Cover page for protocol

Sponsor Name	Ferring Pharmaceuticals A/S
NCT Number	NCT05263388
Sponsor Trial ID:	000401
Official Title of Study	A randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the ovarian response of a starting dose of 15 µg follitropin delta (REKOVELLE) to a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme
Document Date	26 April 2024

CLINICAL TRIAL PROTOCOL

A randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the ovarian response of a starting dose of 15 µg follitropin delta (REKOVELLE) to a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme

Trial 000401

ADAPT-1
(Assessment of Conventional Dosing in Women undergoing ART with Follitropin Delta Treatment)

EudraCT Number:	2021-001785-38
UTN Number:	U1111-1267-1119
Investigational Medicinal Product:	Follitropin delta (REKOVELLE) (Ferring compound ID: FE 999049) human recombinant follicle-stimulating hormone (rFSH)
Indication:	Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle
Phase:	3b
Superseded Version	1.0
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark Tel: (+45) 88 33 88 34 From 01 Feb 2022: Amager Strandvej 405, 2770 Kastrup, Denmark
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the ovarian response of a starting dose of 15 µg follitropin delta (REKOVELLE) to a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme

SIGNATORY INVESTIGATOR(S)

TBD

TRIAL SITES

Approximately 15-20 sites in 3-6 European countries

PLANNED TRIAL PERIOD		**CLINICAL PHASE**
First patient first visit (FPFV):	Q2 2022	3b
Last patient last visit (LPLV) / end-of-trial:	Q3 2023	
Follow-up period (first transfer cycle) completed:	Q1 2024	

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

Follitropin delta (REKOVELLE) is a novel recombinant human follicle-stimulating hormone (rFSH) derived from a human cell line (PER.C6®). It is intended for the development of multiple follicles during controlled ovarian stimulation (COS) in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle. The first Marketing Authorisation approval was obtained by the European Commission in December 2016, and as of 01 May 2021 REKOVELLE is approved in 69 countries and regions worldwide.

The currently approved REKOVELLE dosing regimen is based on each woman's serum anti-Müllerian hormone (AMH) concentration and her body weight, and is a fixed-dose regimen with the daily dose maintained throughout the stimulation period. The approved maximum daily dose of REKOVELLE is 12 µg for the first treatment cycle and 24 µg in subsequent treatment cycles. Other approved rFSH preparations, such as follitropin alfa (GONAL-F) and follitropin beta (PUREGON/FOLLISTIM), apply a conventional dosing approach with a starting dose of 150-225 IU, fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments, with a maximum daily dose of 450 IU.

The present trial will explore the use of REKOVELLE in a conventional dosing approach; i.e. a standard starting dose fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments. Based on clinical trial data from more than 1,500 patients, it has been possible to establish the daily REKOVELLE dose that provides a comparable ovarian response (i.e. number of oocytes retrieved and number of follicles ≥12 mm and serum estradiol at end of stimulation) as 150 IU/day GONAL-F. These clinical trial data suggest that a daily dose of 10.0 [95% CI 9.2; 10.8] µg REKOVELLE provides an ovarian response equal to that obtained with 150 IU GONAL-F. Applying this dose equivalence factor, it is extrapolated that 15 µg/day REKOVELLE will provide an ovarian response comparable to that obtained with 225 IU/day GONAL-F.

OBJECTIVES

Primary Objective

- To compare a starting dose of 15 µg REKOVELLE to a starting dose of 225 IU GONAL-F in conventional regimens with respect to ovarian response in women undergoing controlled ovarian stimulation

Secondary Objectives

- To compare the follicular development, endocrine profile and embryo development associated with conventional dosing of REKOVELLE and GONAL-F
- To compare the treatment efficiency associated with conventional dosing of REKOVELLE and GONAL-F
- To compare the safety profile associated with conventional dosing of REKOVELLE and GONAL-F

ENDPOINTS

Primary Endpoint

- Number of oocytes retrieved

Secondary Endpoints

- Number of follicles (total and by size category) at end-of-stimulation
- Serum concentrations of estradiol and progesterone at end-of-stimulation
- Number of fertilised oocytes and fertilisation rate
- Number of blastocysts (total and by quality)
- Total gonadotropin dose and number of stimulation days

- Early OHSS (overall and by grade) and/or preventive interventions for early OHSS

Exploratory Assessment

- Blood sample on stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response (requires additional, optional consent)

Follow-up Assessments

- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer) in the first transfer cycle
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred) in the first transfer cycle

Note: the first transfer cycle covers cycles with transfer occurring within 3 months after start of stimulation

METHODOLOGY

This will be a randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the ovarian response associated with a starting dose of 15 µg follitropin delta (REKOVELLE) and a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens. The primary endpoint is the number of oocytes retrieved, and secondary endpoints include pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation. Treatment efficiency in terms of gonadotropin use and duration of stimulation will also be evaluated. The assessor-blind design ensures that the investigators and other assessors such as embryologists are blinded to individual treatment allocation. A trial medication delegate will be responsible for all trial medication related issues, both practically at the clinic and in interactions with the subject.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. On day 2-3 of the menstrual cycle, subjects will be randomised in a 2:1 ratio to treatment with either REKOVELLE or GONAL-F, and stimulation will be initiated. Subjects randomised to REKOVELLE will receive a daily starting dose of 15 µg which will be fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the gonadotropin-releasing hormone (GnRH) antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily REKOVELLE dose can be increased or decreased by 5 µg based on the subject's response. The minimum REKOVELLE dose is 5 µg and the maximum REKOVELLE dose is 20 µg. Subjects randomised to GONAL-F will receive a daily starting dose of 225 IU which will be fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and

can occur no more frequently than once every second day. At each dose adjustment, the daily GONAL-F dose may be adjusted by 75 IU based on the subject's response. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU. Subjects can be treated with rFSH for a maximum of 20 days, and coasting is not allowed.

To prevent a premature luteinising hormone (LH) surge, a GnRH antagonist (ganirelix acetate, FYREMADEL, SUN Pharma) will be initiated on stimulation day 5 or day 6 at a daily dose of 0.25 mg and continued throughout the stimulation period. Triggering of final follicular maturation will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed (i.e. on the day or the day after). Triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm are observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering is preferred instead of cycle cancellation. The triggering drug will be either human chorionic gonadotropin (hCG) or GnRH agonist, depending on the extent of ovarian response and whether transfer in the fresh cycle or in a subsequent frozen cycle (including a freeze-all approach) is intended. If transfer in the fresh cycle is intended, 250 µg hCG (choriogonadotropin alfa, OVITRELLE, Merck) will be administered. If there are ≥25 follicles with a diameter ≥12 mm or the serum estradiol is ≥5,000 pg/mL (18,355 pmol/L) (local laboratory) or a freeze-all approach is intended, 0.2 mg GnRH agonist (triptorelin acetate, GONAPEPTYL, Ferring) will be administered. Moreover, if these criteria for triggering with GnRH agonist are not met, but the investigator judges that the subject is at risk of developing early ovarian hyperstimulation syndrome (OHSS) and that triggering with hCG is not advisable, the subject can undergo triggering with GnRH agonist. In case of poor ovarian response, defined as the investigator judging that the triggering criterion cannot be reached by day 20, the cycle is to be cancelled. In case of excessive ovarian response, defined as the investigator judging that triggering of final follicular maturation is not advisable due to safety concerns, the cycle is to be cancelled. The number and size of follicles at the end-of-stimulation will be recorded.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation. All oocytes from follicles with an estimated diameter ≥12 mm must be retrieved. The oocytes can be inseminated by IVF and/or ICSI. Fertilisation will be assessed on day 1 after oocyte retrieval. The number and quality of blastocysts will be assessed at the last day of culture, i.e. day 5 or day 6 (as applicable) after oocyte retrieval. The day 5 / day 6 blastocyst quality assessment will be based on the Gardner & Schoolcraft blastocyst scoring system. Blastocysts that are not transferred in the fresh cycle will be cryopreserved in accordance with local guidelines and/or regulations.

Blood samples will be collected at stimulation day 1 for measurement of AMH, estradiol and progesterone as well as at end-of-stimulation for measurement of estradiol and progesterone. For subjects who provide additional, optional consent, blood samples will be collected at stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response.

For subjects who undergo triggering of final follicular maturation, the end-of-trial visit must take place 9-14 days after triggering to cover the assessment of early OHSS (onset ≤9 days after

triggering). For subjects who do not undergo triggering of final follicular maturation, the end-of-trial assessments must be performed at the subject's last scheduled trial visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit).

If trial procedures and/or assessments are to be performed on Sundays, public holidays or outside the opening hours of the clinic, the procedures and/or assessments can be postponed to the upcoming weekday (maximum one day after original visit schedule).

Follow-up Period

Follow-up information will be collected from the subject's first transfer cycle, irrespective of whether the first transfer takes place in a fresh or frozen cycle. This follow-up covers cycles with the transfer procedure occurring within 3 months after start of stimulation.

Depending on blastocyst availability, it is expected that subjects who underwent triggering of final follicular maturation with hCG will undergo transfer on day 5 after oocyte retrieval and that subjects who underwent triggering of final follicular maturation with GnRH agonist will undergo transfer in a frozen cycle using blastocysts cryopreserved on day 5 or day 6 after oocyte retrieval. The number of transferred blastocyst(s) in the first fresh or frozen cycle will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations. The number and quality of transferred blastocyst(s) will be recorded. Luteal phase support in fresh and frozen cycles as well as potential other medicinal products for programming of frozen cycles will be in accordance with the site's clinical practice.

Clinical pregnancy in the first transfer cycle will be assessed by transvaginal ultrasound 5-6 weeks (35-48 days) after transfer, and the number of gestational sacs will be recorded. For subjects who undergo transfer in the fresh cycle, assessment of late OHSS (onset >9 days after triggering) will take place during the follow-up period.

NUMBER OF SUBJECTS

The total number of subjects to be randomised is approximately 300, i.e. 200 randomised to treatment with REKOVELLE and 100 randomised to treatment with GONAL-F.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

1. Informed Consent Form signed prior to screening evaluations.
2. In good physical and mental health.
3. Pre-menopausal females between the ages of 18 and 40 years. The subjects must be at least 18 years (including the 18th birthday) when they sign the informed consent and no more than 40 years (up to the day before the 41st birthday) at the time of randomisation.

4. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for in vitro fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
5. Infertility for at least one year before randomisation for subjects ≤37 years or for at least 6 months for subjects ≥38 years (not applicable in case of tubal or severe male factor infertility).
6. Regular menstrual cycles of 21-35 days (both inclusive), presumed to be ovulatory.
7. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 3 cm, and no enlarged ovaries or ovarian cyst not due to polycystic ovarian syndrome, which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) within 1 year prior to randomisation. Both ovaries must be accessible for oocyte retrieval.
8. Early follicular phase (cycle day 2-4) serum levels of FSH between 1 and 15 IU/L (results obtained within 3 months prior to randomisation).

Exclusion Criteria

1. Primary ovarian failure.
2. Known endometriosis stage III-IV.
3. Considered unsuitable for controlled ovarian stimulation with a dosing regimen corresponding to approximately 225 IU/day gonadotropin, as judged by the investigator.
4. History of previous episode of OHSS or exuberant ovarian response to gonadotropins, and polycystic ovarian syndrome.
5. One or more follicles ≥10 mm (including cysts) observed on the transvaginal ultrasound prior to randomisation on stimulation day 1 (puncture of cysts is allowed prior to randomisation).
6. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) which can compromise participation in the trial with the exception of controlled thyroid function disease.
7. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
8. Fibroid tumours of the uterus incompatible with pregnancy.
9. Currently breast-feeding.
10. Undiagnosed vaginal bleeding.
11. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.

12. Pregnancy (negative urinary pregnancy tests must be documented at screening and prior to randomisation) or contraindication to pregnancy.
13. Use of fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA) or cycle programming with oral contraceptives, progestogen or estrogen preparations.
14. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
15. Previous participation in the trial.
16. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.

MEDICINAL PRODUCTS

Investigational Medicinal Product

Name	*Active ingredient, pharmaceutical dosage form and concentration*	*Daily dose*
REKOVELLE	Follitropin delta, solution for subcutaneous injection, 72 µg FSH in 2.16 mL.	Daily starting dose of 15 µg fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily REKOVELLE dose can be increased or decreased by 5 µg based on the subject's response. The minimum REKOVELLE dose is 5 µg and the maximum REKOVELLE dose is 20 µg.
GONAL-F	Follitropin alfa, solution for subcutaneous injection, 900 IU FSH in 1.5 mL.	Daily starting dose of 225 IU fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily GONAL-F dose may be adjusted by 75 IU based on the subject's response. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU.

Concomitant Fertility Medication

The non-investigational medicinal products mentioned below are used as concomitant fertility medication during the trial and will be provided by Ferring.

Name	*Drug type*	*Active ingredient and route of administration*	*Dose*
FYREMADEL	GnRH antagonist	Ganirelix acetate, subcutaneous injection	0.25 mg, daily dose
OVITRELLE	hCG	Choriogonadotropin alfa, subcutaneous injection	250 µg, single dose
GONAPEPTYL	GnRH agonist	Triptorelin acetate, subcutaneous injection	2 x 0.1 mg, single dose

DURATION OF TREATMENT

Subjects can be treated with REKOVELLE or GONAL-F for a maximum of 20 days.

STATISTICAL METHODS

Sample Size Justification

In a previous trial (MERIT), 347 subjects aged 22-37 years were treated with a starting dose of 225 IU GONAL-F. In these subjects the mean number of oocytes retrieved was 11.8 and the standard deviation was 5.7. Assuming that the standard deviation for number of oocytes retrieved in this trial will be 6.0, a total sample size of 300 with a 2:1 randomisation will give a 2-sided 95% confidence interval ranging from -1.44 to +1.44 oocytes from the observed difference. This level of precision is considered as sufficient and is also more precise than the equivalence limits of ±3 oocytes that has been applied in previous trials comparing biosimilar FSH compounds.

Primary Analysis

All efficacy analyses will be based on the full analysis set (FAS), including all randomised and exposed subjects. The primary endpoint, number of oocytes retrieved, will be compared between REKOVELLE and GONAL-F using a negative binomial model with treatment and AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as factors. The absolute treatment difference in number of oocytes retrieved and the associated 2-sided 95% confidence interval will be derived from the model estimates using the delta method.

The treatment difference will also be investigated for the two sub-groups AMH <15 pmol/L and AMH ≥15 pmol/L using the same methods as above.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

AMH	anti-Müllerian hormone
ANCOVA	analysis of covariance
ART	assisted reproductive technologies
ATC	Anatomical Therapeutic Chemical Classification System
COS	controlled ovarian stimulation
CRO	contract research organisation
COVID-19	coronavirus disease 2019
DHEA	dehydroepiandrosterone
EDC	electronic data capture system
EU	European Union
EudraCT	European Union Clinical Trial Database
FAS	full analysis set
FPFV	first patient first visit
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
ICH	International Council for Harmonisation
ICMART	International Committee Monitoring Assisted Reproductive Technologies
ICMJE	International Committee of Medical Journal Editors
ICSI	intracytoplasmic sperm injection
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology system
IVF	in vitro fertilisation
LH	luteinising hormone
LLOQ	lower limit of quantification
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health

NIMP	non-investigational medicinal product
NLM	National Library of Medicine
OHSS	ovarian hyperstimulation syndrome
rFSH	recombinant follicle-stimulating hormone
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
ULOQ	upper limit of quantification
U.S.	United States
UTN	Universal Trial Number
WHO	World Health Organisation

Company Names

Ferring will be used as abbreviation for Ferring Pharmaceuticals.

1 INTRODUCTION

1.1 Background

Follitropin delta (REKOVELLE) is a novel human recombinant follicle-stimulating hormone (rFSH) derived from a human cell line (PER.C6®). It is intended for the development of multiple follicles during controlled ovarian stimulation (COS) in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle. The first Marketing Authorisation approval was obtained by the European Commission in December 2016, and as of 01 May 2021 REKOVELLE is approved in 69 countries and regions worldwide.

The currently approved REKOVELLE dosing regimen is based on each woman's serum anti-Müllerian hormone (AMH) concentration and her body weight, and is a fixed-dose regimen with the daily dose maintained throughout the stimulation period. The approved maximum daily dose of REKOVELLE is 12 µg for the first treatment cycle and 24 µg in subsequent treatment cycles. Other approved rFSH preparations, such as follitropin alfa (GONAL-F) and follitropin beta (PUREGON / FOLLISTIM), apply a conventional dosing approach with a starting dose of 150-225 IU, fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments, with a maximum daily dose of 450 IU.

1.2 Scientific Justification for Conducting the Trial

The present trial will explore the use of REKOVELLE in a conventional dosing approach; i.e. a standard starting dose fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments. Based on clinical trial data from more than 1,500 patients, it has been possible to establish the daily REKOVELLE dose that provides a comparable ovarian response (i.e. number of oocytes retrieved and number of follicles ≥12 mm and serum estradiol at end of stimulation) as 150 IU/day GONAL-F.[1] These clinical trial data suggest that a daily dose of 10.0 [95% CI 9.2; 10.8] µg REKOVELLE provides an ovarian response equal to that obtained with 150 IU GONAL-F. Applying this dose equivalence factor, it is extrapolated that 15 µg/day REKOVELLE will provide an ovarian response comparable to that obtained with 225 IU/day GONAL-F.

1.3 Benefit / Risk Aspects

Benefits

The fertility medication used for controlled ovarian stimulation, prevention of premature luteinising hormone (LH) surge, and triggering of final follicular maturation will be provided to the participating subjects free of charge, as Ferring compensates the investigational sites for their expenses. Subjects participating in this trial may benefit by achieving a pregnancy.

Risks

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.

Gonadotropins

In this trial, controlled ovarian stimulation will be performed with one of two rFSH preparations: REKOVELLE or GONAL-F. Both preparations will be administered subcutaneously.

REKOVELLE and GONAL-F are commercially available rFSH preparations with established safety and efficacy.[2,3] The most frequent adverse events in relation to use of REKOVELLE are as follows: headache, pelvic discomfort, ovarian hyperstimulation syndrome (OHSS), pelvic pain, nausea, adnexa uteri pain, and fatigue (all reported as common, i.e. 1% to <10%).[2] The most frequent adverse events in relation to use of GONAL-F are as follows: headache, ovarian cysts and injection site reactions (all reported as very common, i.e. ≥10%) and abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea, and mild or moderate OHSS including associated symptomatology (all reported as common, i.e. 1% to <10%).[3]

The most serious risk associated with gonadotropin treatment is OHSS. OHSS manifests itself with increasing degrees of severity. Moderate / severe OHSS is associated with marked ovarian enlargement, fluid accumulation and other complications. Early OHSS can be prevented by withholding gonadotropins, withholding human chorionic gonadotropin (hCG) or administering gonadotropin-releasing hormone (GnRH) agonist for triggering of final follicular maturation. Very rare cases of serious allergic reactions have been reported after injection of gonadotropins.

Trial Procedures and Concomitant Fertility Medications

Subjects will undergo standard ART treatment procedures (e.g. ovarian stimulation monitoring by transvaginal ultrasound and blood sampling, oocyte retrieval and transfer) and also receive standard concomitant fertility medication as part of this trial. 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. The concomitant fertility medications are generally well-tolerated. The most frequent adverse events are similar to those reported for gonadotropins, such as headache, injection site reactions, pelvic pain, abdominal pain, abdominal distension and allergic reactions.

Pregnancy-related Events

The trial includes a follow-up period with collection of data from the subject's first transfer cycle, if the transfer procedure occurs within 3 months after start of stimulation. In this regard, a serious concern associated with ART cycles is the frequency of multiple pregnancies / births and the related neonatal health problems. The number of blastocysts transferred will, for each subject, depend on the local regulations and clinical practice. Participation in this trial does not imply transfer of more blastocysts than what is judged appropriate by the subject, the investigator and local guidelines and/or regulations. The incidence of miscarriage and ectopic pregnancy is higher in women undergoing controlled ovarian stimulation than in women conceiving spontaneously, though the risk of ectopic pregnancy is mainly higher in patients with a history of tubal infertility. Furthermore, the prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions; this is thought to be due to differences in parental characteristics (e.g. maternal age and sperm characteristics) and multiple pregnancies.

Benefits / Risks

Participation in this trial is not expected to have a negative influence on the subject's likelihood of achieving an adequate ovarian response compared to normal clinical practice. Furthermore, participation does not imply extra risks for the subjects in comparison to routine controlled ovarian stimulation. In conclusion, the evaluation of benefits and risks indicate that participation is this trial is associated with a favourable benefit-risk ratio.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To compare a starting dose of 15 µg REKOVELLE to a starting dose of 225 IU GONAL-F in conventional regimens with respect to ovarian response in women undergoing controlled ovarian stimulation

Secondary Objectives

- To compare the follicular development, endocrine profile and embryo development associated with conventional dosing of REKOVELLE and GONAL-F
- To compare the treatment efficiency associated with conventional dosing of REKOVELLE and GONAL-F
- To compare the safety profile associated with conventional dosing of REKOVELLE and GONAL-F

2.2 Endpoints

Primary Endpoint

- Number of oocytes retrieved

Secondary Endpoints

- Number of follicles (total and by size category) at end-of-stimulation
- Serum concentrations of estradiol and progesterone at end-of-stimulation
- Number of fertilised oocytes and fertilisation rate
- Number of blastocysts (total and by quality)
- Total gonadotropin dose and number of stimulation days
- Early OHSS (overall and by grade) and/or preventive interventions for early OHSS

Exploratory Assessment

- Blood sample on stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response (requires additional, optional consent)

Follow-up Assessments

- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer) in the first transfer cycle
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred) in the first transfer cycle

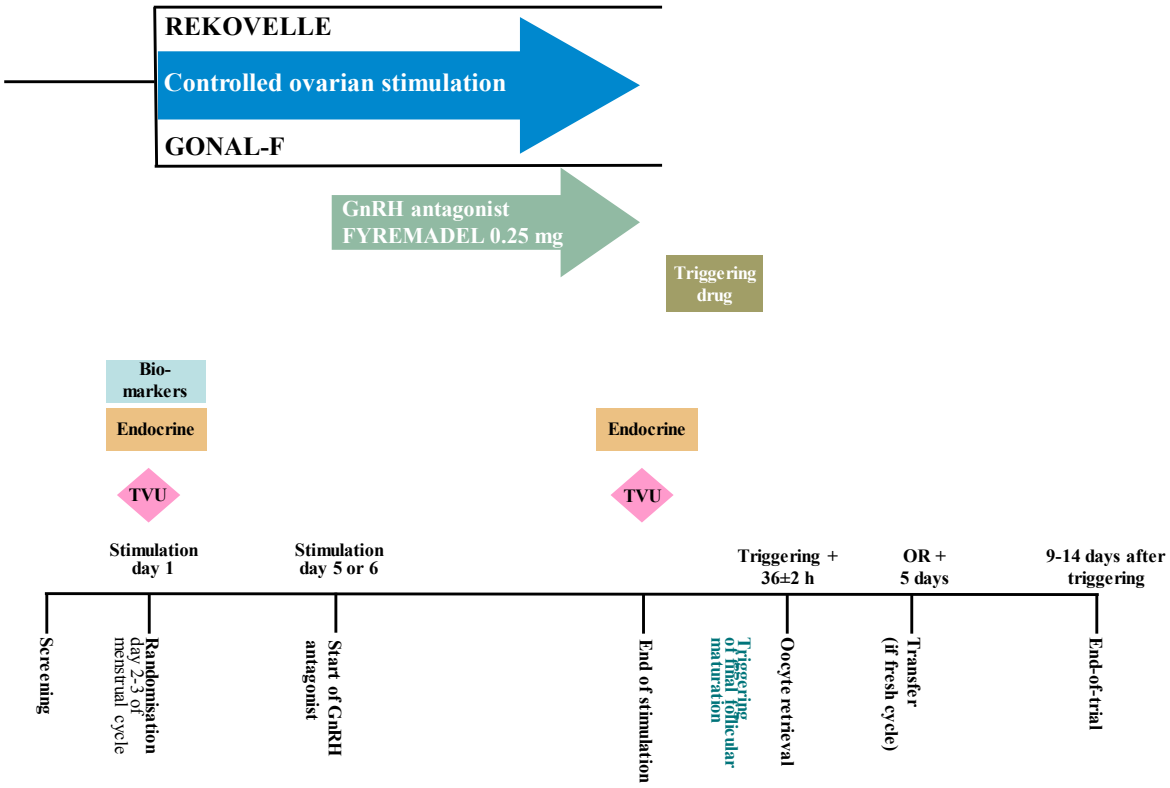
Note: the first transfer cycle covers cycles with transfer occurring within 3 months after start of stimulation

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagrams

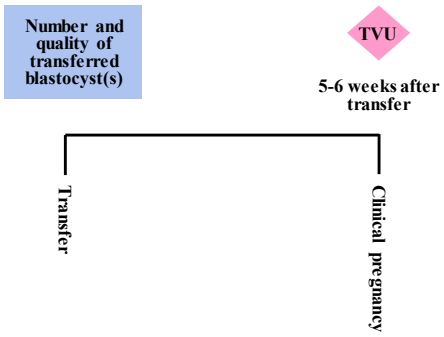
A diagram illustrating the trial period is shown in Figure 3-1.



OR: Oocyte retrieval; TVU: Transvaginal ultrasound

Figure 3-1 Trial Diagram – Trial Period

A diagram illustrating the follow-up period in the first transfer cycle is shown in Figure 3-2.



TVU: Transvaginal ultrasound

Figure 3-2 Trial Diagram – Follow-up Period (First Transfer Cycle)

3.1.2 Overall Design and Control Methods

Trial Period

This will be a randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the ovarian response associated with a starting dose of 15 µg follitropin delta (REKOVELLE) and a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens. The primary endpoint is the number of oocytes retrieved, and secondary endpoints include pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation. Treatment efficiency in terms of gonadotropin use and duration of stimulation will also be evaluated. The assessor-blind design ensures that the investigators and other assessors such as embryologists are blinded to individual treatment allocation. A trial medication delegate will be responsible for all trial medication related issues, both practically at the clinic and in interactions with the subject.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. On day 2-3 of the menstrual cycle, subjects will be randomised in a 2:1 ratio to treatment with either REKOVELLE or GONAL-F, and stimulation will be initiated. Subjects randomised to REKOVELLE will receive a daily starting dose of 15 µg which will be fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily REKOVELLE dose can be increased or decreased by 5 µg based on the subject's response. The minimum REKOVELLE dose is 5 µg and the maximum REKOVELLE dose is 20 µg. Subjects randomised to GONAL-F will receive a daily starting dose of 225 IU which will be fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily GONAL-F dose may be adjusted by 75 IU based on the subject's response.

The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU. Subjects can be treated with rFSH for a maximum of 20 days, and coasting is not allowed.

To prevent a premature LH surge, a GnRH antagonist (ganirelix acetate, FYREMADEL, SUN Pharma) will be initiated on stimulation day 5 or day 6 at a daily dose of 0.25 mg and continued throughout the stimulation period. Triggering of final follicular maturation will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed (i.e. on the day or the day after). Triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm are observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering is preferred instead of cycle cancellation. The triggering drug will be either human chorionic gonadotropin (hCG) or GnRH agonist, depending on the extent of ovarian response and whether transfer in the fresh cycle or in a subsequent frozen cycle (including a freeze-all approach) is intended. If transfer in the fresh cycle is intended, 250 µg hCG (choriogonadotropin alfa, OVITRELLE, Merck) will be administered. If there are ≥25 follicles with a diameter ≥12 mm or the serum estradiol is ≥5,000 pg/mL (18,355 pmol/L) (local laboratory) or a freeze-all approach is intended, 0.2 mg GnRH agonist (triptorelin acetate, GONAPEPTYL, Ferring) will be administered. Moreover, if these criteria for triggering with GnRH agonist are not met, but the investigator judges that the subject is at risk of developing OHSS and that triggering with hCG is not advisable, the subject can undergo triggering with GnRH agonist. In case of poor ovarian response, defined as the investigator judging that the triggering criterion cannot be reached by day 20, the cycle is to be cancelled. In case of excessive ovarian response, defined as the investigator judging that triggering of final follicular maturation is not advisable due to safety concerns, the cycle is to be cancelled. The number and size of follicles at the end-of-stimulation will be recorded.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation. All oocytes from follicles with an estimated diameter ≥12 mm must be retrieved. The oocytes can be inseminated by IVF and/or ICSI. Fertilisation will be assessed on day 1 after oocyte retrieval. The number and quality of blastocysts will be assessed at the last day of culture, i.e. day 5 or day 6 (as applicable) after oocyte retrieval. The day 5 / day 6 blastocyst quality assessment will be based on the Gardner & Schoolcraft blastocyst scoring system.[15] Blastocysts that are not transferred in the fresh cycle will be cryopreserved in accordance with local guidelines and/or regulations.

Blood samples will be collected at stimulation day 1 for measurement of AMH, estradiol and progesterone as well as at end-of-stimulation for measurement of estradiol and progesterone. For subjects who provide additional, optional consent, blood samples will be collected at stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response.

For subjects who undergo triggering of final follicular maturation, the end-of-trial visit must take place 9-14 days after triggering to cover the assessment of early OHSS (onset ≤9 days after triggering). For subjects who do not undergo triggering of final follicular maturation, the end-of-trial assessments must be performed at the subject's last scheduled trial visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit).

If trial procedures and/or assessments are to be performed on Sundays, public holidays or outside the opening hours of the clinic, the procedures and/or assessments can be postponed to the upcoming weekday (maximum one day after original visit schedule).

Follow-up Period – First Transfer Cycle

Follow-up information will be collected from the subject's first transfer cycle, irrespective of whether the first transfer takes place in a fresh or frozen cycle. This follow-up covers cycles with the transfer procedure occurring within 3 months after start of stimulation.

Depending on blastocyst availability, it is expected that subjects who underwent triggering of final follicular maturation with hCG will undergo transfer on day 5 after oocyte retrieval and that subjects who underwent triggering of final follicular maturation with GnRH agonist will undergo transfer in a frozen cycle using blastocysts cryopreserved on day 5 or day 6 after oocyte retrieval. The number of transferred blastocyst(s) in the first fresh or frozen cycle will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations. The number and quality of transferred blastocyst(s) will be recorded. Luteal phase support in fresh and frozen cycles as well as potential other medicinal products for programming of frozen cycles will be in accordance with the site's clinical practice.

Clinical pregnancy in the first transfer cycle will be assessed by transvaginal ultrasound 5-6 weeks (35-48 days) after transfer, and the number of gestational sacs will be recorded. For subjects who undergo transfer in the fresh cycle, assessment of late OHSS (onset >9 days after triggering) will take place during the follow-up period.

3.1.3 Trial Schedule

First patient first visit (FPFV): Q2 2022

Last patient last visit (LPLV) / end-of-trial: Q3 2023

Follow-up period (first transfer cycle) completed: Q1 2024

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomise approximately 300 subjects from 15-20 sites in 3-6 European countries.

3.3 Interim Analysis

No interim analysis is planned.

3.4 Data Monitoring Committee

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

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The primary objective of the trial is to compare a starting dose of 15 µg REKOVELLE to a starting dose of 225 IU GONAL F in conventional regimens with respect to ovarian response in women undergoing controlled ovarian stimulation

This is a randomised controlled trial using an approved gonadotropin preparation as active comparator. It is a parallel group design restricted to a single treatment cycle, as this design is preferred over a cross-over design in fertility trials.[4,5] The trial will be open-label but assessor-blind. 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 blinding and thereby unbiased evaluation by the investigators and other assessors such as embryologists. Similarly, Ferring staff will also remain blinded to individual subject treatment allocation during the conduct of the trial (see section 3.5.3). The trial will be a multi-centre, multinational trial. This set-up ensures that the required number of subjects can be recruited within a reasonable time and also has the advantage of facilitating subsequent generalisation of the results.

Subjects will be randomised in 2:1 ratio to controlled ovarian stimulation with REKOVELLE or GONAL-F following a GnRH antagonist protocol. The selection of doses is described in detail in section 3.5.4. Monitoring of ovarian response by transvaginal ultrasound and blood sampling for assessment of selected endocrine parameters will be performed at start and end-of-stimulation. Follow-up information will be collected from the subject's first transfer cycle, irrespective of whether the first transfer takes place in a fresh or frozen cycle. This follow-up covers cycles with the transfer procedure occurring within 3 months after start of stimulation.

3.5.2 Selection of Endpoints

The primary endpoint of this trial, number of oocytes retrieved, is an objective parameter. The number of oocytes retrieved provides a direct measure of the main pharmacological action of gonadotropin preparations. The number of oocytes retrieved is considered an appropriate marker of ovarian response and thereby of the pharmacodynamics of an FSH preparation.

Secondary endpoints include pharmacodynamic parameters of FSH, such as ovarian response in terms of follicular development, endocrine profile, and also oocyte / blastocyst quality. Follicular development and endocrine profile, represented by estradiol and progesterone, will be evaluated at the end-of-stimulation. In addition, treatment efficiency in terms of gonadotropin use and duration

of stimulation, and a specific relevant clinical safety endpoint covering early OHSS and preventive interventions for early OHSS will also be evaluated.

As obligatory follow-up, pregnancy data at 5-6 weeks (35-48 days) after transfer will be gathered for subjects in the first transfer cycle.

3.5.3 Blinding

The two investigational medicinal products (IMPs), i.e. REKOVELLE and GONAL-F, have different appearances. Blinding would therefore require a double-blind, double-dummy design which is not easily feasible, and furthermore, would add an extra burden on the subjects. The trial, however, is assessor-blind, ensuring unbiased evaluation by the investigators and other assessors such as embryologists. Only the trial medication delegate personnel (persons responsible for IMPs / non-investigational medicinal products [NIMPs]), the monitors, and the participating subjects will know the treatment allocation once the subject is randomised.

The trial medication delegate will be responsible for all trial medication related issues, both practically at the clinic and in interactions with the subject. To maintain the assessor-blinding, the trial medication delegate is not allowed to perform any efficacy or safety assessments in the trial. Information on treatment allocation is only available to the trial medication delegate (the person entering data into the electronic data capture system [EDC] and with access to the interactive response technology system [IRT]). The investigator does not have access to these modules in the EDC and IRT. 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.

Drug accountability forms and other forms identifying treatment allocation are kept unavailable to the blinded trial staff, including the investigator. The subject will during the informed consent process be informed, both verbally and in writing, to not disclose her treatment allocation to the investigator. Trial staff will be provided with training in the importance of maintaining blinding.

The Ferring clinical trial team[a] 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. This will occur after LPLV (last patient's end-of-trial visit), i.e. before completion of the follow-up period (first transfer cycle).

[a] This excludes the representatives from Clinical Trial Supply. Furthermore, it may be necessary for representatives from Pharmacovigilance to unblind an individual subject's treatment during the trial for the purpose of expedited reporting.

3.5.4 Selection of Doses in the Trial

Based on clinical trial data from more than 1,500 patients, it has been possible to establish that a daily dose of 10.0 µg REKOVELLE provides an ovarian response equal to that obtained with 150 IU GONAL-F. The present trial investigates the extrapolation that conventional dosing regimens with a daily starting dose of 15 µg REKOVELLE or 225 IU GONAL-F will result in a similar number of oocytes retrieved. The possible dose adjustments are 5 µg REKOVELLE and 75 IU GONAL-F, and therefore considered to be of similar magnitude. The highest REKOVELLE dose possible to administer as a single injection with the REKOVELLE pre-filled pen is 20 µg, and for patient convenience reasons 20 µg has therefore been set as the maximum daily dose in this trial. Correspondingly, the maximum daily GONAL-F dose has been set at 300 IU.

The doses and overall treatment regimens for the GnRH antagonist (FYREMADEL) and hCG (OVITRELLE) are in line with the recommendations in the respective products' labelling for the indication of ART and/or standard clinical practice. The GnRH agonist (GONAPEPTYL) is included as an option for triggering of final follicular maturation in subjects with ≥25 follicles with a diameter ≥12 mm or serum estradiol concentration ≥5,000 pg/mL (18,355 pmol/L) (local laboratory) or a freeze-all approach is intended, as this approach is associated with almost an elimination of the risk of early moderate / severe OHSS despite high ovarian response. The use of a GnRH agonist for triggering of final follicular maturation in a GnRH antagonist protocol is well described in the literature and considered an acceptable alternative to cycle cancellation. [6,7,8,9,10] The use of 0.2 mg GONAPEPTYL is also in line with literature.[6,7,10,11]

3.5.5 Selection of the Trial Population

This trial will include women who have been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II, or have partners diagnosed with male factor infertility, and who are considered eligible for IVF or ICSI.

The exclusion criteria incorporate the contraindications for the use of gonadotropins.

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

3.5.6 Follow-up Procedures

Follow-up Activities

Follow-up information will be collected from the subject's first transfer cycle, irrespective of whether the first transfer takes place in a fresh or frozen cycle. This follow-up covers cycles with the transfer procedure occurring within 3 months after start of stimulation.

Access to Therapy after End-of-trial

Concerning access to therapy after completion of the trial, both REKOVELLE and GONAL-F are approved for controlled ovarian stimulation and are commercially available.

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. In good physical and mental health.
3. Pre-menopausal females between the ages of 18 and 40 years. The subjects must be at least 18 years (including the 18th birthday) when they sign the informed consent and no more than 40 years (up to the day before the 41st birthday) at the time of randomisation.
4. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for in vitro fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
5. Infertility for at least one year before randomisation for subjects ≤37 years or for at least 6 months for subjects ≥38 years (not applicable in case of tubal or severe male factor infertility).
6. Regular menstrual cycles of 21-35 days (both inclusive), presumed to be ovulatory.
7. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 3 cm, and no enlarged ovaries or ovarian cyst not due to polycystic ovarian syndrome, which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) within 1 year prior to randomisation. Both ovaries must be accessible for oocyte retrieval.
8. Early follicular phase (cycle day 2-4) serum levels of FSH between 1 and 15 IU/L (results obtained within 3 months prior to randomisation).

4.1.2 Exclusion Criteria

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

1. Primary ovarian failure.
2. Known endometriosis stage III-IV.
3. Considered unsuitable for controlled ovarian stimulation with a dosing regimen corresponding to approximately 225 IU/day gonadotropin, as judged by the investigator.
4. History of previous episode of OHSS or exuberant ovarian response to gonadotropins, and polycystic ovarian syndrome.

5. One or more follicles ≥10 mm (including cysts) observed on the transvaginal ultrasound prior to randomisation on stimulation day 1 (puncture of cysts is allowed prior to randomisation).
6. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) which can compromise participation in the trial with the exception of controlled thyroid function disease.
7. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
8. Fibroid tumours of the uterus incompatible with pregnancy.
9. Currently breast-feeding.
10. Undiagnosed vaginal bleeding.
11. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
12. Pregnancy (negative urinary pregnancy tests must be documented at screening and prior to randomisation) or contraindication to pregnancy.
13. Use of fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA) or cycle programming with oral contraceptives, progestogen or estrogen preparations.
14. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
15. Previous participation in the trial.
16. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The participating subjects will be recruited among the patients attending the sites included in the trial. Advertisements may be used if approved by the local Independent Ethics Committee (IECs) / Institutional Review Board (IRB)[b] and regulatory authorities, as applicable according to local regulations.

[b] The term IEC/IRB will be used throughout this document to cover all committees as per local regulations.

4.2.2 Randomisation

On day 2-3 of the menstrual cycle, subjects will be randomised in a 2:1 ratio to treatment with either REKOVELLE or GONAL-F, and stimulation will be initiated. Randomisation is performed centrally through the IRT. 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. 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 Prior and Concomitant Therapies

The subjects must not have used fertility modifiers, including DHEA or cycle programming with oral contraceptives, progestogen, or estrogen preparations during the last menstrual cycle before randomisation.

It is prohibited to administer other gonadotropins than REKOVELLE or GONAL-F, or other concomitant fertility medication not provided as part of the trial regimen. This restriction does not include the follow-up period (first transfer cycle), e.g. luteal phase support as well as potential other medicinal products for programming of frozen cycles.

4.3.2 Prohibited Therapy

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

4.3.3 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 discontinue 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 EDC.

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 Form. The subject can request destruction of samples which would otherwise have been kept in storage.

4.4 Subject Replacement

A subject can only be assigned one screening number and one randomisation number, i.e. a subject cannot be re-screened.

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.

4.5 Trial Stopping Criteria

Occurrence of the following may warrant consideration of trial termination:

- Life-threatening serious adverse events (SAEs) with suspected causality to the IMP

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

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products

On day 2-3 of the menstrual cycle, subjects will be randomised in a 2:1 ratio to either REKOVELLE or GONAL-F, and controlled ovarian stimulation will be initiated.

Subjects randomised to REKOVELLE will receive a daily starting dose of 15 µg, which will be fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily REKOVELLE dose can be increased or decreased by 5 µg based on the subject's response. The minimum REKOVELLE dose is 5 µg and the maximum REKOVELLE dose is 20 µg. Subjects can be treated with REKOVELLE for a maximum of 20 days, and coasting is not allowed.

Subjects randomised to GONAL-F will receive a daily starting dose of 225 IU which will be fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily GONAL-F dose may be adjusted by 75 IU based on the subject's response. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU. Subjects can be treated with GONAL-F for a maximum of 20 days, and coasting is not allowed.

The IMP is administered as a daily subcutaneous injection in the abdomen. The first IMP injection will take place at the clinic and will be performed either by the trial medication delegate or the subject under supervision by the trial medication delegate. Subsequent injections can be done at home or at the clinic. The trial medication delegate will give the subject instructions on how to administer the IMP.

The REKOVELLE and GONAL-F dosing regimen is tabulated in Table 5-1.

Table 5-1 Investigational Medicinal Products

IMP	Active ingredient, pharmaceutical dosage form and concentration	Daily dose [a)]
REKOVELLE	Follitropin delta, solution for subcutaneous injection, 72 µg FSH in 2.16 mL.	Daily starting dose of 15 µg fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily REKOVELLE dose can be increased or decreased by 5 µg based on the subject's response. The minimum REKOVELLE dose is 5 µg and the maximum REKOVELLE dose is 20 µg.
GONAL-F	Follitropin alfa, solution for subcutaneous injection, 900 IU FSH in 1.5 mL.	Daily starting dose of 225 IU fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily GONAL-F dose may be adjusted by 75 IU based on the subject's response. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU.

a) Subjects can be treated for a maximum of 20 days.

5.1.2 Non-investigational Medicinal Products

As concomitant therapy in the controlled ovarian stimulation cycle, subjects will use the following NIMPs as illustrated in Table 5-2.

Table 5-2 Non-Investigational Medicinal Products

NIMP	Trade name	Dose
GnRH antagonist	FYREMADEL[a)]	0.25 mg subcutaneous injection once daily starting on stimulation day 5 or day 6 and continued throughout the stimulation period. FYREMADEL and REKOVELLE / GONAL-F should be administered approximately at the same time. However, the preparations should not be mixed and different injection sites are to be used.
hCG	OVITRELLE	A single 250 µg subcutaneous injection as soon as reaching the criterion for triggering of final follicular maturation with hCG (≥3 follicles with a diameter of ≥17 mm and intended transfer in the fresh cycle. *Note:* triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm are observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering is preferred instead of cycle cancellation).
GnRH agonist	GONAPEPTYL[b)]	Two consecutive subcutaneous injections of 0.1 mg, i.e. a total of 0.2 mg, as soon as reaching the additional criteria for triggering of final follicular maturation with GnRH agonist (≥25 follicles with a diameter of ≥12 mm or serum estradiol concentration ≥5,000 pg/mL (18,355 pmol/L) (local laboratory) or intended freeze-all approach). *Note:* the subject can undergo triggering with GnRH agonist if the investigator judges that the subject is at risk of developing early OHSS.

a) Other tradenames in Europe include FYREMADEL GÉ.
b) Other tradenames in Europe include FERTIPEPTIL and DECAPEPTYL.

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 provide an overview of the presentation of each medicinal product.

Table 5-3 Characteristics of Medicinal Products

IMP / NIMP	Presentation	Manufacturer
REKOVELLE (rFSH)	Pre-filled pen for multiple use containing 72 µg follitropin delta in 2.16 mL.	Ferring Pharmaceuticals
GONAL-F (rFSH)	Pre-filled pen containing 900 IU follitropin alfa in 1.5 mL.	Merck
FYREMADEL (GnRH antagonist)	Pre-filled syringe for single use delivering 0.25 mg of ganirelix acetate in 0.5 mL.	SUN Pharma
OVITRELLE (hCG)	Pre-filled syringe or pre-filled pen for single use delivering 250 µg choriogonadotropin alfa in 0.5 mL.	Merck
GONAPEPTYL (GnRH agonist)	Pre-filled syringe for single use delivering 0.1 mg triptorelin acetate in 1 mL.	Ferring Pharmaceuticals

5.3 Packaging and Labelling

Packaging and labelling of the medicinal products will be performed under the responsibility of the Clinical Trial Supply department at Ferring in accordance with GMP and national regulatory requirements.

Details on the packaging and labelling of each medicinal product are provided in the Trial Supply Manual.

5.4 Conditions for Storage and Use

The investigator will ensure that the medicinal products will be stored under appropriate conditions in a secure location with controlled access. The storage conditions shall be monitored regularly and the temperature shall be documented as instructed in the Trial Supply Manual.

The storage conditions for the medicinal products will be as described on the trial-specific or commercial box labels. Deviations in temperature must be reported to Ferring as instructed in the Trial Supply Manual.

For information on warnings, precautions, and treatment of overdose, please refer to the Summary of Product Characteristics for REKOVELLE[2], GONAL-F[3], FYREMADEL[12], OVITRELLE[13], and GONAPEPTYL[14].

5.5 Blinding / Unblinding

5.5.1 Blinding

The trial is assessor-blind, and all investigators, embryologists, other assessors (e.g. trial nurses, depending on delegation of authority) and central laboratory personnel will be blinded to treatment allocation throughout the trial. The trial medication delegate at site (person responsible for the medicinal products), the 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 medication delegate, and to not 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 in the EDC or IRT will not be accessible to assessors or the Ferring clinical trial team or laboratory personnel during the trial.

The Ferring clinical trial team[c] 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

An emergency unblinding procedure will be available for the investigator and designated personnel at the sponsor through the IRT. It is the investigator's responsibility to decide whether it is medically necessary to know the investigational product the subject receives (i.e. unblinding) to ensure the subject's welfare and safety.

Breaking of the blind for individual subjects in emergency situations could be required in case of suspected unexpected serious adverse reactions (SUSARs) or in case of other important adverse events when the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject. As far as the emergency permits, the need to break the blind will be agreed by the investigator and the sponsor. Where the event requires immediate unblinding by the investigator, the sponsor must be informed of the unblinding as soon as possible and provided with the rationale for unblinding.

The investigator who unblinds a treatment will use the IRT and is required to enter a password before the treatment code can be broken. The IRT records when, and by whom, the code was broken. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

[c] This excludes the representatives from Clinical Trial Supply. Furthermore, it may be necessary for representatives from Pharmacovigilance to unblind an individual subject's treatment during the trial for the purpose of expedited reporting.

In case of accidental unblinding (e.g. the subject tells the investigator), the same procedure as for emergency unblinding must be followed, i.e. the investigator / person who was accidentally unblinded will enter a password in the IRT for unblinding. The IRT records when, and by whom, the code was broken. In addition, the event and reason for unblinding must also be recorded in the subject's medical record.

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

Information on whether the blind has been broken for any subjects is available in the IRT and must be collected before the database is declared clean and locked.

In case the IRT cannot be accessed by the investigator, and hence the emergency unblinding cannot be performed within the IRT, a backup procedure is in place.

5.6 Treatment Compliance, Dispensing and Accountability

All handling of medicinal products will be done by a trial medication delegate at the site and an IRT will be used to assign the medicinal products to the subject.

The trial medication delegate will maintain subject dispensing logs, detailing the dates, quantities and batch numbers of dispensed and returned medicinal products for each subject in the IRT. The trial medication delegate will also manage the overall drug accountability at the site.

The monitor will verify the drug accountability during the trial.

IMP medication errors with and without clinical consequences will be tracked in the EDC and reviewed on an ongoing basis by Ferring Global Pharmacovigilance.

5.7 Auxiliary Supplies

Ferring will supply safety containers for the collection of used needles, etc.

5.8 Return and Destruction of Medicinal Products

All used and unused (non-dispensed / non-allocated) trial medication will be disposed as instructed in the Trial Supply Manual, after drug accountability has been finalised and verified by the monitor, and all issues solved.

6 TRIAL PROCEDURES

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

Table 6-1 Trial Flow Chart – Subject Procedures

	Screening	Stimulation			Oocyte retrieval	End
		Start of stimulation	Start of GnRH antagonist	End-of-stimulation		End-of-trial [a)]
	<90 days before randomisation	Day 1	Day 5 or day 6 [b)]	End	36h ± 2h after triggering	
Written informed consent	X					
Inclusion/exclusion criteria	X	X [c)]				
Demographics	X					
Medical history	X					
Infertility history	X					
Body weight, height	X					
Physical examination	X					X
Gynaecological examination	X					X
Urinary pregnancy test	X	X [c)]				
Transvaginal ultrasound		X [c)]		X		
Blood collection, endocrine [d)]		X [c)]		X		
Blood collection, potential biomarkers [e)]		X [c)]				
Randomisation		X				
IMP dispensing		X	X			
NIMP dispensing			X	X		
Oocyte retrieval					X	
Drug accountability			X	X	X	
Concomitant medication	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

a) For subjects who undergo triggering of final follicular maturation, the end-of-trial visit must take place 9-14 days after triggering to cover the assessment of early OHSS (onset ≤9 days after triggering). For subjects who do not undergo triggering of final follicular maturation, the end-of-trial assessments must be performed at the subject's last scheduled trial visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit).
b) GnRH antagonist will be initiated on stimulation day 5 or day 6.
c) Performed before the first IMP dose.
d) Stimulation day 1: AMH, estradiol and progesterone; end-of-stimulation: estradiol and progesterone.
e) Additional, optional, consent required.

GnRH: gonadotropin-releasing hormone, IMP: investigational medicinal product, NIMP: non-investigational medicinal product, OHSS: ovarian hyperstimulation syndrome

If trial procedures and/or assessments are to be performed on Sundays, public holidays or outside the opening hours of the clinic, the procedures and/or assessments can be postponed to the upcoming weekday (maximum one day after original visit schedule).

6.1 Screening

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

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 (date of birth[d], ethnicity, race)
- Medical history
- Infertility history
- Body weight, height
- Physical examination
- Gynaecological examination
- Urinary pregnancy test must be negative
- Recording of use of any concomitant medication (within the last month prior to signed informed consent)
- Recording of adverse events (from the date of signed informed consent)

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.

6.2 Stimulation

6.2.1 Start of Stimulation – Day 1

Subjects will attend the stimulation day 1 visit on day 2-3 of the menstrual cycle.

The following must take place before administration of the first IMP dose:

- 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)
- Blood collection for central laboratory analysis of endocrine parameters (AMH, estradiol, and progesterone)

[d] Alternatively, age may be recorded in case country-specific restrictions do not permit recording the full date of birth.

- Blood collection for potential future biomarkers (*applicable for subjects who have provided additional, optional consent*)

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

- Randomisation, i.e. assignment to the lowest available subject number and thereby allocation to either REKOVELLE or GONAL-F

Once the above has been completed, the following must be performed by the trial medication delegate. Care must be taken to ensure blinding of the investigator and other assessors.

- Dispensing of IMP according to randomisation and instruct the subject on how to administer the IMP. The subject will self-administer the IMP (at the trial site) as a subcutaneous injection in the lower part of the abdomen. The IMP starting dose of 15 µg/day with REKOVELLE or 225 IU/day with GONAL-F must be maintained for at least 4 days.

Finally, this must be done before the subject leaves the clinic:

- Recording of use of any concomitant medication
- Recording of adverse events

The IMP should preferably be administered at the same time each day during the stimulation period (with the possible exception of stimulation day 1).

6.2.2 Start of GnRH Antagonist – Day 5 or Day 6

The following must take place on stimulation day 5 or day 6:

- Dispensing of IMP
- Evaluation of potential dose adjustments based on the subject's response
- Implementation of dose adjustments, if applicable
  The daily REKOVELLE dose can be increased or decreased by 5 µg based on the subject's response. The minimum REKOVELLE dose is 5 µg and the maximum REKOVELLE dose is 20 µg. The daily GONAL-F dose may be adjusted by 75 IU based on the subject's response. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU.
- Dispensing of GnRH antagonist
  Daily administration of 0.25 mg GnRH antagonist will be initiated on stimulation day 5 or day 6. The subject will self-administer the GnRH antagonist as a subcutaneous injection in the upper thigh throughout the stimulation period. The timing of the GnRH antagonist injections should be aligned with the IMP injections.

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

6.2.3 End-of-stimulation

The end-of-stimulation visit will take place when the subject reaches the criterion for triggering of final follicular maturation. Triggering of final follicular maturation will be done either with hCG or GnRH agonist, depending on the extent of ovarian response and whether transfer in the fresh cycle or in a subsequent frozen cycle (including a freeze-all approach) is intended. Administration of REKOVELLE or GONAL-F after reaching the triggering criterion is not allowed.

Criterion for triggering of final follicular maturation with 250 µg hCG:

- ≥3 follicles with a diameter of ≥17 mm and intended transfer in the fresh cycle [*note:* triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm are observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering is preferred instead of cycle cancellation]

Additional criteria for triggering of final follicular maturation with 0.2 mg GnRH agonist:

- ≥25 follicles with a diameter of ≥12 mm

  or
- serum estradiol concentration ≥5,000 pg/mL (18,355 pmol/L) (local laboratory)

  or
- intended freeze-all approach

Moreover, if these criteria for triggering with GnRH agonist are not met, but the investigator judges that the subject is at risk of developing early OHSS and that triggering with hCG is not advisable, the subject can undergo triggering with GnRH agonist.

In case of poor ovarian response, defined as the investigator judging that the triggering criterion cannot be reached by day 20, the cycle is to be cancelled. In case of excessive ovarian response, defined as the investigator judging that triggering of final follicular maturation is not advisable due to safety concerns, the cycle is to be cancelled.

The investigator also has the option of cancelling the cycle for other relevant medical reasons, including adverse events.

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

- Transvaginal ultrasound of ovaries (number and size of follicles)
- Blood collection for central laboratory analysis of endocrine parameters (estradiol, and progesterone)
- Dispensing of hCG or GnRH agonist, as applicable
- Drug accountability of IMP and GnRH antagonist
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects who receive a triggering drug, the next visit is the oocyte retrieval visit which must be scheduled 36h (±2h) after the administration of hCG or GnRH agonist.

Subjects with cycle cancellation will proceed to end-of-trial assessments.

6.3 Oocyte Retrieval

Oocyte retrieval must take place 36h (±2h) after hCG or GnRH agonist administration. All oocytes from follicles with an estimated diameter of ≥12 mm must be retrieved. The procedures related to subjects attending the oocyte retrieval visit are listed below, while procedures related to the oocytes are described in section 6.4.

The following must take place at the oocyte retrieval visit:

- Oocyte retrieval
- Drug accountability of hCG or GnRH agonist, as applicable
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with oocytes retrieved following hCG administration, the next visit is the transfer visit which takes place on day 5 after oocyte retrieval.

For subjects with oocytes retrieved following GnRH agonist no transfer will take place in the fresh cycle. The oocytes will undergo the procedures described in section 6.4 and the blastocysts available on day 5 / day 6 will be cryopreserved in accordance with local guidelines and/or regulations.

Subjects with no oocytes retrieved will proceed to end-of-trial assessments.

6.4 Oocyte / Blastocyst Evaluation

The laboratory procedures regarding handling and evaluation of oocytes and blastocysts are described in a trial-specific manual. This section provides an overview of the oocyte and blastocyst evaluation. The assessment of blastocyst quality is to be performed on the last day of culture. The flow of the trial procedures for oocytes is shown in Table 6-2.

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

	Day 0 (OR)	Day 1 after OR	Day 5 after OR	Day 6 after OR
Oocyte retrieval (OR)	X			
Insemination by IVF and/or ICSI	X			
Assessment of oocyte fertilisation		X		
Assessment of blastocyst quality [a)]			X	X
Transfer in fresh cycle, if applicable			X	
Cryopreservation			X	X

a) Assessment to be performed on last day of culture only.

ICSI: intracytoplasmic sperm injection, IVF: in vitro fertilisation, OR: oocyte retrieval

Assisted hatching is prohibited.

Day 0 (Oocyte Retrieval)

- Oocyte retrieval before start of the insemination procedure
- Insemination using IVF or ICSI using ejaculated sperm (fresh or frozen) from partner or donor

Day 1 after Oocyte Retrieval

- Assessment of fertilisation

Day 5 after Oocyte Retrieval

- Assessment of number and quality of blastocysts based on the Gardner & Schoolcraft blastocyst scoring system[15] [*note:* this assessment is to be performed on last day of culture only]
- Transfer of blastocyst in fresh cycle, if applicable (section 6.6.1)
- Cryopreservation in accordance with local guidelines and/or regulations

Day 6 after Oocyte Retrieval

- Assessment of number and quality of blastocysts based on the Gardner & Schoolcraft blastocyst scoring system[15] [*note:* this assessment is to be performed on last day of culture only]
- Cryopreservation in accordance with local guidelines and/or regulations

6.5 End-of-trial

For subjects who undergo triggering of final follicular maturation, the end-of-trial visit must take place 9-14 days after triggering to cover the assessments of early OHSS (onset ≤9 days after triggering).

For subjects who do not undergo triggering of final follicular maturation, the end-of-trial assessments must be performed at the subject's last scheduled trial visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit).

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

- Physical examination
- Gynaecological examination
- Recording of use of any concomitant medication
- Recording of adverse events

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

6.6 Follow-up Assessments

Follow-up assessments are to be performed in the first transfer cycle, irrespective of whether the first transfer takes place in a fresh or frozen cycle. The first transfer cycle covers cycles with transfer occurring within 3 months after start of stimulation. The flow of the follow-up trial procedures is shown in Table 6-3.

Table 6-3 Follow-up Trial Flow Chart – First Transfer Cycle

	Transfer		Clinical pregnancy
	Fresh cycle	Frozen cycle	
	Day 5 after oocyte retrieval	Within 3 months after start of stimulation	5-6 weeks (35-48 days) after transfer
Transfer	X		
Number and quality of blastocyst(s) transferred	X		
Transvaginal ultrasound			X
Late OHSS [a)]			X

a) For subjects who undergo transfer in the fresh cycle, assessment of late OHSS (onset >9 days after triggering) will take place during the follow-up period.

OHSS: ovarian hyperstimulation syndrome

6.6.1 Transfer

The first transfer cycle can take place either in a fresh cycle or in a frozen cycle, as applicable, with the transfer occurring within 3 months after start of stimulation.

Blastocyst Transfer in a Fresh Cycle

Transfer is performed on day 5 (blastocyst stage) after oocyte retrieval. Transfer of day 6 (or later) blastocysts is not allowed in the fresh cycle.

The following must take place:

- Transfer of blastocyst(s) [*note:* the number of transferred blastocyst(s) will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations]

Blastocyst Transfer in a Frozen Cycle

Transfer of cryopreserved blastocyst(s) is performed within 3 months after start of stimulation.

The following must take place:

- Transfer of blastocyst(s) [*note:* the number of transferred blastocyst(s) will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations]

6.6.2 Clinical Pregnancy

The subject must attend a visit 5-6 weeks (35-48 days) after the transfer.

The following must take place:

- Transvaginal ultrasound of uterus to assess clinical pregnancy

If at least one gestational sac (either intrauterine or ectopic) is observed, this confirms a clinical pregnancy.

6.6.3 Late OHSS

For subjects who undergo transfer in the fresh cycle, the following will take place during the follow-up period:

- Assessment of late OHSS (>9 days after triggering)

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 Follicles (Total and by Size Category) at End-of-stimulation

Transvaginal ultrasound will be performed at the end-of-stimulation visit to count the number of follicles and measure the size of the follicles. Data will be recorded combined for the right and left ovary.

7.2.2 Serum Concentrations of Estradiol and Progesterone at End-of-stimulation

Blood samples will be drawn at stimulation day 1 and at end-of-stimulation for measurement of estradiol and progesterone. The sample on stimulation day 1 (baseline) will be collected prior to the first dose of REKOVELLE or GONAL-F.

The samples will be analysed at a central laboratory.

7.2.3 Number of Fertilised Oocytes and Fertilisation Rate

The number of pronuclei will be counted after insemination and recorded as 0, 1, 2 or >2. Fertilised oocytes with 2 pronuclei (2PN) will be regarded as correctly fertilised. Fertilisation rate is the number of 2PN oocytes divided by the number of oocytes retrieved.

7.2.4 Number of Blastocysts (Total and by Quality)

The number and quality of blastocysts will be assessed on day 5 or day 6 after oocyte retrieval. The quality evaluation of blastocysts on day 5 or day 6 (as applicable) after oocyte retrieval will consist of assessment of three parameters: blastocyst expansion and hatching status, blastocyst inner cell mass grading, and trophectoderm grading. The scoring is based on the classification system by Gardner & Schoolcraft,[15] with the addition of D-categories for inner cell mass and trophectoderm.

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.
D. Degenerative or no inner cell mass.

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.
D. Degenerative or very large cells.

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

A good-quality blastocyst is defined as a blastocyst of grade 3BB or above.[e]

7.2.5 Total Gonadotropin Dose and Number of Stimulation Days

The administration dates as well as daily dose of IMP will be recorded by the trial medication delegate and used to calculate the total REKOVELLE or GONAL-F dose administered and the number of stimulation days.

[e] 3BB and above defined as: 6AA, 6AB, 6AC, 6BA, 6BB, 6BC, 6CA, 6CB, 6CC, 5AA, 5AB, 5AC, 5BA, 5BB, 5BC, 5CA, 5CB, 5CC, 4AA, 4AB, 4AC, 4BA, 4BB, 4BC, 4CA, 4CB, 4CC, 3AA, 3AB, 3AC, 3BA, or 3BB.

7.2.6 Early OHSS (Overall and by Grade) and/or Preventive Interventions for Early OHSS

Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation.[f] Classification of grade is according to Golan's classification system (see section 8.4 for details) and all OHSS cases will be graded as mild, moderate or severe. Preventive interventions for early OHSS cover cycle cancellation due to excessive ovarian response, triggering of final follicular maturation with GnRH agonist (based on the follicular development and/or serum estradiol criteria) and administration of dopamine agonist (the latter is only considered as preventive intervention in subjects with ≥20 follicles of ≥12 mm).

7.3 Exploratory Assessment

7.3.1 Blood Collection for Potential Biomarkers

For subjects who provide additional, optional consent, blood samples will be collected at stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response.

Results of these potential future exploratory analyses will not be provided to the sites.

7.4 Other Assessments

7.4.1 Demographics

Demographic information will be obtained at screening, including the following: date of birth[g], ethnicity, race.

7.4.2 Medical History

Any relevant medical history will be recorded at screening. This includes diagnoses / symptoms and whether it is a past or ongoing occurrence.

7.4.3 Infertility History

Information about the reasons for infertility, duration of infertility, primary infertility and number of previous controlled ovarian stimulation cycles will be obtained at screening.

[f] Note this includes OHSS with onset during stimulation or before triggering.

[g] Alternatively, age may be recorded in case country-specific restrictions do not permit recording the full date of birth.

7.4.4 Body Measurements

Body height and weight will be measured at screening. Body weight will be done without shoes and overcoat and using a calibrated scale.

7.4.5 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 in 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.

7.4.6 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 in 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.

7.4.7 Concomitant Medication

The use of any concomitant medication within the last month prior to 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 medication or treatment must be recorded at each visit.

7.4.8 Drug Dispensing and Accountability

The following information will be recorded by the trial medication delegate: 1) dates of administration and daily doses of IMP, 2) time of first IMP administration, 3) dates of administration and daily doses of GnRH antagonist, 4) date and time of administration as well as dose of hCG or GnRH agonist. Details on drug dispensing and accountability are provided in section 5.6.

7.5 Assessments Related to Follow-up Information

If a subject achieves a clinical pregnancy after the first transfer cycle, irrespective of whether the first transfer takes place in a fresh or frozen cycle, it will be recorded. Clinical pregnancy will be defined as at least one gestational sac, either intrauterine or ectopic, 5-6 weeks (35-48 days) after transfer. 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.[h,16] For intrauterine and ectopic pregnancies, the number of gestational sacs with fetal heart beat as well as without fetal heart beat will be recorded. Vital pregnancy will be defined as at least one intrauterine sac with fetal heart beat 5-6 weeks (35-48 days) after transfer.

The number of blastocysts transferred in the first transfer cycle will also be recorded, allowing for calculation of implantation rate (number of gestational sacs 5-6 weeks (35-48 days) after transfer divided by number of blastocysts transferred).

7.6 Handling of Biological Samples

A trial-specific laboratory manual will be provided to the participating sites, describing in detail how to handle, store, and transport the biological samples (blood) in this trial. The biological samples analysed at central laboratories will be maintained in storage after the end of the trial. Destruction will take place within 2 years after reporting of the trial. Exceptions are the blood samples collected for potential future analysis of possible biomarkers associated with ovarian response, as well as blood samples for which methods / results have not been adequately validated; these will be stored for a maximum of 10 years after reporting of the trial, prior to destruction in line with local regulations. Potential additional blood samples analysed at local laboratories as part of screening assessments or monitoring of the subject during the trial (e.g. criterion for triggering of final follicular maturation and evaluation of OHSS), will be destroyed after analysis. The processes related to handling of biological samples will be described in the Informed Consent Form, and biobank / data protection legislation including local legislation will be adhered to.

[h] 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. In addition to intrauterine pregnancy, it includes ectopic pregnancy.

7.7 Implications of COVID-19 Pandemic

The following considerations must be taken into account due to the current coronavirus disease 2019 (COVID-19) pandemic:

- Vaccination against COVID-19
  Vaccination against COVID-19 will be recorded at screening as part of the subject's medical history and/or throughout the trial as concomitant medication, and should be reported using the term "COVID-19 immunisation". Based on the currently available information and the ESHRE position on COVID-19 vaccination and assisted reproduction[17], Ferring's risk assessment is that there will be no protocol-specific requirements on COVID-19 vaccination.
- Medical history related to COVID-19
  Past or ongoing occurrence of COVID-19 will be recorded at screening as part of the subject's medical history, and should be reported using the term "COVID-19".
- Adverse events related to COVID-19
  In case of confirmed COVID-19 by a SARS-CoV-2 positive test, the term "COVID-19" should be used to report the adverse event irrespective of the type of test. In case of suspected COVID-19 infection, the term "Suspected COVID-19" should be used to report the adverse event. In case of recording concomitant medication against COVID-19, the indication should be "COVID-19" irrespective of the treatment.
- Missing visits / missing data
  In case subjects are prevented from attending scheduled visits due to the COVID-19 pandemic, the investigator (or designee) will attempt to contact the subject by phone or other ways to inquire about potential adverse events and changes to concomitant medication. In case not attending scheduled visits due to the COVID-19 pandemic may have any implications in the drug accountability of IMP or NIMP, it should be documented by the trial medication delegate.
- Protocol deviations due to COVID-19 illness and/or COVID-19 control measures
  Protocol deviations should be avoided whenever possible except when necessary to eliminate an immediate hazard to the subject. If deviations occur they will be documented as per standard practice, with additional specification whether they were related to the COVID-19 pandemic.

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: pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events, but are recorded as medical history.]
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.

All adverse events will be coded using MedDRA (the MedDRA version will be documented).

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the last visit (end-of-trial visit). In addition, for subjects who undergo transfer in the fresh cycle, assessment of late OHSS (onset >9 days after triggering) will take place during the follow-up period.

The sources of adverse events cover:

- The subject's response to questions about his/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 for each subject in the EDC with information about:

- Adverse event description
- Date and time of onset (time can be omitted, if applicable) [note: if date of onset of an event is the same as the date of informed consent or date of IMP administration, time is important and should not be omitted]
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- End date and time (time can be omitted, if applicable)
- 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.[i] If a subject suffers from a pre-existing medical condition that worsens in intensity after signed informed consent, it should be recorded as an adverse event.

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).

[i] Exception: if an adverse event with onset before the first IMP administration (i.e. a pre-treatment adverse event) worsens in intensity after IMP administration, this must be recorded as two separate events. The initial adverse event should be recorded with outcome "not recovered", without recording end date and time. The second adverse event should be recorded with date and time of onset when the intensity changed.

Date and Time of Onset

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

Intensity

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

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

Moderate: Disruption of usual activities (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.

An adverse drug reaction is defined as an adverse event assessed to be related to the administration of IMP with a reasonable possibility.

Action Taken to IMP

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

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

Other Action Taken

Adverse events requiring therapy must be treated with 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 (the event is improving)
- Not recovered
- Fatal

8.3 Adverse Events of Special Interest

8.4 Ovarian Hyperstimulation Syndrome

Symptoms and Classification

OHSS is an adverse event of special interest during controlled ovarian stimulation. Investigators will record OHSS symptoms using a classification system based on Golan's classification system[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 (Based on Golan's Classification System)

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)] Hospitalisation due to OHSS symptoms.

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

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

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

d) 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 SAEs 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[j] and late OHSS will be defined as OHSS with onset >9days after triggering of final follicular maturation.

Subject narratives will be prepared for all moderate and severe OHSS cases.

Preventive Interventions of Early OHSS

Preventive interventions of early OHSS include the following:

- Cycle cancellation due to excessive ovarian response
- Triggering of final follicular maturation with GnRH agonist
- Administration of dopamine agonist (this is only considered as preventive intervention in subjects with ≥20 follicles of ≥12 mm)

Investigations in case of OHSS

The following investigations are recommended for moderate / severe OHSS:

- Blood sample for local laboratory analysis of the following:
  - Progesterone and estradiol
  - CBC
  - CHEM-20
  - Coagulation parameters (prothrombin time, activated partial thrombin time)

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

[j] Note this includes OHSS with onset during stimulation or before triggering.

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event 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.

8.5.2 Collection, Recording and Reporting of Serious Adverse Events in Core Trial

Serious Adverse Event Reporting by the Investigator

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

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

The same timelines and requirements apply for both the SAE Report Form and any follow-up with additional information regarding the SAE, i.e. 24 hours within obtaining knowledge of the follow-up information and 3 calendar days for providing the fullest possible details.

Serious Adverse Event Report Form

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

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: Safety.Mailbox@ferring.com
Fax: (+45) 88 38 01 47

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 EDC for Ferring Pharmacovigilance to access the information.

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

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

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

Expedited Reporting by Ferring

Ferring will report all adverse events according to local regulations.

8.6 Follow-up of Adverse Events and Serious Adverse Events

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

During the trial, the investigator must follow-up on each adverse event until the subject's last visit. 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 as specified in section 8.5.2. Follow-up must continue until the outcome of recovered, recovered with sequelae, or fatal, has been reached. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.6.2 Collection of Serious Adverse Events with Onset after Last Visit in the Trial

If an investigator becomes aware of a SAE after the subject's last visit, diagnosed either to the subject herself or to the fetus / neonate, and the investigator assesses the SAE to have a reasonable possible causality to the IMP / NIMP where Ferring is the Marketing Authorisation Holder, the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place. Follow-up must continue until the outcome of recovered, recovered with sequelae, or fatal, has been reached. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.7 Technical Complaints

If a technical complaint is identified, the investigator must assess whether it may be associated with an adverse event and/or an IMP medication error. Technical complaints are reported in accordance with the Trial Supply Manual.

9 STATISTICAL METHODS

9.1 Justification of Sample Size

In a previous trial (MERIT)[19], 347 subjects aged 22-37 years were treated with a starting dose of 225 IU GONAL-F. In these subjects the mean number of oocytes retrieved was 11.8 and the standard deviation was 5.7. Assuming that the standard deviation for number of oocytes retrieved in this trial will be 6.0, a total sample size of 300 with a 2:1 randomisation will give a 2-sided 95% confidence interval ranging from -1.44 to +1.44 oocytes from the observed difference. This level of precision is considered as sufficient and is also more precise than the equivalence limits of ±3 oocytes that has been applied in previous trials comparing biosimilar FSH compounds.

9.2 Subject Disposition

The subject disposition will include all screened subjects and describe the number of randomised, treated, completed and discontinued subjects, including reason for discontinuation. For screening failures, the primary reason for screening failure will be described.

9.3 Protocol Deviations

Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the trial data or that might significantly affect a subject's rights, safety, or well-being. Important protocol deviations will be summarised by category and treatment group to reflect general protocol adherence. No protocol deviations will lead to exclusion of data from the efficacy analyses. Protocol deviations related to the COVID-19 pandemic will be identified.

9.4 Analysis Sets

9.4.1 Full Analysis Set

The full analysis set (FAS) will consist of all randomised subjects exposed to IMP. Subjects will be analysed according to the planned (randomised) treatment.

9.4.2 Safety Analysis Set

The safety analysis set will consist of all randomised subjects exposed to IMP. Subjects will be analysed according to the actual treatment received.

9.5 Trial Population

Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics (body measurements, ultrasound parameters, endocrine parameters) will be presented for the FAS. A summary of demographic characteristics will be presented by trial site.

Medical History

Medical history will be coded using MedDRA. The version of MedDRA will be documented. Medical history will be summarised for the FAS.

Infertility History

Infertility history will be summarised for the FAS.

Physical Examination and Gynaecological Examination

Physical examination and gynaecological examination performed during screening will be summarised for the FAS.

Concomitant Medication

Concomitant medications will be coded using the WHO Drug Reference List. Prior and concomitant medication will be summarised by Anatomical Therapeutic Chemical Classification System (ATC) classification first level (alphabetically) and ATC classification second level for the FAS. The following definitions will be used:

- Prior medication: medication taken exclusively prior to treatment (i.e. with stop date / time before date / time of first IMP administration)
- Concomitant medication: medication taken during the treatment period (i.e. medication that was not stopped before date / time of first IMP administration and not started after the end-of-trial visit)

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

9.6 Treatment Compliance

Use of IMP and NIMP will be described for the FAS.

9.7 Endpoint Assessments

9.7.1 General Considerations

Analyses of efficacy endpoints will be based on the FAS. Description of safety data will be based on the safety analysis set. Results of statistical analyses will include the estimated treatment difference (or ratio), a 95% confidence interval for the difference (or ratio), and the p-value for the test of no treatment difference. All analyses are of descriptive nature and no adjustments for multiple tests will be applied.

Missing data will in general not be imputed. For subjects without oocyte retrieval, the number of oocytes, fertilised oocytes, and blastocysts will be regarded as zero. For pregnancy data, lack of data will be interpreted as a negative pregnancy.

9.7.2 Primary Endpoint

The primary endpoint, number of oocytes retrieved, will be compared between REKOVELLE and GONAL-F using a negative binomial model with treatment and AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as factors. The absolute treatment difference in number of oocytes retrieved, the associated 95% confidence interval, and the p-value for no treatment difference will be derived from the model estimates using the delta method.

The distribution of the number of oocytes retrieved will be described using kernel estimates. Furthermore, the ovarian response will be grouped according to the following classification:

- <4 oocytes or cycle cancellation due to poor ovarian response
- 4-7 oocytes
- 8-14 oocytes
- 15-19 oocytes
- ≥20 oocytes or cycle cancellation due to excessive ovarian response
- Cycle cancellation due to another reason than poor or excessive ovarian response

The treatment difference will also be investigated for the two sub-groups AMH <15 pmol/L and AMH ≥15 pmol/L using the same methods as above.

9.7.3 Secondary Endpoints

Number of Follicles (Total and by Size Category) at End-of-stimulation

The follicle cohort at end-of-stimulation will be summarised by treatment on the subject level (total number of follicles, and number of follicles ≥10 mm, ≥12 mm, ≥15 mm and ≥17 mm).

The mean number of follicles ≥10 mm, ≥12 mm, ≥15 mm and ≥17 mm at end of stimulation will (in separate analyses) be compared between treatments using the same negative binomial regression model as used for the primary endpoint.

Serum Concentrations of Estradiol and Progesterone at End-of-stimulation

Serum concentrations of estradiol and progesterone at the end-of-stimulation visit will be compared between treatments using analysis of covariance (ANCOVA) models with treatment and AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as factors and with the serum concentration at stimulation day 1 as a covariate. Multiplicative models will be used, i.e. the serum concentrations will be log-transformed before analysis. The results of the analyses will be back-transformed and presented as estimated geometric means and mean treatment ratios with 95% confidence intervals and p-values. Values below the lower limit of quantification (LLOQ) will be estimated with LLOQ/2. Potential values above the upper limit of quantification (ULOQ) will be included as ULOQ.

Number of Fertilised Oocytes and Fertilisation Rate

An oocyte is defined as fertilised if it is scored as 2 pronuclei on day 1 after oocyte retrieval. The mean number of fertilised oocytes will be compared between treatments using the same analysis method as for the primary endpoint.

The proportion of oocytes becoming fertilised will be estimated and compared between treatments using a mixed effect binomial model with treatment and AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as fixed factors, and subject as random factor, assuming normally distributed log-odds. The treatment difference in fertilisation probability and the associated 95% confidence interval will be derived using the delta method. This analysis is based on subjects with >0 oocytes retrieved only and is therefore not randomisation based. The fertilisation ratio is expected to be equal for the two treatments. If this is not the case, the reason for differences will be further explored by including e.g. number of oocytes retrieved as a covariate in the analysis model.

Number of Blastocysts (Total and by Quality)

The number and quality of blastocysts on day 5 or day 6 will be described.

Total Gonadotropin Dose and Number of Stimulation Days

The total gonadotropin dose, the average daily dose, and the number of stimulation days will be described for each treatment and also for the subgroups of subjects with AMH <15 pmol/L and AMH ≥15 pmol/L. Occurrence of dose adjustments during stimulation will be described.

The number of stimulation days will be compared between treatments using an analysis of variance model with treatment and AMH level at stimulation at day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as factors.

Early OHSS (Overall and by Grade) and/or Preventive Interventions for Early OHSS

Incidence of early OHSS will be summarised by classification (mild, moderate, severe, moderate or severe) and grade (1, 2, 3, 4, 5). Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation.[k]

Preventive interventions for early OHSS, as well as early OHSS and/or preventive interventions for OHSS will be summarised.

Data will be described for each treatment and also for the subgroups of subjects with AMH <15 pmol/L and AMH ≥15 pmol/L.

9.8 Exploratory Assessment

Blood Collection for Potential Biomarkers

Potential future analysis of possible biomarkers associated with ovarian response will be reported separately from the clinical trial report.

9.9 Adverse Events

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

[k] Note this includes OHSS with onset during stimulation or before triggering.

Treatment-emergent adverse events will be presented in summary tables and listings. Pre-treatment adverse events will be presented in a listing only. Treatment-emergent adverse events will be summarised overall and tabulated by System Organ Class (SOC) and Preferred Term (PT). The total number of subjects reporting an adverse event, the percentage of subjects with an adverse event, and the number of events reported will be described.

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.

For adverse events, a worst-case approach will be used for causality, intensity, seriousness, and outcome, in case these would be missing. If the timing of the onset of an adverse event cannot be established in relation to IMP, it will be considered as a treatment-emergent adverse event.

9.10 Additional Safety Evaluations

Physical Examination

Physical examination at screening and end-of-trial will be summarised in shift tables.

Gynaecological Examination

Gynaecological examination at screening and end-of-trial will be summarised in shift tables.

9.11 Follow-up Assessments

For subjects with a clinical pregnancy, the type of clinical pregnancy (intrauterine or ectopic) will be described. For subjects with a vital pregnancy, the number of intrauterine gestational sacs with fetal heart beat and the number of fetal heart beats will also be described.

Pregnancy rates in the first transfer cycle will be compared between treatments using logistic regression models with treatment and age group (<35, 35-37, or 38-40 years) as factors. The results of these analyses (in terms of odds for pregnancy) will be converted into proportions, differences in proportions, and 95% CIs for differences in proportions using the delta method. In these analyses subjects with no transfer or missing data on pregnancy will be regarded as non-pregnant.

The implantation rate in the first transfer cycle will be estimated and compared between treatments using a mixed effect logistic regression model with treatment, age group (<35, 35-37, or 38-40 years), and number of blastocysts transferred (single or multiple) as fixed factors, and subject as random factor, assuming normally distributed log-odds. The estimated treatment difference in

probability of implantation and the associated 95% confidence interval will be calculated from the model estimates using the delta method. This analysis is based on subjects with transfer only and is therefore not randomisation based. The treatment difference for implantation rate is expected to be consistent with the treatment difference for pregnancy rates. If this is not the case, the reason for differences will be further explored by including e.g. day of transfer as a factor in the analysis model.

For subjects who undergo transfer in the fresh cycle, incidence of late OHSS will be summarised by classification (mild, moderate, severe, moderate or severe) and grade (1, 2, 3, 4, 5). Late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation. Data will be described for each treatment and also for the subgroups of subjects with AMH <15 pmol/L and AMH ≥15 pmol/L.

9.12 Interim Analyses

No interim analysis is planned.

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 screened, the investigator will indicate as a minimum in the source documents, that the informed consent is obtained, that the subject participates in this trial, and whether the subject is a screening failure and the reason for screening failure, if applicable. In addition, for each subject randomised the investigator will indicate in the source documents at least the following information, if applicable:

- Existence of subject (initials, date of birth)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent (date and time of obtaining written informed consent)
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical history and infertility history
- Body weight and height
- Visit dates
- Dates and daily doses of IMP
- Dates and daily doses of NIMP
- Dates and dosage regimen of concomitant medication
- Follicular development

- Date of oocyte retrieval and number of oocytes retrieved
- Number and quality of blastocysts
- Adverse events (description as well as start / stop date and time)
- OHSS symptoms, preventive interventions, investigations and treatments
- Reason for discontinuation, if applicable
- Event of unblinding, including the reason for unblinding
- Date of transfer and number of blastocysts transferred (first transfer cycle)
- Ultrasound results at clinical pregnancy visit (first transfer cycle)

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

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

The source data for the endocrine parameters will be available at the central laboratory.

10.2 EDC

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

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

The investigator will, in a timely manner, approve / authorise the EDC 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 EDC and the database will be hosted at the independent third-party CRO. 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 subject treatment allocation, audit trail, electronic signature and queries) as write-protected pdf-files produced by the independent third-party CRO. The pdf-files will be stored in an electronic format and will be provided to the investigator before access to the EDC is revoked.

Errors occurring in the EDC entries 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, Ferring. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection and validation.

The data management plan will also include information about the intended use of computerised systems, a description of the security measures employed to protect the data, and a description of the electronic data flow.

10.4 Provision of Additional Information

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

11 MONITORING PROCEDURES

11.1 Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Council for Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of EDC 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. Clinical trial site monitoring may also be conducted remotely. In addition to on-site monitoring visits, remote monitoring is also an option. Remote monitoring is conducted off-site and may include video conference, telephone contact, and remote review of trial systems.

When the first subject is randomised at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of monitoring visits per site will be determined through a risk-based approach depending on recruitment rate, observed data quality, and overall site performance. The source data verification process and definition of key variables to be monitored will be described in detail in the Monitoring Plan for the trial.

11.2 Audit and Inspection

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

The main purposes of an audit or inspection are to evaluate trial conduct and compliance with the trial protocol, ICH-GCP, including the Declaration of Helsinki[20] 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 IECs/IRBs may wish to inspect their medical records. During audits / inspections the auditors / inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomisation number will appear on these copies.

The investigator should notify Ferring without any delay of any inspection by a regulatory authority or IEC/IRB.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the EDC 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, if applicable, prior to its implementation. Amendments may be submitted for consideration to the approving IECs/IRBs and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to IEC/IRB approval or favourable opinion.

12.2 Deviations from the Protocol

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

12.3 Premature Trial Termination

At any time, the investigator has the right to terminate his/her participation in the trial, and Ferring has the right to terminate the trial at any time. Should termination 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 IECs/IRBs will be informed.

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

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory investigator. The signatory investigator will be one of the principal investigators participating in the trial who will be assigned by Ferring prior to initiation of this trial. The choice of the signatory investigator among the participating investigators will be based on several criteria, such as previous participation in GCP trials, national recognition as a fertility expert, and willingness to support this trial including signing the clinical trial report.

13.2 Confidentiality and Ownership of Trial Data

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

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and Ferring. In a multi-site trial, any publication must acknowledge all sites, and the results must be reported in a responsible and coherent manner. Ferring requires that the results from multi-site trials are published only in their entirely, and not as individual site data.

In addition, the following requirements must be adhered to:

(i) a presentation or publication of the results must not take place until eighteen (18) months after locking of the trial database, unless a) the results of the trial have already been published by Ferring, or b) specific written permission for publication is obtained in advance from Ferring;

(ii) at least sixty (60) days in advance of any publication or presentation (or submission hereof) related to the trial, a copy of the relevant publication or presentation must be furnished to Ferring for review and redaction of confidential information. At Ferring's request, investigator(s) must delay the publication or presentation for up to an additional ninety (90) days to enable Ferring to file patent applications or other intellectual property protection;

(iii) Ferring must be identified as the sponsor of the trial in any publication and presentation (including professional meetings and symposia).

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

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

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate public registry, e.g. www.clinicaltrials.gov; a website maintained by the National Library of Medicine (NLM) at the U.S. National Institutes of Health (NIH). The trial will also be made publicly available at the EU Clinical Trials Register at www.clinicaltrialsregister.eu. Trial registration may occur in other registries in accordance with local regulatory requirements. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee / Institutional Review Board

An IEC/IRB will review the protocol, any potential protocol amendments and potential advertisements used for recruitment. The IEC/IRB will review the Informed Consent Form, its updates (if any), and any written materials given to the subjects. A list of all IECs/IRBs to which the protocol has been submitted and the name of the committee chairmen will be included in the Clinical Trial Report.

14.2 Regulatory Authorities Authorisation / Approval / Notification

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

14.3 End-of-trial and End-of-trial Notification

The end of the trial is defined as the date of LPLV (last patient's end-of-trial visit).

The primary completion date is when the last subject undergoes oocyte retrieval.

The sponsor shall make an end-of-trial declaration to the regulatory authorities and the concerned IEC/IRBs in the participating countries, when the last data in the post-trial follow-up period has been collected in all participating countries.

In the case of early termination, Ferring must notify the end of the trial to the national regulatory authorities and the concerned IECs/IRBs 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 IECs/IRBs.

14.4 Ethical Conduct of the Trial

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

14.5 Subject Information and Consent

Informed Consent Form

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 must be signed and dated by the subject and the investigator (or the person delegated by the investigator) who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility.

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

The subject will receive a copy of the 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 IECs/IRBs (and regulatory authorities, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

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

Optional Consent for Potential Future Analysis of Possible Biomarkers

The investigator (or the person delegated by the investigator) will obtain, within the same Informed Consent Form, additional, optional consent from the subject after an appropriate explanation of the potential future analysis of possible biomarkers associated with ovarian response, and information that participation is optional.

The investigator (or the person delegated by the investigator) will explain that the subject is completely free to refuse to consent to this optional extra blood sample, without any consequences for her further care and without the need to justify her decision.

Partner Privacy Notice

The privacy notice explains the possibility that the partner's personal information (such as name, infertility diagnosis, etc.) may be included in the subject's medical records.

The partner will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, IEC/IRB representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may have access to the partner's personal information (such as name, infertility diagnosis, etc.). Protection of personal data will be handled in accordance with national / local regulations. Ferring will not collect, use or store any of the partner's personal data. The partner privacy notice must be given to the partner before the subject is randomised.

14.6 Trial Participation Card

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

- That she is participating in a clinical trial
- That the trial involves controlled ovarian stimulation with recombinant FSH
- The name and phone number of the investigator
- The name, address, and phone number of Ferring contact (as required by local regulations).

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

14.7 Compliance Reference Documents

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

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor and the investigator 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, including being responsible for all trial-related medical decisions, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

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

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records that enable the conduct of the trial at the site to be fully understood, and for maintaining a record of the location of their essential documents including source documents, in accordance 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 EDC 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.

17 REFERENCES

1 Arce J-C, Larsson P, García-Velasco JA. Establishing the follitropin delta dose that provides a comparable ovarian response to 150 IU/day follitropin alfa. Reprod Biomed Online 2020; 41: 616-622.

2 REKOVELLE Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/rekovelle-epar-product-information_en.pdf

3 GONAL-F Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/gonal-f-epar-product-information_en.pdf

4 Daya, S. Issues in assessing therapeutic equivalence. Evidence-based Obstetrics and Gynecology 2001; 3: 167-168.

5 Daya, S. Pitfalls in the design and analysis of efficacy trials in subfertility. Hum Reprod 2003; 18: 1005-1009.

6 Griesinger G, von Otte S, Schroer A, Ludwig AK, Diedrich K, Al-Hasani S, Schultze-Mosgau A. Elective cryopreservation of all pronuclear oocytes after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS: a prospective, observational proof-of-concept study. Hum Reprod 2007; 22: 1348-1352.

7 Griesinger G, Kolibianakis EM, Papanikolaou EG, Diedrich K, Van Steirteghem A, Devroey P, Ejdrup Bredkjær H, Humaidan P. Triggering of final oocyte maturation with gonadotropin-releasing hormone agonist or human chorionic gonadotropin. Live birth after frozen-thawed embryo replacement cycles. Fertil Steril 2007; 88: 616-621.

8 Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril 2008; 89: 84-91.

9 Humaidan P, Papanikolaou EG, Tarlatzis BC. GnRHa to trigger final oocyte maturation: a time to reconsider. Hum Reprod 2009; 24: 2389-2394.

10 Herrero L, Pareja S, Losada C, Cobo AC, Pellicer A, García-Velasco JA. Avoiding the use of human chorionic gonadotropin combined with oocyte vitrification and GnRH agonist triggering versus coasting: a new strategy to avoid ovarian hyperstimulation syndrome. Fertil Steril 2011; 95: 1137-1140.

[11] Bodri D, Guillén JJ, Trullenque M, Schwenn K, Esteve C, Coll O. Early ovarian hyperstimulation syndrome is completely prevented by gonadotropin releasing-hormone agonist triggering in high-risk oocyte donor cycles: a prospective, luteal-phase follow-up study. Fertil Steril 2010; 93: 2418-2420.

[12] FYREMADEL Summary of Product Characteristics.

[13] OVITRELLE Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/ovitrelle-epar-product-information_en.pdf

[14] GONAPEPTYL Summary of Product Characteristics.

[15] Gardner DK, Schoolcraft WB. In vitro culture of human blastocysts. In: Towards reproductive certainty (Eds Jansen R & Mortimer D). The plenary proceedings of the 11th world congress on in vitro fertilisation and human reproductive genetics. The Parthenon Publishing Group. 1999. Pp 378-388.

[16] Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, Rienzi L, Sunde A, Schmidt L, Cooke ID, Simpson JL, van der Poel S. The International Glossary on Infertility and Fertility Care, 2017, 2017. Fertil Steril 2017; 1083: 393-406.

[17] European Society of Human Reproduction and Embryology (ESHRE) statement on COVID-19 vaccination and medically assisted reproduction. https://www.eshre.eu/Europe/Position-statements/COVID19/vaccination (Accessed on 23 April 2021)

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

[19] Nyboe Andersen A, Devroey P, Arce J-C. Clinical outcome following stimulation with HP-hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Hum Reprod 2006; 21: 3217-3227.

[20] World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

STATISTICAL ANALYSIS PLAN

A randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the ovarian response of a starting dose of 15 µg follitropin delta (REKOVELLE) to a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme

Trial 000401

ADAPT-1
(Assessment of Conventional Dosing in Women undergoing ART with Follitropin Delta Treatment)

Investigational Medicinal Product:	Follitropin delta (REKOVELLE) (Ferring compound ID: FE 999049) human recombinant follicle-stimulating hormone (rFSH)
Indication:	Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle
Phase:	3b

Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes
1.0	08OCT2024	First version	None
2.0		Technical update of header to include REAL ID. No change in content.	1.0

TABLE OF CONTENTS

List of Tables

List of Figures

1 INTRODUCTION

This document describes the planned statistical analyses for the trial 000401 and is based on the final Clinical Trial Protocol version 2.0 dated 21st of January 2022. If there are any differences between the statistical analysis plan (SAP) and the protocol, the SAP will reflect the updated statistical analyses. Main changes to the statistical analyses compared to the protocol, and the reasons for these, are described in Section 13.

1.1 Abbreviations

AE	adverse event
AMH	anti-müllerian hormone
ART	assisted reproductive technologies
ATC	anatomic therapeutic chemical
BMI	body mass index
EOS	end-of-stimulation
FAS	full-analysis set
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
ICSI	intracytoplasmic sperm injection
IMP	investigational medicinal product
IU	international units
IVF	in vitro fertilisation
LH	luteinising hormone
LLOQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities
NIMP	non-investigational medicinal product
OHSS	ovarian hyperstimulation syndrome
OR	oocyte retrieval
PD	protocol deviation
PN	pronuclei
PP	per-protocol
PT	preferred term
rFSH	recombinant follicle-stimulating hormone
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
ULOQ	upper limit of quantification

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To compare a starting dose of 15 µg REKOVELLE to a starting dose of 225 IU GONAL-F in conventional regimens with respect to ovarian response in women undergoing controlled ovarian stimulation

Secondary Objectives

- To compare the follicular development, endocrine profile and embryo development associated with conventional dosing of REKOVELLE and GONAL-F
- To compare the treatment efficiency associated with conventional dosing of REKOVELLE and GONAL-F
- To compare the safety profile associated with conventional dosing of REKOVELLE and GONAL-F

2.2 Endpoints

Primary Endpoint

- Number of oocytes retrieved

Secondary Endpoints

- Number of follicles (total and by size category) at end-of-stimulation
- Serum concentrations of estradiol and progesterone at end-of-stimulation
- Number of fertilised oocytes and fertilisation rate
- Number of blastocysts (total and by quality)
- Total gonadotropin dose and number of stimulation days
- Early OHSS (overall and by grade) and/or preventive interventions for early OHSS

Exploratory Assessment

- Blood sample on stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response (requires additional, optional consent)

Follow-up Assessments

- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer) in the first transfer cycle

- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred) in the first transfer cycle

Note: the first transfer cycle covers cycles with transfer occurring within 3 months after start of stimulation

3 TRIAL DESIGN

3.1 Overall Design and Control Methods

Trial period

This is a randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the ovarian response associated with a starting dose of 15 µg follitropin delta (REKOVELLE) and a starting dose of 225 IU follitropin alfa (GONAL-F) in conventional regimens. The primary endpoint is the number of oocytes retrieved, and secondary endpoints include pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation. Treatment efficiency in terms of gonadotropin use and duration of stimulation will also be evaluated. The assessor-blind design ensures that the investigators and other assessors such as embryologists are blinded to individual treatment allocation. A trial medication delegate will be responsible for all trial medication related issues, both practically at the clinic and in interactions with the subject.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. On day 2-3 of the menstrual cycle, subjects will be randomised in a 2:1 ratio to treatment with either REKOVELLE or GONAL-F, and stimulation will be initiated. Subjects randomised to REKOVELLE will receive a daily starting dose of 15 µg which will be fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily REKOVELLE dose can be increased or decreased by 5 µg based on the subject's response. The minimum REKOVELLE dose is 5 µg and the maximum REKOVELLE dose is 20 µg. Subjects randomised to GONAL-F will receive a daily starting dose of 225 IU which will be fixed for at least the first four stimulation days. Dose adjustments may be implemented on the day of starting the GnRH antagonist (stimulation day 5 or day 6) or later, and can occur no more frequently than once every second day. At each dose adjustment, the daily GONAL-F dose may be adjusted by 75 IU based on the subject's response. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU. Subjects can be treated with rFSH for a maximum of 20 days, and coasting is not allowed.

To prevent a premature LH surge, a GnRH antagonist (ganirelix acetate, FYREMADEL, SUN Pharma) will be initiated on stimulation day 5 or day 6 at a daily dose of 0.25 mg and continued throughout the stimulation period. Triggering of final follicular maturation will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed (i.e. on the day or the day after). Triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm are observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering

is preferred instead of cycle cancellation. The triggering drug will be either human chorionic gonadotropin (hCG) or GnRH agonist, depending on the extent of ovarian response and whether transfer in the fresh cycle or in a subsequent frozen cycle (including a freeze-all approach) is intended. If transfer in the fresh cycle is intended, 250 µg hCG (choriogonadotropin alfa, OVITRELLE, Merck) will be administered. If there are ≥25 follicles with a diameter ≥12 mm or the serum estradiol is ≥5,000 pg/mL (18,355 pmol/L) (local laboratory) or a freeze-all approach is intended, 0.2 mg GnRH agonist (triptorelin acetate, GONAPEPTYL, Ferring) will be administered. Moreover, if these criteria for triggering with GnRH agonist are not met, but the investigator judges that the subject is at risk of developing OHSS and that triggering with hCG is not advisable, the subject can undergo triggering with GnRH agonist. In case of poor ovarian response, defined as the investigator judging that the triggering criterion cannot be reached by day 20, the cycle is to be cancelled. In case of excessive ovarian response, defined as the investigator judging that triggering of final follicular maturation is not advisable due to safety concerns, the cycle is to be cancelled. The number and size of follicles at the end-of-stimulation will be recorded.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation. All oocytes from follicles with an estimated diameter ≥12 mm must be retrieved. The oocytes can be inseminated by IVF and/or ICSI. Fertilisation will be assessed on day 1 after oocyte retrieval. The number and quality of blastocysts will be assessed at the last day of culture, i.e. day 5 or day 6 (as applicable) after oocyte retrieval. The day 5 / day 6 blastocyst quality assessment will be based on the Gardner & Schoolcraft blastocyst scoring system.[1] Blastocysts that are not transferred in the fresh cycle will be cryopreserved in accordance with local guidelines and/or regulations.

Blood samples will be collected at stimulation day 1 for measurement of AMH, estradiol and progesterone as well as at end-of-stimulation for measurement of estradiol and progesterone. For subjects who provide additional, optional consent, blood samples will be collected at stimulation day 1 for potential future analysis of possible biomarkers associated with ovarian response.

For subjects who undergo triggering of final follicular maturation, the end-of-trial visit must take place 9-14 days after triggering to cover the assessment of early OHSS (onset ≤9 days after triggering). For subjects who do not undergo triggering of final follicular maturation, the end-of-trial assessments must be performed at the subject's last scheduled trial visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit). If trial procedures and/or assessments are to be performed on Sundays, public holidays or outside the opening hours of the clinic, the procedures and/or assessments can be postponed to the upcoming weekday (maximum one day after original visit schedule).

Follow-up Period – First Transfer Cycle
Follow-up information will be collected from the subject's first transfer cycle, irrespective of whether the first transfer takes place in a fresh or frozen cycle. This follow-up covers cycles with the transfer procedure occurring within 3 months after start of stimulation.

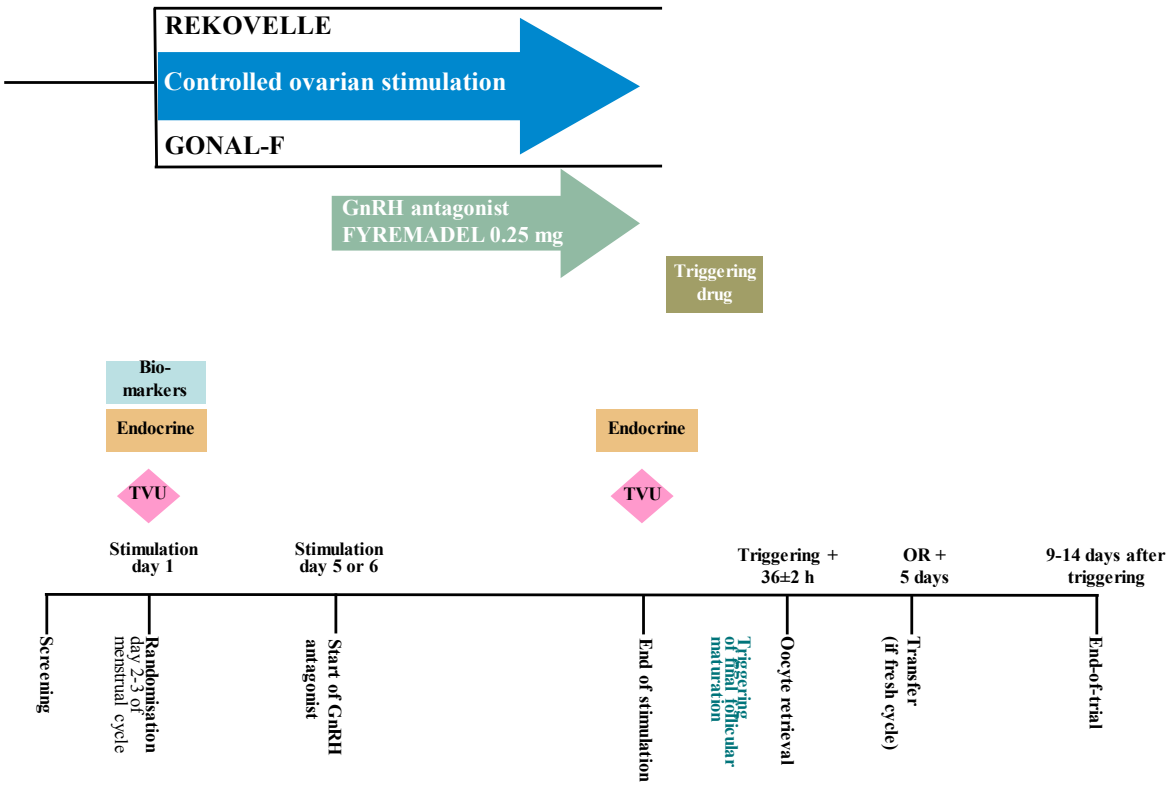
Depending on blastocyst availability, it is expected that subjects who underwent triggering of final follicular maturation with hCG will undergo transfer on day 5 after oocyte retrieval and that

subjects who underwent triggering of final follicular maturation with GnRH agonist will undergo transfer in a frozen cycle using blastocysts cryopreserved on day 5 or day 6 after oocyte retrieval. The number of transferred blastocyst(s) in the first fresh or frozen cycle will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations. The number and quality of transferred blastocyst(s) will be recorded. Luteal phase support in fresh and frozen cycles as well as potential other medicinal products for programming of frozen cycles will be in accordance with the site's clinical practice.

Clinical pregnancy in the first transfer cycle will be assessed by transvaginal ultrasound 5-6 weeks (35-48 days) after transfer, and the number of gestational sacs will be recorded. For subjects who undergo transfer in the fresh cycle, assessment of late OHSS (onset >9 days after triggering) will take place during the follow-up period.

3.1.1 Trial Design Diagrams

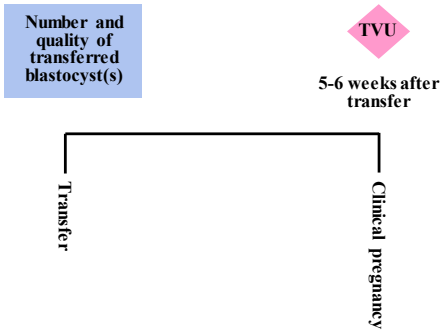
A diagram illustrating the trial period is shown in Figure 3-1.



OR: Oocyte retrieval; TVU: Transvaginal ultrasound

Figure 3-1 Trial Diagram – Trial Period

A diagram illustrating the follow-up period in the first transfer cycle is shown in Figure 3-2.



TVU: Transvaginal ultrasound

Figure 3-2 Trial Diagram – Follow-up Period (First Transfer Cycle)

3.1.2 Trial Flow Chart – Subject Procedures

The flow of the trial procedures for subjects is shown in Table 3-1.

Table 3-1 Trial Flow Chart – Subject Procedures

	Screening	Stimulation			Oocyte retrieval	End
		Start of stimulation	Start of GnRH antagonist	End-of-stimulation		End-of-trial [a]
	<90 days before randomisation	Day 1	Day 5 or day 6 [b]	End	36h ± 2h after triggering	
Written informed consent	X					
Inclusion/exclusion criteria	X	X [c]				
Demographics	X					
Medical history	X					
Infertility history	X					
Body weight, height	X					
Physical examination	X					X
Gynaecological examination	X					X
Urinary pregnancy test	X	X [c]				
Transvaginal ultrasound		X [c]		X		
Blood collection, endocrine [d]		X [c]		X		
Blood collection, potential biomarkers [e]		X [c]				
Randomisation		X				
IMP dispensing		X	X			
NIMP dispensing			X	X		
Oocyte retrieval					X	
Drug accountability			X	X	X	
Concomitant medication	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

a) For subjects who undergo triggering of final follicular maturation, the end-of-trial visit must take place 9-14 days after triggering to cover the assessment of early OHSS (onset ≤9 days after triggering). For subjects who do not undergo triggering of final follicular maturation, the end-of-trial assessments must be performed at the subject's last scheduled trial visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit).
b) GnRH antagonist will be initiated on stimulation day 5 or day 6.
c) Performed before the first IMP dose.
d) Stimulation day 1: AMH, estradiol and progesterone; end-of-stimulation: estradiol and progesterone.
e) Additional, optional, consent required.

GnRH: gonadotropin-releasing hormone, IMP: investigational medicinal product, NIMP: non-investigational medicinal product, OHSS: ovarian hyperstimulation syndrome

3.1.3 Trial Flow Chart - Oocyte / Blastocyst Procedures

The flow of the trial procedures for oocytes and blastocysts is shown in Table 3-2.

Table 3-2 Trial Flow Chart – Oocyte / Blastocyst Procedures

	Day 0 (OR)	Day 1 after OR	Day 5 after OR	Day 6 after OR
Oocyte retrieval (OR)	X			
Insemination by IVF and/or ICSI	X			
Assessment of oocyte fertilisation		X		
Assessment of blastocyst quality [a)]			X	X
Transfer in fresh cycle, if applicable			X	
Cryopreservation			X	X

a) Assessment to be performed on last day of culture only.

ICSI: intracytoplasmic sperm injection, IVF: in vitro fertilisation, OR: oocyte retrieval

3.2 Determination of Sample Size

In a previous trial (MERIT)[2], 347 subjects aged 22-37 years were treated with a starting dose of 225 IU GONAL-F. In these subjects the mean number of oocytes retrieved was 11.8 and the standard deviation was 5.7. Assuming that the standard deviation for number of oocytes retrieved in this trial will be 6.0, a total sample size of 300 with a 2:1 randomisation will give a 2-sided 95% confidence interval ranging from -1.44 to +1.44 oocytes from the observed difference. This level of precision is considered as sufficient and is also more precise than the equivalence limits of ±3 oocytes that has been applied in previous trials comparing biosimilar FSH compounds.

4 SUBJECT DISPOSITION

The subject disposition will include all screened subjects and describe the number of randomised, treated, completed and discontinued subjects, including reason for discontinuation. Screened subjects who discontinue from the trial prior to randomisation are classified as screening failures. Screening failures and the primary reason for screening failure will be described. Subject disposition with respect to analysis sets will also be tabulated and will include the number of subjects in the Intention-To-Treat (ITT) Analysis Set, the Full Analysis Set (FAS), the Per-Protocol (PP) Analysis Set and the Safety Analysis Set. Subject disposition tables will be produced overall and by AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) and will include the two treatment groups (i.e. REKOVELLE and GONAL-F) and a total column.

5 PROTOCOL DEVIATIONS

Important protocol deviations (PDs) will be rated as either minor or major. Protocol deviations substantially impacting the primary endpoint and thereby affecting the conclusions of the trial will be rated as major. Major protocol deviations will lead to exclusion of data from the PP analysis set. Data will not be excluded from the data analysis in case of minor protocol deviations.

The rating of the important PDs as 'minor' and 'major' will be decided by the Statistician and Medical responsible based on a blinded review of data before declaration of clean file and lock of database. Major protocol deviations will be summarised by category and treatment group to reflect general protocol adherence.

Major protocol deviations will be tabulated and listed by subject for the FAS. The list will be sorted by country, centre and subject number.

6 ANALYSIS SETS

6.1 Intention-To-Treat Analysis Set

The intention-to-treat (ITT) analysis set comprises all randomised subjects. Subjects will be analysed according to the planned (randomised) treatment.

6.2 Full Analysis Set

The full analysis set (FAS) will consist of all randomised subjects exposed to IMP. Subjects will be analysed according to the planned (randomised) treatment.

6.3 Per-Protocol Analysis Set

The Per-Protocol (PP) analysis set is defined as all randomised and exposed subjects except those with major protocol deviations as described in Section 5.

6.4 Safety Analysis Set

The safety analysis set will consist of all randomised subjects exposed to IMP. Subjects will be analysed according to the actual treatment received.

7 TRIAL POPULATION

7.1 Demographics and other Baseline Characteristics

All relevant baseline data obtained before first exposure to IMP will be based on the FAS and tabulations will be produced overall and by AMH level at stimulation day 1 (AMH<15 pmol/L, AMH ≥15 pmol/L, or missing) and will include both treatment groups and a total column. Baseline data will not be compared using statistical tests. 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. Missing data will not be imputed.

7.1.1 Demographics

The following demographic information will be tabulated: Age at randomisation (years), age category at randomisation (<35, 35-37, 38-40), ethnicity, race and country.

7.1.2 Body Measurements

The following body measurements at screening will be summarised: Body weight (kg), body weight category (<45, 45-<55, 55-<65, 65-<75, 75-<85, 85-<95, ≥95), height (m), BMI (kg/m^2), BMI category (<18.5, 18.5-<25.0, 25.0-<30.0, ≥30.0).

7.1.3 Endocrine Parameters

The following endocrine parameters measured at stimulation day 1 will be tabulated: AMH (pmol/L), AHM category (<15 pmol/L, ≥15 pmol/L, missing), progesterone (nmol/L) and estradiol (pmol/L).

7.1.4 Transvaginal ultrasound

The number of antral follicles on stimulation day 1 will be summarised and tabulated using categories (0-4, 5-9 and ≥10 antral follicles).

7.1.5 Medical History

Medical history recorded at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarised. The version of MedDRA will be documented.

7.1.6 Infertility History and Previous Fertility Treatment

The following data on infertility history will be tabulated: Number of subjects with primary infertility, duration of infertility (months) and primary reason for infertility.

The following data on previous fertility treatment cycles will be tabulated: Number of subjects with at least one previous fertility treatment cycle and number of previous fertility treatment cycles per subject.

7.1.7 Gynaecological Examination

Gynaecological examination performed at screening covers the categories breast, external genitalia, vagina, cervix, uterus, ovaries and fallopian tubes. Each category will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Gynaecological examination at screening will be summarised by category.

7.1.8 Physical Examination

Physical examination performed at screening covers the categories general appearance, central and peripheral nervous system, head and neck, respiratory system, cardiovascular system, gastrointestinal system, lymphatic system, urinary system, musculoskeletal system and skin. Each category will be evaluated as normal, abnormal not clinically significant, abnormal clinically significant or not done. Physical examination at screening will be summarised by category.

8 PRIOR AND CONCOMITANT MEDICATION

Medications will be coded using the World Health Organization Drug Reference List and categorised as either

- Prior medication: medication taken exclusively prior to treatment (i.e. with stop date/time before date/time of first IMP administration)
- Concomitant medication: medication taken during the treatment period (i.e. medication that was not stopped before date/time of first IMP administration and not started after the end-of-trial visit)

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

Prior and concomitant medication will be summarised by Anatomical Therapeutic Chemical Classification System (ATC) classification first level (alphabetically) and ATC classification second level for the FAS and produced by treatment group and in total.

9 EXPOSURE AND TREATMENT COMPLIANCE

9.1 Extent of Exposure

Duration of treatment (days) is defined as the number of days from first exposure to the day of last exposure (both inclusive). If a subject misses an intermediate dose she will still be considered as being under treatment. Tabulations will be produced for the Safety Analysis Set and the FAS (in case they differ) and will include both treatment groups and a total column.

9.1.1 IMP (Gonadotropins)

Exposure to gonadotropins will be summarised as the total dose administered, the average daily dose and duration of treatment (days). The total dose will be reported in µg for REKOVELLE and both in IU and µg for GONAL-F (using the conversion factor of 150 IU=11 µg). This table will be produced overall and for subjects that completed stimulation, i.e. subjects that had hCG or GnRH agonist administered for triggering of final follicular maturation.

9.1.2 GnRH Antagonist

Exposure to GnRH antagonist will be summarised as the total dose administered (mg) and duration of treatment (days). This table will be produced overall and for subjects that completed stimulation, i.e. subjects that had hCG or GnRH agonist administered for triggering of final follicular maturation.

9.1.3 Triggering of Final Follicular Maturation

Triggering of final follicular maturation will be done by either an injection of hCG or GnRH agonist. The drug used for triggering (hCG or GnRH agonist) will be tabulated for subjects undergoing triggering.

9.1.4 Treatment Compliance

Subjects not receiving the scheduled dose will be listed by centre and subject number.

10 EFFICACY

Unless otherwise specified, analyses of efficacy endpoints will be based on the FAS and summary tables for the primary and secondary efficacy endpoints will be presented in total and by treatment group. 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.

Results of statistical analyses will be based on least-squares means using the observed margins and include the estimated treatment difference (or ratio), a 95% confidence interval for the difference (or ratio), and the p-value for the test of no treatment difference. All analyses are of descriptive nature and no adjustments for multiple tests will be applied.

Missing observations for the endpoints number of oocytes retrieved, number of fertilised oocytes, and number of blastocysts will be replaced with zero (i.e. worst-case imputation technique) irrespective of the reason why data is not recorded. For pregnancy data, lack of data will be interpreted as a negative pregnancy.

10.1 Primary Efficacy Endpoint

The primary endpoint, number of oocytes retrieved, will be compared between REKOVELLE and GONAL-F using a negative binomial regression model with treatment and AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as factors. The absolute treatment difference in number of oocytes retrieved, the associated 95% confidence interval, and the p-value for no treatment difference will be derived from the model estimates using the delta method.

The distribution of the number of oocytes retrieved will be visualised in histograms. Furthermore, the number of oocytes will be grouped and presented in tables and figures using the following classification:

- <4 oocytes or cycle cancellation due to poor ovarian response
- 4-7 oocytes
- 8-14 oocytes
- 15-19 oocytes
- ≥20 oocytes or cycle cancellation due to excessive ovarian response
- Cycle cancellation due to another reason than poor or excessive ovarian response

The treatment difference will also be investigated for sub-groups defined by AMH level at stimulation day 1 (i.e. <15 pmol/L, AMH ≥15 pmol/L or missing) using the same methods as above for each sub-group separately.

No formal hypothesis testing will be conducted using these methods.

As a supplementary analysis, the analysis of the primary endpoint will be repeated using the PP analysis set and corresponding summary tables will be presented.

10.2 Secondary Efficacy Analyses

In addition to summary tables, some secondary endpoints will be compared between REKOVELLE and GONAL-F using statistical models. An overview is shown in Table 10-1 and further details on the statistical models are provided below.

Table 10-1 Overview of analysis methods for secondary endpoints

Secondary Endpoints	Analysis method			
	Summary tables	***Negative binomial regression***	***ANCOVA***	***ANOVA***
Number of follicles in total and by size category at EOS	X	X		
Serum concentration of estradiol at EOS	X		X	
Serum concentration of progesterone at EOS	X		X	
Number of fertilised oocytes (2PN)	X	X		
Fertilisation rate	X	X		
Number of blastocysts in total and by quality	X	X		
Gonadotropin dose in total and average daily dose	X			
Number of dose adjustments	X			
Number of stimulation days	X			X
Incidence of early OHSS overall and by grade	X			
Preventive interventions for early OHSS	X			

Number of Follicles at End-of-stimulation

The follicle cohort at end-of-stimulation (EOS) will be summarised by treatment on the subject level (i.e. total number of follicles, and number of follicles ≥10 mm, ≥12 mm, ≥15 mm and ≥17 mm). Additionally, the mean number of follicles ≥10 mm, ≥12 mm, ≥15 mm and ≥17 mm at EOS will (in separate analyses) be compared between treatments using the same negative binomial regression model as used for the primary endpoint.

Serum Concentrations of Estradiol and Progesterone at End-of-stimulation

Serum concentrations of estradiol and progesterone at EOS will be compared between treatments using analysis of covariance (ANCOVA) models with treatment and AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as factors and with the serum concentration (log-transformed) at stimulation day 1 as a covariate. Multiplicative models will be used, i.e. the serum concentrations will be log-transformed before analysis. The results of the analyses will be back-transformed and presented as estimated geometric means and mean treatment ratios with 95% confidence intervals and p-values. Values below the lower limit of quantification (LLOQ) will be estimated with LLOQ/2. Potential values above the upper limit of quantification (ULOQ) will be included as ULOQ.

Number of Fertilised Oocytes and Fertilisation Rate

An oocyte is defined as correctly fertilised if it is scored as 2 pronuclei (PN) on day 1 after oocyte retrieval. The mean number of correctly fertilised oocytes will be compared between treatments using the same analysis method as for the primary endpoint.

For subjects with >0 oocytes retrieved, the rate of correctly fertilised oocytes to oocytes retrieved will be estimated and compared between treatments using a negative binomial regression model with treatment and AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as factors and the number of retrieved oocytes (log-transformed) as an offset. The treatment difference in fertilisation rate and the associated 95% confidence interval will be derived using the delta method.

Number of Blastocysts (Total and by Quality)

The total number and quality of blastocysts on day 5 or day 6 will be compared between treatments using the same negative binomial regression model as used for the primary endpoint.

Total Gonadotropin Dose and Number of Stimulation Days

Tables will be produced overall and by AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) for the total gonadotropin dose, the average daily dose, the number of stimulation days and the occurrence of dose adjustments during stimulation (i.e. number of dose increases and decreases).

The number of stimulation days will be compared between treatments using an analysis of variance model with treatment and AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) as factors.

Early OHSS (Overall and by Grade) and/or Preventive Interventions for Early OHSS

Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation (including OHSS with onset during stimulation or before triggering). Incidence of early OHSS will be summarised by classification (mild, moderate, severe) and grade (1, 2, 3, 4, 5).

Preventive interventions for early OHSS (i.e. cycle cancellation due to excessive ovarian response, triggering of final follicular maturation with GnRH agonist based on follicular development and/or serum estradiol criteria, and/or administration of dopamine agonist if ≥20 follicles of ≥12 mm is observed) will be summarised.

The tabulations will be produced overall and by AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) and will include both treatment groups and a total column.

10.3 Exploratory Assessment

Blood Collection for Potential Biomarkers

Potential future analysis of possible biomarkers associated with ovarian response will be reported separately from the clinical trial report.

10.4 Follow-up Assessments

Follow-up assessments will be based on the FAS. Unless otherwise specified, summary tables will include both treatment groups and a total column. An overview of the methods used for follow-up assessments is provided in Table 10-2 and described in detail below.

Table 10-2 Overview of analysis methods for follow-up assessments

Follow-up Assessments	Analysis method		
	Summary tables	***Logistic regression***	***Negative binomial regression***
Clinical pregnancy by type	X		
Vital pregnancy	X		
Pregnancy rate	X	X	
Implantation rate	X		X
Incidence of late OHSS	X		

Pregnancy

For subjects with a clinical pregnancy (at least one gestational sac 5-6 weeks after transfer), the type of clinical pregnancy (intrauterine or ectopic) will be described. For subjects with a vital pregnancy (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer), the number of intrauterine gestational sacs with fetal heart beat will also be described.

Pregnancy rates in the first transfer cycle will be compared between treatments using a logistic regression model with treatment and age group (<35, 35-37, or 38-40 years) as factors. The estimated probabilities, difference in probabilities and 95% CIs for the estimated difference in probabilities will be presented based on the delta method. In these analyses subjects with no transfer or missing data on pregnancy will be regarded as non-pregnant.

Implantation rate

The implantation rate (i.e. number of gestational sacs 5-6 weeks after transfer relative to number of blastocysts transferred) in the first transfer cycle will be estimated and compared between treatments using a negative binomial regression model with treatment and age group (<35, 35-37, or 38-40 years) as factors and the number of transferred blastocysts (log-transformed) as an offset. The treatment difference in implantation rate and the associated 95% confidence interval will be derived using the delta method. This analysis is based on subjects with transfer only and is therefore not randomisation based. The treatment difference for implantation rates is expected to be consistent with the treatment difference for pregnancy rates. If this is not the case, the reason for differences will be further explored by including e.g. day of transfer as a factor in the analysis model.

Late OHSS

For subjects who undergo transfer in the fresh cycle, incidence of late OHSS will be summarised by classification (mild, moderate, severe) and grade (1, 2, 3, 4, 5). Late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation. The tabulations will be produced overall and by AMH level at stimulation day 1 (AMH <15 pmol/L, AMH ≥15 pmol/L, or missing) and will include both treatment groups and a total column.

OHSS (Early and/or Late)

OHSS for each treatment group will be tabulated by classification (mild, moderate, severe) and grade (1, 2, 3, 4, 5). The following endpoints are defined:

- Subjects with early and/or late OHSS
- Subjects with early and/or late OHSS of moderate or severe grade

For each endpoint the proportion of subjects will be tabulated by treatment.

11 SAFETY

11.1 General Considerations

Safety parameters will be evaluated for the safety analysis set, i.e. data will be reported according to actual treatment received. Tabulations will be prepared overall, i.e. not by AMH level at stimulation day 1.

11.2 Adverse Events

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 the first dose of IMP, or a pre-existing medical condition that worsens in intensity after signed informed consent but before the first dose of IMP.

- Treatment-emergent adverse event, i.e. any adverse event occurring after the first dose 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 the first dose 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. Treatment-emergent adverse events will be summarised overall and tabulated by System Organ Class (SOC) and Preferred Term (PT). The total number of subjects reporting an adverse event, the percentage of subjects with an adverse event, and the number of events reported will be described.

Summary tables will be produced for the following treatment-emergent adverse events: 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.

For adverse events, a worst-case approach will be used for causality, intensity, seriousness, and outcome, in case these would be missing. If the timing of the onset of an adverse event cannot be established in relation to IMP, it will be considered as a treatment-emergent adverse event.

11.3 Additional Safety Evaluations

Physical Examination

Physical examination at screening and end-of-trial will be listed for subjects with abnormal findings.

Gynaecological Examination

Gynaecological examination at screening and end-of-trial will be listed for subjects with abnormal findings.

12 INTERIM ANALYSES

No interim analysis is planned.

13 DEVIATIONS FROM THE PROTOCOL

This SAP introduces the following changes to the analyses described in the trial protocol:

- A supplementary analysis of the primary efficacy endpoint using the PP analysis set (Section 10.1).
- Fertilisation rates (Section 10.2) and implantation rates (Section 10.4) will be estimated using negative binomial models with an offset to account for the differences in retrieved

oocytes and transferred blastocysts, respectively. This method was considered more appropriate than the mixed effects models described in the protocol as the proportion of subjects with a single observation is expected to be substantial.

- Exposure and treatment compliance (Section 9) will be tabulated for the Safety Analysis Set instead of the Full Analysis Set

14 REFERENCES

1 Gardner DK, Schoolcraft WB. In vitro culture of human blastocysts. In: Towards reproductive certainty (Eds Jansen R & Mortimer D). The plenary proceedings of the 11th world congress on in vitro fertilisation and human reproductive genetics. The Parthenon Publishing Group. 1999. Pp 378-388.

2 Nyboe Andersen A, Devroey P, Arce J-C. Clinical outcome following stimulation with HP-hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Hum Reprod 2006; 21: 3217-3227.