will be followed till delivery to gather information on pregnancy outcome, e.g. live birth. Furthermore, data will be gathered on neonatal health at birth, including gender, birth weight and length as well as information on minor/major congenital anomalies.

These data will be reported separately.

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. All biological samples will be analysed 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 is the blood sample for βhCG, which is analysed by a local laboratory at the trial clinic 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, and biobank / 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 unfavourable 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 gynaecological examination assessed as clinically significant by the investigator [*note*: findings from assessments and examinations done during screening are not adverse events, but are recorded as medical history.]
- Accidental injuries, reasons for any change in medication (drug and/or dose) (not applicable for HP-hMG dose adjustment), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors that relate to IMP with and without clinical consequences.

All adverse events will be coded by Ferring Global Pharmacovigilance using 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. hospitalisation).

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.[c]

Note: A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalisation is not an adverse event; the reason for hospitalisation 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.

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

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.

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

Examples:

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

Action Taken to IMP

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

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

Other Action Taken
Adverse events requiring therapy must be treated with recognised 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
- Not yet recovered
- Fatal

8.3 Adverse Events of Special Interest

8.3.1 Ovarian Hyperstimulation Syndrome (OHSS)

Symptoms and Classification
OHSS is an adverse event of special interest during controlled ovarian stimulation. Investigators will record OHSS symptoms and will use Golan's system[18] 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

Mild OHSS	
Grade 1	Abdominal distension and discomfort
Grade 2	Features of grade 1 plus nausea/vomiting and/or diarrhoea. 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 haemoconcentration, coagulation abnormalities, and diminished renal perfusion and function.[d)]

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

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

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

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

All cases of OHSS must be reported as adverse events. Those that fall under the category serious adverse events must be reported as such. Note that the classification ‘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).

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.

8.3.2 Local Tolerability

Injection site reactions after administration of IMP are only to be reported as adverse events if they require active management, i.e. 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.

8.3.3 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.

8.3.4 Pregnancy Loss

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 an 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

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within 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 **hospitalisation** or prolongation of existing hospitalisation	The term hospitalisation means that the subject was admitted to hospital or that existing hospitalisation was extended as a result of an event. Hospitalisation 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 hospitalisation. 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). Hospitalisations for administrative or social purposes do not constitute a serious adverse event. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability / incapacity**	Disability / incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly / birth defect observed in any offspring of the subject conceived during treatment with the IMP.
is an **important medical event**	Important medical events are events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include adverse events that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a medicinal product.

Serious Adverse Event during Post-trial Follow-up

The following untoward medical occurrences reported as part of the pregnancy outcome and neonatal health data collection will be recorded as serious adverse events. Data will be collected at birth.

- Death of mother in connection with pregnancy or labour
- Death of neonate
- Stillbirth
- Neonate admitted to the neonatal intensive care unit (NICU) or neonatal care unit (NCU)
- Congenital anomaly / birth defect

In case of admission to NICU or NCU, the reason for admission must be reported as a serious adverse event, rather than just the act of hospitalisation.

Congenital anomalies will be coded using both MedDRA and ICD-10 and classified as minor or major[d] in accordance with the EMA guideline.[19]

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

Serious Adverse Event Reporting by the Investigator

All serious adverse events must be reported **immediately** to Ferring Global Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of a serious adverse event.

The investigator is responsible for submitting the completed Serious Adverse Event (SAE) Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the serious adverse event.

Serious Adverse Event (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 from cannot be filled in within the e-CRF system, a paper SAE report form should be used and sent to Ferring Global Pharmacovigilance using the contact details below.

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: safety.mailbox@ferring.com
Fax: (+45) 8838 0147

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 Global Pharmacovigilance to access the information.

[d] 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.

Additional information relevant to the serious adverse events 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 Global 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 EC with any additional requested information such as results of post-mortem examinations and hospital records.

Expedited Reporting by Ferring

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

The expectedness is assessed by Ferring according to the Investigator's Brochure for CHORAPUR and the SPC for OVIDREL.

Serious adverse events will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the protocol, Investigator's Brochure and labelling.

8.5 Follow-up of Adverse Events and Serious Adverse Events

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

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

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

8.5.2 Collection of Serious Adverse Events with Onset after End-of-Trial

If an investigator becomes aware of a serious adverse event after the end of the trial, and he/she assesses the serious adverse event to have a reasonable possible causality to the IMP (HP-hCG IM, HP-hCG SC or rhCG SC) or a NIMP where Ferring is Marketing Authorisation Holder (i.e. HP-hMG), the case will have to be reported to Ferring Global Pharmacovigilance (safety.mailbox@ferring.com), regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

The Ferring Global Biometrics Department will be responsible for the statistical analyses of the primary and secondary endpoints. This section details the planned statistical analyses for the primary endpoint and outlines the planned statistical analyses 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) available before breaking the blind of the trial. A separate SAP will be prepared to cover reporting of the post-trial activities (pregnancy outcome and neonatal health at birth).

9.1 Determination of Sample Size

The primary objective of this trial is to demonstrate non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg for triggering of final follicular maturation with respect to number of oocytes retrieved in women undergoing controlled ovarian stimulation. The primary endpoint is the number of oocytes retrieved.

The trial has three arms: HP-hCG 5,000 IU IM, HP-hCG 5,000 IU SC, and rhCG 250 µg SC.

Non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg will be established by doing the comparisons in sequential order as follows:

1) HP hCG 5,000 IU IM vs. rhCG 250 µg SC
2) HP hCG 5,000 IU SC vs. rhCG 250 µg SC
   This will only be evaluated if the first comparison establishes non-inferiority

The non-inferiority margin has been set at -3.0 oocytes (section 3.5.1). Non-inferiority will be evaluated using a two-sided 95% confidence interval for the difference between treatment groups. Non-inferiority will be claimed if the lower limit of this confidence interval is greater than the non-inferiority margin.

The trial is dimensioned to have 90% power of achieving the primary objective for the first comparison and approximately 80% power for establishing non-inferiority for both comparisons.

Since this is a non-inferiority trial, the per-protocol (PP) and the intention-to-treat (ITT) analyses are equally important, i.e. non-inferiority should be established for both populations in order to have a robust conclusion.[20, 21]

The primary analysis will be based on an analysis of variance (ANOVA) model including treatment, randomisation stratum and trial site as factors. It is assumed that the three treatments are equivalent with respect to number of oocytes retrieved. The number of oocytes retrieved is assumed to follow a normal distribution with a mean of 10-12 and a standard deviation of 6.0. Under these assumptions, a sample size of 86 subjects per group will result in approximately 90% power to establish non-inferiority of the first comparison by using a non-inferiority margin of -3.0 oocytes. It is expected that the difference in the number of oocytes retrieved between the HP-hCG groups and the rhCG group has to be less than 1.2 in order to meet the non-inferiority margin of -3.0. As an example, if the average number of oocytes retrieved in the rhCG group is 12.0, the average number of oocytes retrieved in the HP-hCG groups has to be at least 10.8 in order to establish non-inferiority.

The number of subjects with major protocol deviations affecting the primary endpoint is assumed to be negligible. Therefore the sample size has not been adjusted to account for major protocol deviations affecting the primary endpoint.

The standard deviation of the number of oocytes retrieved will be evaluated in a blinded manner. If the standard deviation is larger than 6.0, the sample size may be increased to a maximum of 348 subjects (116 subjects per group) corresponding to a standard deviation of 7.0. Blinded monitoring of the assumptions underlying the sample size is recommended specifically for non-inferiority trials by FDA[20] and in general by EMA.[21]

9.2 Subject Disposition

All screened subjects will be accounted for.

Screened subjects who discontinue from the trial prior to randomisation are regarded as screening failures. Screening failures and their primary reason for screening failure will be tabulated. Screening failures will not otherwise be accounted for.

Subject disposition with respect to analysis sets will be tabulated by treatment group overall and by randomisation stratum for all randomised subjects. This table will include the number of completed and discontinued subjects including reason for discontinuation. A separate table will summarise the subject disposition with respect to analysis sets by trial site overall and by stratum.

The number of subjects completed and discontinued (including reason) will be tabulated by treatment group overall and by randomisation stratum for the following trial parts: triggering of final follicular maturation, oocyte retrieval, transfer, pregnancy monitoring and end-of-trial. This table will be produced for the ITT analysis set overall and by stratum. A separate table will summarise the details on embryo / blastocyst transfer including day of transfer and number of transferred embryos / blastocysts.

Subject disposition with respect to analysis sets will be listed for all randomised subjects including information on trial completion and reason for discontinuation for non-completers. Subjects who discontinued from the trial will also be listed separately.

9.3 Protocol Deviations

Protocol deviations will be rated as minor or major. Major protocol deviations impacting the primary endpoint and thereby affecting the conclusions will lead to exclusion of subjects from the PP analysis set. Subjects will not be excluded from the PP analysis set in case of only minor protocol deviations.

The list of major protocol deviations impacting the primary endpoint includes, but is not restricted to the following:

1) hCG administered but triggering criterion is not met
2) Wrong dose of hCG administered
3) Oocyte retrieval not performed 36h (±2h) after hCG administration

The sponsor's Medical Officer at Ferring Global Clinical R&D, the sponsor's Medical Officer in Brazil, and the project-responsible statistician at Ferring Global Biometrics will perform a blinded review of data before declaration of clean file and lock of database and rate protocol deviations as minor or major. The list of major protocol deviations will be detailed and documented in the clean file document prior to database release. Major protocol deviations impacting the primary endpoint will be tabulated and listed by subject for the ITT analysis set.

9.4 Analysis Sets

9.4.1 Intention-to-Treat (ITT) Analysis Set

The ITT analysis set is defined as all randomised subjects. Subjects will be analysed according to planned (randomised) treatment.

9.4.2 Full Analysis Set (FAS)

The full analysis set (FAS) is defined as all subjects randomised and exposed to IMP. Subjects will be analysed according to planned (randomised) treatment received.

9.4.3 Per-Protocol (PP) Analysis Set

The PP analysis set is defined as all subjects randomised and exposed to IMP except those excluded as a result of major protocol deviations as described in section 9.3. Subjects will be analysed according to actual treatment received.

9.4.4 Safety Analysis Set

The safety analysis set is defined as all subjects randomised and exposed to IMP. Subjects will be analysed according to actual treatment received.

9.5 Trial Population

9.5.1 General Considerations

All relevant baseline data will be tabulated by treatment group and overall. Continuous variables will be presented with number of subjects, mean, standard deviation, median, inter-quartile range, minimum, and maximum. Categorical variables will be presented with number and percentage of subjects within each specific category. The purpose of these tabulations is to characterise the treatment groups and assess the degree of similarity achieved by the randomisation. Baseline data will not be compared using statistical tests. Unless otherwise noted, tabulations will be produced overall and by randomisation stratum for both the ITT and the PP analysis sets.

All baseline data will be listed by subject for the ITT analysis set.

Unless otherwise noted, missing data will not be imputed.

9.5.2 Demographics

Age, 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) will be tabulated.

9.5.3 Body Measurements

Height (m), weight (kg) and BMI (kg/m^2) obtained at screening will be tabulated.

9.5.4 Number and Size of Follicles during Stimulation

The number of follicles and the average follicle size will be tabulated for stimulation day 1, stimulation day 6 and end of stimulation.

9.5.5 Endocrine Parameters

The following endocrine parameters obtained on the day of triggering before exposure to IMP will be tabulated: estradiol (pmol/L), progesterone (nmol/L), and hCG (IU/L). Values below the lower limit of quantification (LLOQ) will be included as LLOQ/2. Values above the upper limit of quantification (ULOQ) will be included as ULOQ.

9.5.6 Medical History

All recorded medical history will be coded using MedDRA. The version of MedDRA will be documented. Medical history will be summarised for each medical item. This summary table will only be produced overall (i.e. not by stratum) for the ITT.

9.5.7 Infertility History

Primary reason for infertility and duration of infertility will be tabulated. The table will also include the proportion of subjects with primary infertility. Primary infertility is defined as no previous clinical pregnancy. Information on previous fertility treatment will be summarised including type of treatment and outcome.

9.5.8 Menstrual History

The average cycle length (days) will be tabulated.

9.5.9 Reproductive History

Reproductive history regarding natural conception will be tabulated including number of clinical pregnancies, number of fetuses and outcome.

9.5.10 Physical Examination and Gynaecological Examination

Physical examination and gynaecological examination will be listed by subject and summarised per category. These summary tables will only be produced overall (i.e. not by stratum) for the ITT analysis set.

9.5.11 Concomitant Medication

Concomitant medications will be coded using the WHO Drug Reference List. Prior and concomitant medication will be summarised by ATC classification 1st level alphabetically and ATC classification 2nd level in decreasing order of frequency. These medications will be tabulated separately for:

- Prior medication, i.e. medication taken exclusively prior to treatment (i.e. stopped before IMP administration)
- Concomitant medication, i.e. medication taken during the treatment period (i.e. medication that was not stopped before IMP administration and not started after the end-of-trial visit)

These summary tables will only be produced overall (i.e. not by stratum) for the ITT analysis set.

If the timing of the dose of a medication cannot be established in relation to the administration IMP, it will be considered as concomitant medication. Concomitant medications will be listed by subject.

9.6 Extent of Exposure and Treatment Compliance

Treatment non-compliance will be presented in listings, as non-compliance is expected to be limited.

9.7 Endpoint Assessments

9.7.1 General Considerations

The result of the analysis of the primary endpoint (number of oocytes retrieved) is essential for the non-inferiority claim. The number of MII oocytes (only applicable for insemination using ICSI) and the number of 2PN oocytes are considered the key secondary endpoints supportive of the primary endpoint. The analyses of the remaining secondary efficacy endpoints are intended to provide additional characterisation of the treatment effect.

The randomisation is stratified by the number of follicles ≥12 mm at the end of stimulation (two strata: <10 follicles and ≥10 follicles). Summary tables for the primary endpoint and the secondary efficacy endpoints will be presented overall and by randomisation strata for both the ITT and the PP analysis sets.

All statistical tests will be performed using a two-sided test at a 5% significance level. Treatment differences will, where appropriate, be presented with two-sided 95% confidence intervals and p-values corresponding to the hypothesis of "equal effect" against the alternative "different effect".

All primary and secondary efficacy endpoints will be listed for the ITT analysis set.

Multiplicity

No adjustment for multiplicity is required for the primary analysis, since there is only one primary endpoint and the evaluation is performed in a sequential manner. Concerning the secondary endpoints, no formal adjustment for multiplicity will be utilised. Statistically significant results among these secondary endpoints will be interpreted cautiously.

Missing Observations

Missing observations for the primary endpoint (number of oocytes retrieved) will be imputed as zero irrespective of the reason why data is not recorded.

Missing observations for the number of 2PN oocytes will be imputed as zero. This also includes subjects with no oocytes retrieved; these will have the number of 2PN oocytes set to zero.

For subjects who have all oocytes inseminated using ICSI, missing observations for the number of MII oocytes will be imputed as zero. For subjects who do not have any oocytes inseminated using ICSI, missing observations for the number of MII oocytes will not have a value imputed.

Missing observations for the βhCG assessment will be imputed as negative, unless a positive result is observed at the clinical pregnancy visit. For example, if the outcome of βhCG is missing but clinical pregnancy is "positive", βhCG will be imputed as "positive".

Missing observations for the clinical pregnancy assessment and vital pregnancy assessment will be imputed as "negative" irrespective of why data were not recorded.

9.7.2 Primary Endpoint

The primary objective of this trial is to demonstrate non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg for triggering of final follicular maturation with respect to number of oocytes retrieved in women undergoing controlled ovarian stimulation. The non-inferiority margin for the difference between treatments (HP-hCG 5,000 IU versus rhCG 250 µg) is set to -3.0 oocytes.

HP-hCG 5,000 IU is included in the trial using two different routes of administration, IM and SC. Non-inferiority of HP-hCG 5,000 IU compared with rhCG 250 µg will be established by doing the comparisons in sequential order as follows:

1) HP-hCG 5,000 IU IM vs. rhCG 250 µg SC
2) HP-hCG 5,000 IU SC vs. rhCG 250 µg SC
   This will only be evaluated if the first comparison establishes non-inferiority

The non-inferiority hypothesis to be tested for the primary endpoint is

$$H_0: OR_{HP\text{-}hCG} - OR_{rhCG} \leq -3.0$$

against the alternative

$$H_A: OR_{HP\text{-}hCG} - OR_{rhCG} > -3.0$$

where $OR_{HP\text{-}hCG}$ and OR_{rhCG} denotes the number of oocytes retrieved with HP-hCG 5,000 IU (IM or SC) and rhCG 250 µg SC, respectively.

For each comparison, the null hypothesis (H_0) will be tested against the alternative (H_A) by constructing a two-sided 95% confidence interval for the difference in number of oocytes retrieved. The confidence interval will be based on ANOVA model including treatment, randomisation stratum and trial site as factors. The primary endpoint will be analysed for the ITT and the PP analysis sets. Since this is a non-inferiority trial, the ITT and the PP analysis sets will have equal importance and should lead to similar conclusions for a robust interpretation.

Comparison 1: HP-hCG 5,000 IU IM versus rhCG 250 µg SC

If the lower-limit of the 95% confidence interval is greater than the non-inferiority limit (-3.0 oocytes), the null hypothesis will be rejected and it would be claimed that HP-hCG 5,000 IU IM is non-inferior to rhCG 250 µg SC with respect to number of oocytes retrieved.

Comparison 2: HP-hCG 5,000 IU SC versus rhCG 250 µg SC

If Comparison 1 establishes non-inferiority, the second comparison will be performed. If the lower-limit of the 95% confidence interval is greater than the non-inferiority limit (-3.0 oocytes), the null hypothesis will be rejected and it would be claimed that HP-hCG 5,000 IU SC is non-inferior to rhCG 250 µg SC with respect to number of oocytes retrieved.

If the 95% confidence interval for the treatment difference not only lies above the non-inferiority limit but also above zero, there is evidence of superiority in terms of statistical significance at the two-sided 5% level. In this case, the p-value from the test for superiority will be reported. There is no need for a multiplicity adjustment, since it is a simple closed test procedure. This interpretation is in line with EMA's "Points to consider on switching between superiority and non-inferiority".[22]

9.7.3 Secondary Endpoints

Number of Metaphase II Oocytes

Oocytes undergoing ICSI will have their maturity stage assessed prior to insemination. The number of MII oocytes per subject will be analysed in a similar manner as the primary endpoint. However, non-inferiority does not need to be formally established for this secondary endpoint. The number of MII oocytes per subject will be tabulated including both summary statistics and a frequency table. The table will also summarise the percentage of MII oocytes to oocytes retrieved for subjects who have all oocytes inseminated using ICSI.

Number of Fertilised Oocytes

The number of 2PN oocytes per subject will be tabulated including both summary statistics and a frequency table. The number of 2PN oocytes per subject will be analysed in a similar manner as the primary endpoint. However, non-inferiority does not need to be formally established for this secondary endpoint.

Fertilisation Rate

For subjects with oocytes retrieved, the rate of 2PN oocytes to oocytes retrieved will be tabulated. For subjects with all oocytes inseminated using ICSI, the rate of 2PN oocytes to MII oocytes will

be tabulated.

Number and Quality of Embryos on Day 3
The number of embryos and the number of good quality embryos available on day 3 will be tabulated. For embryos transferred on day 3, the number of blastomeres and the degree of fragmentation will be tabulated.

Number and Quality of Blastocysts on Day 5
The number of blastocysts and the number of good quality blastocysts available on day 5 will be tabulated. For blastocysts transferred on day 5, the blastocyst expansion and hatching status, blastocyst inner cell mass grading, trophectoderm grading and the combined score will be tabulated.

Positive βhCG Rate
The positive βhCG rate is defined as the proportion of subjects with positive serum βhCG test 13-15 days after transfer. No formal treatment comparison is planned since the trial is not powered for this secondary endpoint. The positive βhCG rate will be tabulated including two-sided 95% Clopper-Pearson confidence intervals for the within treatment effect. In addition, the positive βhCG rate may be presented by day of transfer (day 3 / day 5), number of embryos / blastocysts transferred (single transfer / double transfer) or quality of embryos / blastocysts transferred.

Clinical Pregnancy Rate
The clinical pregnancy rate is defined as the proportion of subjects with at least one gestational sac, either intrauterine or ectopic, 5-6 weeks after transfer. No formal treatment comparison is planned since the trial is not powered for this secondary endpoint. The clinical pregnancy rate will be tabulated including two-sided 95% Clopper-Pearson confidence intervals for the within treatment effect. For subjects with a positive clinical pregnancy assessment, the type of clinical pregnancy (intrauterine or ectopic) will be tabulated. In addition, the clinical pregnancy rate may be presented by day of transfer (day 3 / day 5), number of embryos / blastocysts transferred (single transfer / double transfer), or quality of embryos / blastocysts transferred.

Vital Pregnancy Rate
The vital pregnancy rate is defined as the proportion of subjects with at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer. No formal treatment comparison is planned since the trial is not powered for this secondary endpoint. The vital pregnancy rate will be tabulated including two-sided 95% Clopper-Pearson confidence intervals for the within treatment effect. For subjects with a positive vital pregnancy assessment, the number of intrauterine gestational sacs with fetal heart beat and the number of fetuses with fetal heart beat will be tabulated. In addition, the vital pregnancy rate may be presented by day of transfer (day 3 / day 5) , number of embryos / blastocysts transferred (single transfer / double transfer), or quality of embryos / blastocysts transferred.

Circulating Concentrations of Endocrine Parameters

Blood samples drawn at end-of-stimulation, at transfer and at the βhCG visit (13-15 days after transfer) are analysed for estradiol, progesterone and hCG. Each parameter and the change from baseline for post-baseline measurements will be tabulated. Values below the lower limit of quantification (LLOQ) will be included as LLOQ/2. Values above the upper limit of quantification (ULOQ) will be included as ULOQ.

For each parameter, the change from baseline will be compared between treatment groups using a linear normal model. In this model, change from baseline in ln-transformed measurements will be the dependent variable and the linear predictor will include treatment and randomisation stratum as factors and baseline measurement (ln-transformed) as covariate. The estimated treatment difference with two-sided 95% confidence interval will be presented on the scale of measurement (i.e. exp-transformed) and accompanied by the p-value for test of no treatment difference.

9.8 Safety

9.8.1 General Considerations

Safety parameters will be evaluated for the safety analysis data set.

9.8.2 Adverse Events

Adverse events will be coded using MedDRA. The version of MedDRA will be documented.

Adverse events will be grouped according to start of IMP as follows:

- Pre-treatment adverse event, i.e. any adverse event occurring after signed informed consent and before administration of IMP, or a pre-existing medical condition that worsens in intensity after signed informed consent but before administration of IMP
- Treatment-emergent adverse event, i.e. any adverse event occurring after administration of IMP and before the end-of-trial visit, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after administration of IMP and before the end-of-trial visit

Treatment-emergent adverse events will be presented in summary tables and listings. Pre-treatment adverse events will be presented in a listing only.

A treatment-emergent adverse event overview table will be prepared including 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 events, severe adverse events, adverse reactions, adverse events leading to discontinuation, serious adverse events and deaths. An adverse reaction is an adverse event judged by the investigator to be related to IMP with a reasonable possibility.

Treatment-emergent adverse events will be tabulated by system organ class (SOC) alphabetically and preferred term (PT) in decreasing order of frequency. 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.

Summary tables will be produced for the following: all adverse events, adverse events by causality (reasonable possibility / no reasonable possibility), adverse events leading to death, adverse events by intensity (mild / moderate / severe), adverse reactions by intensity (mild / moderate / severe), serious adverse events, adverse events leading to discontinuation, adverse events with an incidence of ≥5% in any treatment group, and non-serious adverse events with an incidence of ≥5% in any treatment group.

9.8.3 Early and Late OHSS

Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation. Late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation. Early and late OHSS will be tabulated by classification (mild, moderate, severe) and grade (1, 2, 3, 4, 5).

9.8.4 Injection Site Reactions

For each injection site reaction (redness, pain, itching, swelling and bruising), the number of events will be tabulated by time (immediately, 30 minutes, 24 hours) and intensity (none, mild, moderate and severe).

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(s) (date and time of oral information, date and time of handing out Informed Consent Form, date and time of obtaining written informed consent(s))
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical history, infertility history, menstrual history and reproductive history
- Visit dates
- Dates of administration of IMP
- Injection site reactions after IMP administration – diary
- Dates and daily doses of NIMP
- Dates and daily doses of concomitant medication
- Date of oocyte retrieval and number of oocytes retrieved
- Number of MII oocytes (only applicable for insemination using ICSI)
- Number of fertilised (2PN) oocytes
- Number and quality of embryos / blastocysts transferred and date of transfer
- Number of embryos / blastocysts and number of good-quality embryos / blastocysts available on the day of transfer
- Results of βhCG test and ultrasound at clinical pregnancy visit
- Pregnancy outcome, i.e. live birth or pregnancy loss, and neonatal health at birth
- Adverse events (description as well as start/stop date and time)

- OHSS symptoms and management
- 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, certified copies of medical records will be used to capture source data as applicable.

The source data for the endocrine parameters as well as anti-hCG antibodies (if analysed) will be available at the central laboratory. Laboratory reports will be available at the sites.

10.2 e-CRF

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

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

The investigator will approve / authorise 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 Target Health Inc. After the trial database is declared clean and locked, 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 Target Health Inc. The pdf-files will be stored on a CD and will be provided to the investigator before access to the e-CRF is revoked.

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

10.3 Data Management

A data management plan will be created under the responsibility of the Global Biometrics Department of 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 describe captured methods, who is authorised to enter the data, decisions about ownership of data, source data storage, which data will be transferred (including

timing of data transfers), the origin and destination of the data and who will have access to the data at all times.

10.4 Provision of Additional Information

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

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference of Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of 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 co-operate 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. The monitoring procedures are described in further detail in the Monitoring Plan.

11.2 Audit and Inspection

The investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by Ferring, or to domestic / foreign regulatory inspectors or representatives from EC who may audit / inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki[23] and all other relevant regulations.

The subjects must be informed by the investigator and in the Informed Consent Form that authorised Ferring representatives and representatives from regulatory authorities and ECs 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 / randomisation number will appear on these copies.

The investigator should notify Ferring without any delay of any inspection by regulatory authorities or ECs.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. On e-CRFs 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 Form, 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 ECs 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 EC approval or favourable opinion.

12.2 Deviations from the Protocol

Protocol deviations should not occur. If deviations from the protocol occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented in a protocol deviation report. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and the Trial Master File.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the 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 ECs will be informed.

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

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory investigator.

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 investigators 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 criteria established by the International Committee of Medical Journal Editors (ICMJE).[24] 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 contract research organisation or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the investigator wishes to independently publish/present any results from the trial, the draft manuscript / presentation must be submitted in writing to Ferring for comment prior to submission. Comments will be given within 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 appropriate public registries, including

www.ClinicalTrials.gov, which is sponsored by National Institutes of Health and the local registry Registro Brasileiro de Ensaios Clinicos (ReBEC).

14 ETHICAL AND REGULATORY ASPECTS

14.1 National Ethics Committee

ECs will review the protocol and any amendments and advertisements used for recruitment. ECs will also review the Subject Informed Consent Form, their updates (if any), and any written materials given to the subjects. A list of all ECs to which the protocol has been submitted and the name of the committee chairman will be included in the Clinical Trial Report.

14.2 Regulatory Authority Authorisation

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 LPLV.

At the end of the clinical trial, the sponsor shall notify the national regulatory authorities and the concerned ECs about the completion of the clinical trial.

In the case of early termination, Ferring must notify the end of the trial to the national regulatory authorities and the concerned ECs immediately and at the latest within 15 days after the trial is halted, 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 a summary of the final Clinical Trial Report to the national regulatory authorities and the concerned ECs.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial, before the consent is obtained. The Informed Consent Form (a consolidated document consisting of subject information and signature sheet) must be signed and dated by the subject and the investigator who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility.

The investigator (or the person delegated by the investigator) will explain that the subject is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for her further care and without the need to justify her decision.

The subject will receive a copy of her signed Informed Consent Form.

If new information becomes available that may be relevant to the trial subject's willingness to continue participation in the trial, a new Informed Consent Form will be forwarded to the EC (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, ECs' representatives or regulatory authorities' inspector(s), in accordance with applicable regulatory requirements, may review her source records and data. Data protection will be handled in compliance with national/local regulations.

14.6 Subject Information Card

The subject will be provided with a Subject Information Card bearing at least the following information:

- That she is participating in a clinical trial
- That the trial involves controlled ovarian stimulation for an IVF/ICSI cycle and thereby includes a treatment regimen with HP-hMG, a GnRH antagonist, a progesterone preparation, as well as randomisation to a single dose of either HP-hCG IM, HP-hCG SC or rhCG SC
- The name and phone number of the investigator

The subject will be asked to return the Subject Information Card at the end-of-trial visit.

14.7 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP, and other national law(s) in the country 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

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

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 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 Form 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.

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