Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for follitropin delta (rhu)

Proprietary Product Name: Rekovelle

Sponsor: Ferring Pharmaceuticals Pty Ltd

Date of first round report: 18 July 2016

Date of second round report: 10 October 2016

TGA Health Safety Regulation

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- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
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List of abbreviations

Abbreviation	Meaning
AMH	Anti-Müllerian hormone
ART	Assisted reproductive technologies
CHO	Chinese hamster ovary
CL/F	Apparent clearance
DHEA	dehydroepiandrosterone
EMA	European Medicines Agency
FDA	Food and Drug Administration
Rekovelle	Alternative name for follitropin delta or Rekovelle
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GMP	Good manufacturing practice
GnRH	Gonadotropin releasing hormone
ICSI	Intracytoplasmic sperm injection
IMP	Investigational medicinal product
IQ range	Interquartile range (25^{th}-75^{th} percentile)
ITT	Intention to treat
IVF	In vitro-fertilisation
k_a	Absorption rate constant
LH	Luteinising hormone
LLUQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
MII	Metaphase II
NONMEM	Nonlinear mixed effects modelling software
OHSS	Ovarian hyperstimulation syndrome

Abbreviation	Meaning
PER.C6®	Host cell line of human origin
PP	Per protocol
R^2	Coefficient of variation (measure of variation explained by a model)
rFSH	Recombinant FSH
SAE	Serious adverse event
t_{lag}	Lag time
TSH	Thyroid stimulating hormone
ULOQ	Upper limit of quantification
US	ultrasound
WHO	World health organisation

1. Introduction

1.1. Submission type

This is a category 1 type A submission to register a new biological entity.

1.2. Drug class and therapeutic indication

ABN- follitropin delta (rhu)

Class: Gonadotropin- human recombinant follicle stimulating hormone

Indication: Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies such as IVF or ICSI.

1.3. Dosage forms and strengths

Solution for injection- as a cartridge for use with an injection pen

12 µg/0.36 mL

36 µg/1.08 mL

72 µg /2.16mL

1.4. Dosage and administration

From the PI:

Treatment with Rekovelle should be initiated under the supervision of a physician experienced in the treatment of fertility problems. Patients must be educated on how to use the Rekovelle injection pen and to perform injections.

The dosage of Rekovelle is individualised for each patient to obtain an ovarian response with favourable safety/efficacy profile. Rekovelle is dosed in micrograms and not in international units (IU) of biological activity. The dosing regimen is specific for Rekovelle and the microgram dose cannot be applied to other gonadotropins.

For the first treatment cycle, the individual daily dose will be determined on the basis of the woman's serum AMH concentration, which is a biomarker of ovarian response to gonadotropins, and her body weight. The dose should be based on a recent determination of AMH (i.e. within the last 12 months) measured by the following diagnostic test from Roche: Elecsys® AMH immunoassay. The individual daily dose is to be maintained throughout the stimulation period. For women with AMH <15 pmol/L the daily dose is 12 micrograms, irrespective of body weight. For women with AMH ≥15 pmol/L the daily dose decreases from 0.19 to 0.10 micrograms/kg by increasing AMH concentration (Table 6). The dose is to be rounded off to the nearest 0.33 micrograms to match the dosing scale on the injection pen. The maximum daily dose for the first treatment cycle is 12 micrograms.

The AMH concentration is to be expressed in pmol/L and is to be rounded off to the nearest integer (Table 6). If the AMH concentration is in ng/mL, the concentration should be converted to pmol/L by multiplying by 7.14 (ng/mL x 7.14 = pmol/L) before use.

Table 6: Dosing regimen based on AMH concentration and body weight

AMH concentration* (pmol/L)	Daily dose fixed throughout stimulation
<15	12 micrograms
15 – 16	0.19 micrograms/kg
17	0.18 micrograms/kg
18	0.17 micrograms/kg
19 – 20	0.16 micrograms/kg
21 – 22	0.15 micrograms/kg
23 – 24	0.14 micrograms/kg
25 – 27	0.13 micrograms/kg
28 – 32	0.12 micrograms/kg
33 – 39	0.11 micrograms/kg
≥40	0.10 micrograms/kg
Example of rounding-off AMH concentration: AMH: 16.6 pmol/L is rounded off to 17 pmol/L (nearest integer)	

**AMH concentration measured with Roche Elecsys® AMH immunoassay*

Dosing with Rekovelle should be initiated Day 2 or 3 after start of menstrual bleeding, and continue until adequate follicular development has been achieved as assessed by monitoring with ultrasound alone or in combination with measurement of serum oestradiol levels. Adequate follicular development is achieved on average by the ninth day of treatment (range 5 to 20 days). As soon as ≥3 follicles ≥17 mm are observed, a single injection of 250 micrograms recombinant human chorionic gonadotropin (hCG) or 5,000 IU hCG is administered to induce final follicular maturation. In patients with excessive ovarian response at risk of ovarian hyperstimulation syndrome (OHSS), administration of a GnRH agonist instead of hCG could be considered for triggering of final follicular maturation. Administration of GnRH agonist can reduce, but not eliminate, the risk for OHSS and is applicable only for GnRH antagonist cycles. In case of GnRH agonist administration, embryos should not be replaced in the fresh cycle but cryopreserved for later use. In patients with excessive ovarian response of >35 follicles with a diameter ≥12 mm, triggering of final follicular maturation should not be performed and the cycle cancelled.

For subsequent treatment cycles, the daily dose of Rekovelle should be maintained or modified according to the patient's ovarian response in the previous cycle. The maximum daily dose is 24 micrograms.

If the patient had adequate ovarian response in the previous cycle without developing OHSS, the same daily dose of Rekovelle should be used.

In case of ovarian hypo-response in the previous cycle, the daily dose of Rekovelle in the subsequent cycle should be increased by 25% or 50%, according to the extent of response observed.

In case of ovarian hyper-response in the previous cycle, the daily dose of Rekovelle in the subsequent cycle should be decreased by 20% or 33%, according to the extent of response observed.

In patients who developed OHSS or were at risk of OHSS in a previous cycle, the daily dose of Rekovelle for the subsequent cycle is 33% lower than the dose used in the cycle where OHSS or risk of OHSS occurred.

2. Background

2.1. Information on the condition being treated

2.1.1. Infertility

The prevalence of infertility in Australia varies with the population studied. For example, in young married couples the prevalence is in the order of 6-10% where as in couples where the women is > 40years it is in the order of 17-30%.

Australia has the third highest rate of ART in the world (954 cycles per 100 000 women of reproductive age), largely due to the financial support given by the government. According to the 2007 data, 3.1% of babies born in Australia are as a result of ART.

In Australia in 2010, there were 56 489 ART cycles in 30 588 women. The average age of women undergoing autologous cycles was 36 years. Of these, approximately 23.9% resulted in a clinical pregnancy and 18.1% in a live delivery.

Thus, infertility is a common condition and drugs used to treat this condition will be commonly used.

2.1.2. Assisted reproductive technology

Controlled ovarian stimulation with gonadotropins aims to obtain an adequate number of competent oocytes to be used for ART procedure with minimal risk for the woman. The dose of gonadotropins influences the magnitude of the ovarian response and therefore the risk for iatrogenic conditions such as ovarian hyperstimulation syndrome (OHSS). There is a wide variability in ovarian response across patients given the same dose of gonadotropin. Administering the same dose to someone with low ovarian result could result in low efficacy, but the same dose in someone with high ovarian reserve could result in OHSS. The NICE guidelines from the UK recommend considering individualised starting doses of gonadotropins by using predictive factors such as patient characteristics and diagnostic markers of ovarian reserve. Serum AMH has been established as the preferred predictor of ovarian response to exogenous gonadotropins.

The most common reason for a failure of an IVF cycle is failure of implantation. This may be due to poor quality embryo or a problem with the uterus and lining. Of these, poor quality embryos are the major cause. The incidence of chromosomal abnormalities in mature eggs increases with age.

Comment: It is usual practice in IVF clinical to investigate causes of male and female infertility. This involves a history, examination, blood tests and investigations. Testing AMH levels is commonly done as part of this work up.

2.2. Current treatment options

Alternative treatment options to stimulate ovulation include:

Clomiphene- the supply of this medicine is currently problematic in Australia

Human menopausal gonadotrophin- Menopur

Human chorionic gonadotrophin-Pregnyl

Follitropin alfa- Bemfola

Follitropin alfa- Gonal-F

Follitropin beta- Puregon

2.3. Clinical rationale

This new biological medicine is proposed to have advantages over other available products in that the pen allows accurate dosing, and the dosing algorithm aims at an optimal ovarian response (8 to 14 oocytes) without dose adjustment during controlled ovarian stimulation, resulting in less cycle cancellation, less OHSS and lower gonadotropin consumption.

The currently available rFSH products (follitropin alfa (Gonal-F) and follitropin beta (Puregon)) are derived from Chinese hamster ovary (CHO) cell lines. Rekovelle is derived from a human cell line. The relevance of this is uncertain.

2.4. Formulation

2.4.1. Formulation development

Rekovelle (also referred to as FE 999049 in some tables and figures in this report) is expressed from a host cell line of human fetal retinal origin (PER.C6). The selected cell line was genetically engineered to contain genes coding for equal amounts of the α and β-FSH subunits and for a sialyl transferase enzyme.

The glycosylation profile of Rekovelle differs from that found in CHO derived FSH products.

In humans, daily multiple dose administration of identical IU units of Rekovelle and Gonal- f resulted in different PK profiles and PD effects. The consistent drug protein quality profile supported the use of the protein content (expressed in micrograms) to define the dose.

2.4.2. Excipients

All excipients are approved for subcutaneous administration in the concentration used. The excipients include phenol, polysorbate 20, methionine, sodium sulphate, sodium phosphate, dibasic dodecahydrate, phosphoric acid, sodium hydroxide, water for injections.

There are no animal derived raw materials in the drug substance or excipients.

2.5. Guidance

Early in the scientific development programme, National Scientific Advices were obtained from the MHRA in the United Kingdom, the Danish Health and Medicines Agency (DMA) and the Medicines Evaluation Board in the Netherlands. However these advices were obtained before the Phase I multiple dose trial demonstrated a lack of PK and PD comparability leading to major changes in the clinical development program.

The design of the Phase III study ESTHER was reviewed and endorsed by the European Medicines Agency during scientific advice consultation; this included the individualised dosing regimen.

2.6. Evaluator's commentary on the background information

There was adequate background information provided in the dossier.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The following clinical information was submitted (Table 1):

Table 1: Submitted clinical studies

Type of Trial	Trial Identifier	Primary Objective of the Trial	Trial Design and Type of Control	Test Products; Dosage, Regimen;	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Trial Status; Type of
Single-dose PK	CS01	To assess the safety and tolerability of single ascending doses of FE 999049 administered as subcutaneous abdominal injections in healthy women	Within dose group randomised, placebo-controlled, double-blind, sequential dose escalation	FE 999049: 37.5, 75, 150, 225, 450 IU SC Placebo SC	Total: 40 FE 999049: 30	Healthy female volunteers, 21-35 years	Single dose	Complete; Full report
Multiple-dose PK and PD	CS02	To assess the safety and tolerability of FE 999049, given as multiple subcutaneous doses of 225 IU in healthy women	Randomised, active-controlled, double-blind, parallel groups	FE 999049: 225 IU SC GONAL-F: 225 IU SC	Total: 49 FE 999049: 24	Healthy female volunteers, 21-39 years	7 days	Complete; Full report
Single-dose PK in Japanese and Caucasian	CS03	To assess the safety and tolerability of single ascending doses of FE 999049 administered as subcutaneous abdominal injections in healthy Japanese women To determine single-dose pharmacokinetics of FE 999049 in healthy Japanese women	Within dose group randomised, placebo-controlled, double-blind, sequential dose escalation	FE 999049: 75, 150, 225, 450 IU SC Placebo SC	Total: 39 FE 999049: 29 (23 Japanese, 6 Caucasian)	Healthy Japanese and Caucasian female volunteers, 21-35 years	Single dose	Complete; Full report
Absolute bio-availability	000020	To determine and compare the absolute bioavailability of FE 999049 and GONAL-F after a single subcutaneous dose of 450 IU compared to an intravenous dose of 225 IU in healthy women To explore the absorption, distribution and elimination after intravenous and subcutaneous administration of FE 999049 and GONAL-F	Randomised, active-controlled, open- label, parallel group, within treatment cross-over	FE 999049: 225 IU IV and 450 IU SC GONAL-F: 225 IU IV and 450 IU SC	Total: 50 FE 999049: 25	Healthy female volunteers, 21-35 years	Single dose	Complete; Full report

Note: In the clinical trials Rekovelle is referred to as Rekovelle (FE 999049)

Table 1 continued: Submitted clinical studies

Type of Trial	Trial Identifier	Primary Objective of the Trial	Trial Design and Type of Control	Test Products; Dosage, Regimen;	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Trial Status; Type of Report
Dose-response	000009	To investigate the dose-response relationship of FE 999049 with respect to ovarian response in patients undergoing controlled ovarian stimulation	Randomised, controlled, assessor-blind, parallel groups, multicentre, multinational	FE 999049: 5.2 µg, 6.9 µg, 8.6 µg, 10.3 µg or 12.1 µg SC Reference: GONAL-F 11 µg filled-by-mass (150 IU) SC Fixed dose throughout stimulation	Total: 265 FE 999049: 222	IVF/ICSI patients, 18-37 years	Maximum 16 days	Complete; Full report
Efficacy	ESTHER-1, 000004	To demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate and ongoing implantation rate in the fresh cycle in women undergoing controlled ovarian stimulation	Randomised, controlled, assessor-blind, parallel groups, multicentre, multinational	FE 999049: individualised dosing regimen based on AMH and body weight (max daily dose 12 µg SC); fixed dose throughout stimulation GONAL-F: starting dose of 11 µg filled by mass (150 IU) SC; potential dose adjustments after the first 5 days	Total: 1,326 FE 999049: 665	IVF/ICSI patients, 18-40 years	Maximum 20 days	Complete; Full report
Pregnancy follow-up	ESTHER-1, 000004	To evaluate the live birth rate and neonatal health, including congenital anomalies, at birth and at 4 weeks after birth in the fresh cycle	N/A	N/A	Interim data on patients who had ongoing pregnancy in ESTHER-1 Total: 234 FE 999049: 119	IVF/ICSI patients, 18-40 years	N/A	Ongoing; Interim report
Safety, immunogenicity	ESTHER-000071	To evaluate the FE 999049 and on the presence of antibodies and their capacity in women repeated controlled stimulation cycles	Controlled, blind, multicentre, multinational	FE 999049: dosing regimen ovarian previous (max daily dose 24 µg SC in and COS cycle respectively); throughout GONAL-F: based on ovarian the previous potential dose after the first 5 days	COS cycle 2 Total: 513 FE 999049: COS cycle 3 Total: 188 FE 999049: 95	IVF/ICSI 18-40 years at randomisation ESTHER-1, ongoing in ESTHER-1	Maximum 20 days	Complete; Full report

Table 1 continued: Submitted clinical studies

Type of Trial	Trial Identifier	Primary Objective of the Trial	Trial Design and Type of Control	Test Products; Dosage, Regimen; Route	Number of Subjects	Healthy Subjects or Diagnosis of	Duration of Treatment	Trial Status; Type of Report
Pregnancy follow-up	ESTHER-2, 000071	To evaluate the live birth rate and neonatal health, including congenital anomalies, at birth and at 4 weeks after birth for each fresh cycle	N/A	N/A	Interim data on patients who had ongoing pregnancy in ESTHER-2 COS cycle 2: Total: 51 FE 999049: 27 COS cycle 3: Total: 5 FE 999049: 3	IVF/ICSI patients, 18-40 years at randomisation in ESTHER-1, no ongoing pregnancy in ESTHER-1	N/A	Ongoing: Interim report
Cryopreserved cycles	ESTHER-1, 000004 ESTHER-2, 000071	To evaluate the cryopreserved cycles initiated within one year after the subject's date of randomisation for subjects enrolled in ESTHER-1, and within one year after the subject's start of stimulation of the last repeated COS cycle for subjects enrolled in ESTHER-2	N/A	N/A	Interim data on patients who had initiated a cryopreserved cycle Total: 338 FE 999049: 171	IVF/ICSI patients, 18-40 years at randomisation in ESTHER-1	N/A	Ongoing: Interim report
Dose-response in Japanese	000124	To investigate the dose-response relationship of FE 999049 with respect to ovarian response in patients undergoing controlled ovarian stimulation	Randomised, controlled, assessor-blind, parallel groups, multicentre	FE 999049: 6 µg, 9 µg or 12 µg SC Standard therapy: FOLLISTIM 150 IU SC Fixed dose throughout stimulation	Planned total: 144; planned FE 999049: 108; Current total: 57	IVF/ICSI patients, 20-39 years, Japanese	Maximum 16 days	Ongoing; Protocol available

Separate reports on the immunogenicity and PK-PD modelleing were also included.

The population PK studies were reviewed and addressed in separate evaluation report.

3.2. Paediatric data

This medication is not proposed for use in children.

3.3. Good clinical practice

The clinical trials were performed in compliance with good clinical practice. Local ethics approval was granted at each site.

3.4. Evaluator's commentary on the clinical dossier

The dossier was comprehensive.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

The following PK studies were submitted (Table 2):

Table 2: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*	Synopsis
PK in healthy adults	General PK - Single dose	CS01	*	To assess the safety and tolerability of single ascending doses of Rekovelle: 37.5, 75, 150, 225 and 450IU
	- Multi-dose	CS02	*	Safety and tolerability of multiple subcutaneous doses of 225IU
	Absolute bioavailability	000020	*	To determine and compare the absolute bioavailability of Rekovelle and Gonal-F after a single subcutaneous dose of 45IU compared to an intravenous dose of 225
PK (dose response) in women undergoing IVF/ICSI	- Multi-dose	000009	*	To investigate the dose response relationship of Rekovelle with respect to ovarian response in women undergoing IVF/ICSI
Population PK analyses	Healthy subjects			See separate report summarised below.
	Target population			

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations.

Table 2A: Pharmacokinetic results excluded from consideration.

Study ID	Subtopics	PK results excluded
CS03	Single dose PK in Japanese and	Other PK studies evaluated. Although Australia has some Japanese women, the other studies were more

Study ID	Subtopics	PK results excluded
	Caucasian	relevant to our population

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

The Rekovelle drug substance is a clear or slightly turbid colourless solution. The pH range of Rekovelle drug substance is 6.2-7.5.

Rekovelle (33.3µg/mL) is a sterile aqueous solution is supplied in a cartridge with the active drug product and excipients.

4.2.2. Pharmacokinetics in healthy subjects

Single dose PK data was available from three Phase I clinical trials (CS01, CS03, 000020) in healthy volunteers; a multi-dose trial (CS02) in healthy volunteers, and multi dose trial in patients undergoing IVF/ICSI (00009).

4.2.3. Absorption

Rekovelle is administered subcutaneously by injection. The absorption is slower after a single dose than multiple doses (after a single dose T_{max} 24 hours, after multiple doses T_{max} 10 hours).

4.2.4. Bioavailability

Absolute bioavailability

The mean absolute bioavailability of Rekovelle in study 000020 was around 64% and comparable to Gonal-F (60%).

Dose proportionality

In healthy female subjects, dose proportionality of C_{max} and AUC was demonstrated for the dose range 8.8-26.3 µg (CS01). In IVF/ICSI patients, dose proportionality was demonstrated for the range 5.2-12.1 µg (CS 00009).

Bioavailability during multiple-dosing

In healthy female subjects, daily subcutaneous administration resulted in a steady state level of FSH on day 6-7 at which time the C_{max} concentrations were 2.5-3 times higher than those obtained after a single dose. The time to steady state was longer for Rekovelle than for Gonal-F (3-4 days), in line with the longer $T_{1/2}$ of Rekovelle.

4.2.5. Distribution

Volume of distribution

The 'apparent volume of distribution' after subcutaneous injection (Vz/F) was 25 L in healthy subjects and patients undergoing IVF/ICSI. The mean volume of distribution at steady state after single intravenous administration was 9 L. This is consistent with other FSH products on the market.

Plasma protein binding

The sponsor has justified the lack of plasma protein binding studies on the basis of Rekovelle being a protein, thus unlikely that it would bind to plasma proteins. This is acceptable.

4.2.6. Metabolism

No dedicated investigations into the metabolism and excretion of Rekovelle were performed. Rekovelle is thought to be metabolised like other FSH preparation, that is, predominantly in the kidneys.

The sponsor has stated that as Rekovelle is a protein, it is unlikely to interact with the CYP 450 system and therefore no interactions with other medicinal products are anticipated. Clinically relevant interactions of exogenous FSH with other drugs have not been described in the literature.

4.2.7. Elimination

The clearance after IV administration was 0.3 L/h. the apparent clearance (CL/F) following subcutaneous administration was 0.5 L/h.

The terminal half-life following subcutaneous administration was longer (38 hours) than after IV administration (24 hours) indicating that absorption is the rate limiting step for elimination. This has also been described for Gonal-F.

After multiple subcutaneous injections, the terminal half-life of FE999049 was 28 hours, compared to 18 hours for Gonal-F. This has been attributed to the lower clearance of Rekovelle (0.56L/h) compared to Gonal-F (0.92 L/h). The difference in clearance is related to the difference in glycosylation of Rekovelle which leads to decreased metabolic clearance.

4.2.8. Intra and inter individual variability of pharmacokinetics

The sponsor will be asked to provide more information about this.

4.2.9. Pharmacokinetics in the target population

The target population is healthy women undergoing IVF/ICS. The pharmacokinetics in this population is likely to be similar to that in otherwise healthy women.

4.2.10. Pharmacokinetics in special populations

4.2.10.1. Pharmacokinetics in subjects with impaired hepatic function and impaired renal function

This was not formally assessed

4.2.10.2. Pharmacokinetics according to weight

The exposure of recombinant FSH preparations has previously been shown to be inversely proportional to body weight. This was also demonstrated in the PK and population PK studies of Rekovelle.

4.2.10.3. Intrinsic and extrinsic factors

In the Phase III trials, the influence of age on the efficacy and safety has been evaluated.

Data on ethnicity, smoking and alcohol has been collected in the clinical studies, however due to the homogeneity of the population have not been analysed.

4.2.11. Population pharmacokinetics

The dossier contained a population PK-PD modelling report. This was reviewed by an external evaluator and is described in detail in a separate report.

Two population PK models were constructed. Firstly, using the Phase I trial CS01 a single dose study. The second used trial 000009 which was a multidose study. Both models used nonlinear mixed effects modelling and employed NONMEM 7.1 (ICON development solutions).

4.2.11.1. PopPK analysis for multidose study 00009

This analysis was critical for the development of the dosing algorithm used for the clinical trials.

AMH was measured at screening using Beckman-Coulter Gen II Elisa at ICON Laboratories, Dublin, Ireland. FSH was measured on Days 1, 4 and 6 and then every second day until follicles were > 15mm when blood was taken daily. The dataset contained 1383 FSH measurements obtained from 265 individuals. The PK model was estimated using the first order conditional estimation method with interaction on untransformed observations.

Because the measured FSH concentration is a function of endogenous and exogenous FSH, an equation to estimate endogenous FSH was developed. This was a function of baseline FSH, IT_{50} (time taken to suppress endogenous FSH by 50%) and time since Rekovelle dosing and GnRH dosing.

The model for exogenous FSH consisted of a central compartment with first order elimination and first order absorption preceded by a lag time. The values for K_a, t_{lag} and V/F were set to estimates from the single dose Phase I trial. However this may have created errors as the PK after single dosing is different to that after multiple dosing.

The model to fit the PK data was found to have good correspondence between the model and data. Exposure was dose proportional in the dose range 5.2-12.1 µg. FSH concentrations decreased with increasing body weight, the slope estimate was 0.98.

For the PD modelling of oocyte response, data from 220/222 treated subjects was included. A negative binomial model was used.

The expected number of oocytes was a function of the maximum expected number of oocytes, the weight adjusted dose and dose achieving half of E_{max} for a subject weighing 62 kg.

Figure 1: Estimated number of oocytes retrieved by Rekovelle dose for increasing levels of AMH between 5 and 14pmol/L (A) and between 15 and 45pmol/L(B)

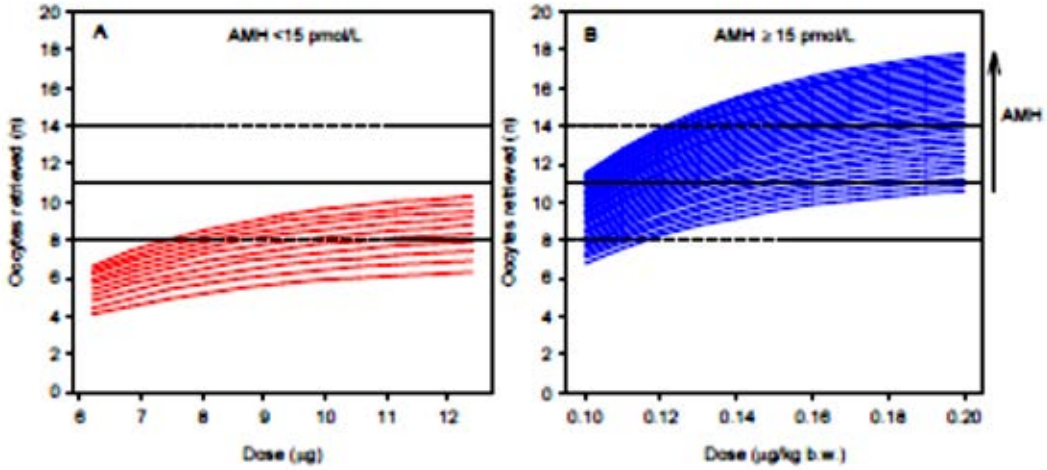
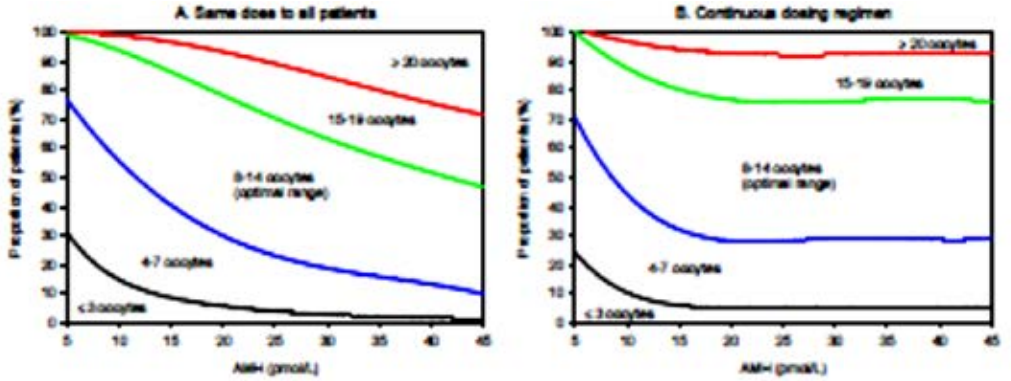


Figure 2: stimulated distribution of ovarian response by AMH level when all subjects are either administered same dose Rekovelle of 9µg or according to the proposed doing algorithm



Comments: The population PK analysis was used to create a dosing algorithm for Rekovelle based on baseline AMH and body weight. It is unclear why more studies (CS 02, CS03) were not used in this population PK analysis. The model was built on a number of assumptions. Equations were used to differentiate endogenous from exogenous FSH. PK parameters from studies after a single dose regime were used to inform these calculations- these are not valid as the t_{max} and $T_{1/2}$ were different after single or multiple doses. The simulated distribution of ovarian response shows a reduction in the number of excessive oocytes as a result of a continuous individualised regime. However there appears to be very little improvement in the number of oocytes retrieved with low baseline AMH.

Conclusion of the formal population PK-PD assessment (see also separate Section below):

The purpose of the analysis was to identify an exposure – response model for the key PD endpoint (nOR) to permit individualised dosing of Rekovelle. To this end, the population PK of FSH following administration of Rekovelle in the Phase I trial CS01 and the Phase II trial 000009 were characterised, exposure–response relationships for nOR and other biomarkers of ovarian response in trial 000009 were characterised, and simulations were performed to establish an individualised dosing regimen for Rekovelle based on the selected exposure-response model.

On the basis of this evaluation, it was concluded:

The final PK models, and variations of these models including the base models, were successfully replicated, verifying the models and the reported PK parameters in the report.

A population PK model was developed using data from a sparsely sampled Phase II trial 000009 using absorption and distribution parameters fixed to those estimated using Phase I trial CS01 data. However, the assumption that the absorption and distribution parameters were similar following a single SC dose and multiple SC doses was flawed since half-life and Tmax of FSH have been shown to be reduced after multiple SC administrations compared with single SC administration, Furthermore, the covariate development process yielded a final PK model that included correlated covariates and covariates of low clinical relevance. Model refinement was lacking.

The PK model was used to calculate individual exposures (AUC) for subsequent exposure-response analyses. However, dose selection was based on exposure-response models that used body weight-adjusted dose rather than AUC as the exposure metric. Consequently, there was no subsequent application of the PK modelling effort. It is recommended that modelling assumptions, model building methods and model selection criteria be thoroughly reviewed prior to application of the model for other purposes in the future.

Exposure-response analyses revealed body weight-adjusted dose and baseline serum AMH concentrations to be predictors of ovarian response including the primary PD response, nOR. Diagnostic plots showed good agreement between observations and model predictions overall and stratified by baseline serum AMH concentrations.

Dosing of Rekovelle per kg of body weight and adjusted for baseline serum AMH concentration maybe expected to result in an optimized nOR response with fewer subjects expected to experience extreme responses. The proposed dosing regimen remains to be evaluated prospectively.

Implications of findings

Using the dose-response model developed for nOR, individualised dosing regimens based on body weight and baseline serum AMH concentration were developed. Risk-benefit assessment of the proposed dosing algorithm remains to be evaluated.

A minor consideration with regard to the proposed Australian Product Information (API) is as follows:

Pharmacokinetics, Absorption

Estimates of half-life after single and multiple SC dosing were stated in the Pharmacokinetics, Elimination section. However, in the Absorption section, the time to maximum concentration after multiple SC doses (but not after a single dose) was stated. While this statement is correct: "After daily SC administration of Rekovelle, the time to maximum concentration is 10 h", it might be worthy of consideration to include that after a single CS administration, the mean time to maximum concentration is estimated to be 20 h.

4.2.12. Pharmacokinetic interactions

No interaction studies have been performed. No potentially clinically relevant drug interactions have been found with other FSH products.

4.2.13. Clinical implications of in vitro findings

Not relevant.

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics have been well described and are similar to other FSH products. One major difference is the slower clearance, higher exposure, and longer $T_{1/2}$ life with Rekovelle versus GONAL –f. The implications that this has on dosing has been explored. However it is not clear if the implications that this may have on the timing of the development of oocytes or other hormonal parameters have been adequately discussed.

There were some deficiencies identified in the development of the population PK model. However, the model was considered adequate for the development of a dosing algorithm. The clinical implications of the dosing algorithm will be tested in the clinical trials.

All injections were performed in the abdomen. The PK of other sites has not been established.

5. Pharmacodynamics

Rekovelle is demonstrated to have specific affinity for and functional activity at the human FSH receptor which the sponsor states in women is only expressed in the granulosa cells of the ovary.

5.1. Studies providing pharmacodynamic information

The following studies provided pharmacodynamic information.

Table 3: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on PD parameter FSH in healthy subjects	CS02	*
	Effect on oocyte number, hormonal profile and live pregnancy rates in patients undergoing IVF/ICSI	000009	*

* Indicates the primary PD aim of the study.

5.2. Summary of pharmacodynamics

In the ovary, the FSH receptor is necessary for follicular development and expressed on the granulosa cells. In the uterus, the FSH receptor is expressed during the luteal phase in the secretory endometrium of the uterus. The FSH receptor is also selectively expressed on the surface of blood vessels of a wide range of carcinogenic tumours. Oestrogen upregulates FSH receptors. The FSH receptor can become desensitized when exposed to FSH for some time. Polymorphisms of the FSH receptor populations lead to poor response in infertile women receiving FSH for IVF.

5.3. Mechanism of action

Rekovelle stimulates the FSH receptor leading to the stimulation of oocyte number and maturation.

5.4. Pharmacodynamic effects

5.4.1. Primary pharmacodynamic effects

Rekovelle leads to an increase in follicle number and size, and increased oestrogen levels in healthy women and women undergoing IVF/ICSI.

5.4.2. Secondary pharmacodynamic effects

Increased follicle number and size increases the ability of technicians to retrieve oocytes which were subsequently fertilised and reimplanted. A number of other factors will determine whether this results in a pregnancy and delivery of a live infant.

5.4.3. Time course of pharmacodynamic effects

After multiple dosing, FSH increases within the first day of the dose, and increases for around 6 days then stabilises.

5.4.4. Relationship between drug concentration and pharmacodynamic effects

Higher drug concentrations lead to greater pharmacodynamic effects. However if the drug dose is too high, the risk of complications such as OHSS develops.

5.4.5. Genetic, gender and age related differences in pharmacodynamic response

The PK model did not identify age a significant co-variate. The centre in which the IVF procedure was performed did have an effect.

5.5. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamics were well described and as expected for a recombinant FSH product.

6. Medical device issues

6.1. AMH (Anti-Müllerian Hormone) assay

The use of Rekovelle according to the product information requires the use of a biomarker (AMH).

AMH is used as a biomarker for relative size of ovarian reserve. In IVF, AMH can predict excessive response to ovarian hyper stimulation with a sensitivity of 82% and specificity of 76%. However there are situations such as in PCOS where it can be misleading. AMH levels correlate with natural fertility in women aged 30-44 years but not in women aged 20-35 years. There are a number of problems with the available AMH assays. Firstly, different methods will produce different results (eg Beckman Coulter versus DSL); there is high within patient variability; the levels changes in samples with pre-mixing of buffers, storage at room temperature or freezing, and dilution.

The sponsor has recommended that AMH levels used for the dosing of Rekovelle are measured using a fully automated elecsys AMH assay from Roche. The Roche Elecsys AMH test system has a CE mark in Australia and is registered for quantifying serum AMH for the assessment of ovarian reserve. The assay is currently being assessed in Europe for the additional purpose of dosing Rekovelle. Once the CE mark has been achieved for this indication in Europe, an application for approval of this indication will be submitted in Australia.

In the Phase II dose response trial, AMH was measured using the Beckman Coulter Gen II ELISA assay. The Phase III trials used the Elecsys AMH assay. The sponsor justified the use of two different assays by the following arguments: 1) analysis of the Phase II samples using the Elecsys AMH assay showed good overall agreement with no systemic bias when the results of the two assays were directly compared 2) the parameter estimates obtained for the model underlying the Rekovelle dosing algorithm were comparable. This is acceptable.

6.1.1. Summary of elecsys AMH Plus assay from information sheet

Intended Use: Immunoassay for the in vitro quantitative determination of AMH in human serum and plasma

The electrochemiluminescence immunoassay is intended for use on Elecsys and cobas e immunoassay analysers. Samples for analysis are taken in lithium heparin tubes and would be stable for 5 days at 20-25 degrees C.[1] Measuring range 0.07pmol/L-164 pmol/L. Precision (repeatability) CV<2%.

The sponsor has provided the following short reports:

[1] Sponsor clarification: Samples for analysis are taken in lithium heparin tubes and would be stable for 3 days at 20-25 degrees C , 5 days at 2-8 degrees C and 6 months at -20(±5) degrees C.

6.1.1.1. Comparison of the Elecsys AMH assay and the AMH Gen II Elisa based on samples from the Phase II trial 000009

The relation between Gen II ELISA and Elecsys assay was modelled by Roche Biostatistics using a simple linear regression in the log-log concentration space. This resulted in the following conversion formulae:

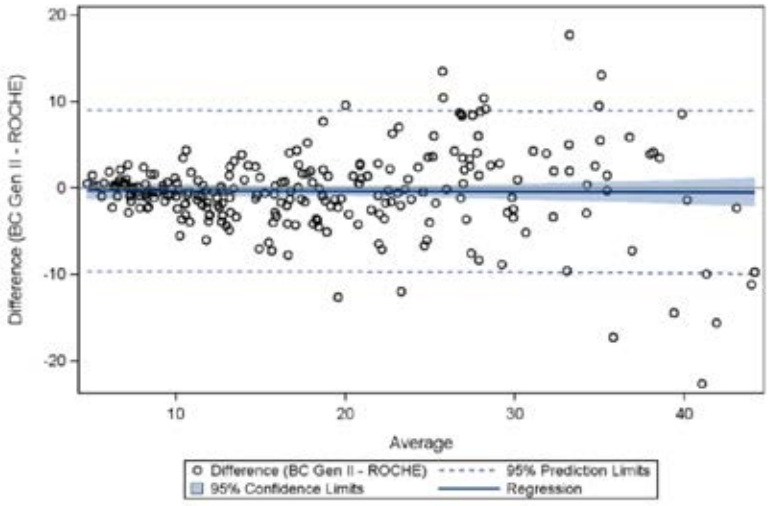
$AMH_{MP}=10^{(0.17 + 0.92*\log_{10}(AMH_{DR}))}$.

The analyses are based on the converted values. All AMH results are reported in pmol/L.

For each subject the difference between the two assays was calculated and summarised. The level of agreement between the two assays was described graphically using a Bland-Altman plot of the within subject difference against the within subject average.

The overall agreement between the two assays was good; mean (SD) difference of-0.4 (4.71) and a median (inter-quartile range) difference of -0.3 (-2.3; 1.7). The Bland-Altman plot comparing the AMH Gen II ELISA and the Elecsys® AMH Plus assay further illustrates the agreement between the two assays. The fitted line is not significantly different from the horizontal line through zero indicating no systematic bias. The observed variation increases as the average increases and this is expected for an endocrine parameter (the plot displays absolute differences), see Figure 3.

Figure 3: Bland-Altman plot of AMH (pmol/L) measured by the Elecsys AMH Plus assay and AMH Gen II ELISA



Comment: This shows good correlation for the lower range of AMH, although at higher levels of AMH there was considerable disagreement between the two assays.

6.1.1.2. Clinical Implications of potential AMH measurement error when applying the Rekovelle dosing regimen

According to the PK-PD model, the dose of Rekovelle per body weight is a non-linear decreasing function of the AMH concentration. This implies a positive measurement error may lead to lower doses and thereby potentially fewer oocytes retrieved while a negative measurement may lead to a higher dose and thereby more oocytes retrieved. As the dosing scale has AMH values grouped in categories, the impact of the measurement error only has impact if it results in the measured value being in a different category.

The sponsor performed a study calculating the impact of AMH measurement errors on the number of oocytes retrieved for a 62 kg subject.

The expected impact on the number of oocytes retrieved due to potential measurement errors in the analysed range from -25% to 25% ranged from -2.0 to 2.3 oocytes with the impact being in the range from -1.5 to 1.7 oocytes across almost the entire range of AMH levels. For true AMH concentrations ≤12 pmol/L measurement errors have no impact on the expected number of oocytes retrieved as the maximum dose will be delivered. For true AMH concentrations in the range from 13 to 39 pmol/L the impact of potential measurement errors increases. For true AMH concentrations ≥40 pmol/L a positive measurement error ≤25% does not impact the dose since the minimum dose is reached when AMH ≥40 pmol/L.

For measurement errors in the range from -15% to 15% the expected impact on the number of oocytes retrieved is in the range from -1.2 to 1.3 oocytes. For true AMH concentrations ≤34 pmol/L the expected impact is at most ±0.9 oocytes. For true AMH concentrations >46 pmol/L a measurement error in the range from -15% to 15% does not impact the dose recommendation.

Comment: This model is based on a number of assumptions. Firstly- that AMH is an accurate surrogate marker of ovarian reserve and ovarian response. Secondly, that the PK-PD model is valid method of calculating the Rekovelle dose. Thirdly, the Rekovelle dose only affects the oocyte retrieved and no other parameters related to pregnancy outcome or complications (eg giving too high a dose may lead to an increased risk of OHSS).

Regardless of this, it appears that even a measurement 'error' of 25% in AMH is unlikely to cause significant difference in the number of oocytes retrieved.

6.1.1.3. Evaluation of serum AMH concentrations over time measured with the Elecsys AMH immunoassay in IVF/ICSI patients undergoing up to 3 controlled Ovarian Stimulation cycles.

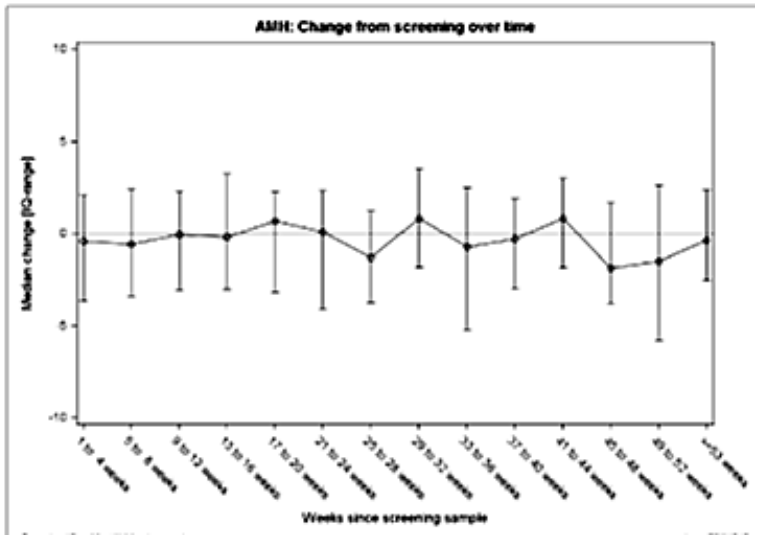
The aim of this study was to evaluate the population average change in serum AMH concentration for a period of up to a year based on repeated measures obtained in the Rekovelle Phase III programme.

The analysis is based on the 1326 subjects randomised and exposed in ESTHER-1. All 1326 subjects had their AMH measured at screening as this was a prerequisite for randomisation. A total of 1324 of these subjects had their AMH measured on stimulation day 1 in COS cycle 1, while 512 and 188 had AMH measured on stimulation Day 1 in COS Cycle 2 and COS Cycle 3, respectively (see Table 4 and Figure 4).

Table 4: Difference between AMH at stimulation day 1 and AMH at screening by COS cycle

Cycle	Visit	N	Mean (SD)	Median	[IQ-range]	[p10;p90]
All	Stimulation day 1	2024	-0.7 (5.65)	-0.3	[-3.4; 2.3]	[-7.0; 5.6]
COS 1	Stimulation day 1	1324	-0.7 (5.43)	-0.3	[-3.3; 2.3]	[-6.9; 5.2]
COS 2	Stimulation day 1	512	-0.6 (6.25)	-0.2	[-3.8; 2.4]	[-7.6; 6.4]
COS 3	Stimulation day 1	188	-0.2 (5.40)	-0.3	[-3.0; 2.5]	[-6.2; 6.6]

Figure 4: Difference between AMH at stimulation day 1 and at screening by weeks since screening



Comment: The most important parameter here is the intra-individual variability in serum AMH over time. Although it is reassuring that there was very little change in the mean value over 12 months, this does not necessarily show the change an individual may have had.

The 90% IQ range varied from approximately -7 to +6. This will have little impact on measurements at the extreme; it may have considerable influence on the dose given for measurements between 12 and 40pmol/L.

6.2. Injection pen and needles

Rekovelle is to be administered with the Rekovelle injection pen. This is a non-sterile, reusable medical device designed for use with replacement cartridges of 3 ml capacity. The pens allow patients to set doses from 0.33 micrograms to 24.0 micrograms in increments of 0.33 µg. The injection pen will be registered in Australia following granting of the CE mark in Europe.

The pen and cartridges are compatible with the Omnican fine 29GX12mm and Clickfine 29GX12mm needles which are CE marked in Australia.

6.3. Dose calculator app

The PI includes a dosing algorithm table to guide health professionals in the dosing of Rekovelle based on serum AMH and body weight. The sponsor is developing a mobile device app to have available to health care professionals as a medical device.

7. Dosage selection for the pivotal studies

7.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The dosing regimen for the Phase III clinical trials was derived from a Phase II study and a population PK model.

The sponsor chose the number of oocytes retrieved to be outcome of interest when developing the model. A search of the literature for the optimal number of oocytes for achieving a

pregnancy, and avoiding adverse events such as OHSS, cycle cancellations was performed. The appropriate ovarian response for the Rekovelle dosing regime was defined as 8-14 oocytes.

As the starting dose of Rekovelle is individualised, a fixed dose regime without dose adjustments during the stimulation period was proposed. The sponsor stated that several studies have indicated that increasing the gonadotropin dose after the first 5 days in anticipation of a low response does not rectify the response.

7.1.1. Modelling and simulation of the Rekovelle dosing regime

The overall objective of the modelling activities was to identify a model relating to dose or exposure of Rekovelle to the number of oocytes retrieved.

The steps for identifying the individualised starting dose of Rekovelle consisted of the following steps:

Table 5: Modelling and simulation of the Rekovelle dosing regimen: Steps

Steps		Evaluator comments
1	Development of a PK model to obtain estimates of serum FSH exposure (AUC) after dosing with Rekovelle	The use of PK parameters from a single dose study to estimate FSH exposure for a multidose study is not ideal
2	Development of a PD model to identify factors that affect the number of oocytes retrieved after dosing with Rekovelle, including biomarkers of ovarian response to gonadotrophins such as basal FSH, AMH, inhibin B, antral follicle count, age	exposure decreased with increasing body weight due to the effects on volume of distribution and clearance AMH was the best predictor of ovarian response based on forward modelling
3	Establishment of target ovarian stimulation based on clinical assumptions	This was well justified
4	Identification of an individualised Rekovelle dosing regimen in accordance with the established target for ovarian stimulation	This is accepted.

Figure 5: Rekovelle and the effect of AMH level of FE dose

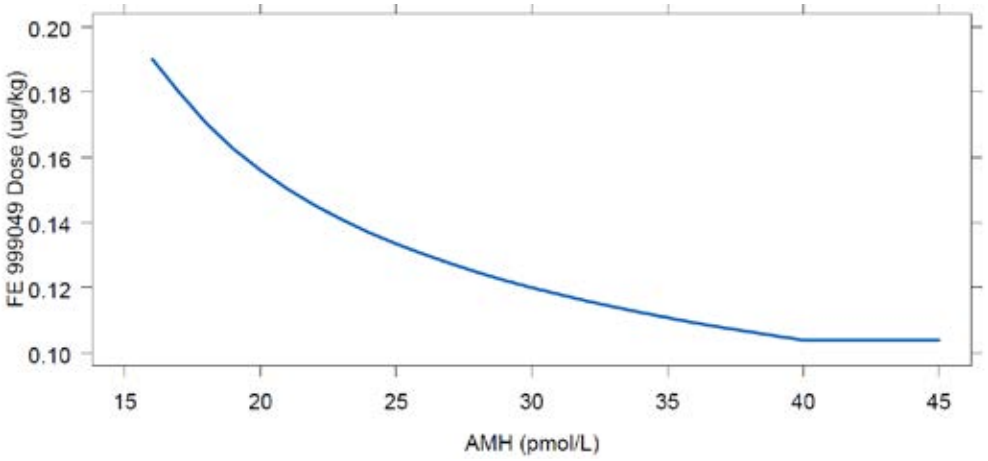


Table 6: Rekovelle and dosing regimen

Treatment group	AMH concentration (pmol/L)	Daily dose fixed throughout stimulation	Maximum daily dose
FE 999049	<15	12 µg	12 µg
	15-16	0.19 µg/kg	12 µg
	17	0.18 µg/kg	12 µg
	18	0.17 µg/kg	12 µg
	19-20	0.16 µg/kg	12 µg
	21-22	0.15 µg/kg	12 µg
	23-24	0.14 µg/kg	12 µg
	25-27	0.13 µg/kg	12 µg
	28-32	0.12 µg/kg	12 µg
	33-39	0.11 µg/kg	12 µg
	≥40	0.10 µg/kg	12 µg

AMH concentration was rounded off to integers.
Subjects could be treated for a maximum of 20 days.

7.2. Evaluator's conclusions on dose finding for the pivotal studies

The ability to extrapolate the doses to AMH levels < 5pmol/L or > 40pmol/L is not provided. The dosing algorithm used in the Phase III studies is the same as that recommended in the PI. The same formulation of Rekovelle was used in the Phase III studies as is planned to be marketed.

8. Clinical efficacy

8.1. Studies providing evaluable efficacy data

ESTHER-1 (Evidence based stimulation trial with Rekovelle in Europe and Rest of World Trial) 00004: use of Rekovelle at the initial COS cycle.

ESTHER II Trial 00071: use of Rekovelle with repeated COS cycles.

8.2. Pivotal efficacy studies

8.2.1. Study 00004- ESTHER I

8.2.1.1. Study design, objectives, locations and dates

This was a randomised, controlled, assessor-blinded parallel group, multicentre, multinational trial comparing the efficacy and safety of Rekovelle with follitropin alfa (Gonal-F) in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme. There were 37 investigational sites. There were no Australian sites.

The first patient visit was on 8 October 2013. The last patient visit was on 11 May 2015.

Primary objective

To demonstrate non-inferiority of Rekovelle compared with Gonal-F with respect to ongoing pregnancy rate and ongoing implantation rate in the fresh cycle in women undergoing controlled ovarian stimulation

Secondary objectives

- To compare the clinical benefits of Rekovelle in its dosing regimen to those of Gonal-F with respect to efficacy and safety
- To compare Rekovelle with Gonal-F with respect to ovarian response including follicular development and endocrine profile, as well as with respect to embryo development
- To compare Rekovelle with Gonal-F with respect to treatment efficiency
- To compare Rekovelle with Gonal-F with respect to safety profile, including adverse events, routine safety laboratory parameters and local tolerability
- To evaluate the immunogenicity of Rekovelle after one treatment cycle
- To compare Rekovelle with Gonal-F with respect to cost-effectiveness (not in this report)

8.2.1.2. Inclusion and exclusion criteria

- aged 18 to 40 years
- undergoing their first IVF/ICSI controlled ovarian stimulation for IVF or ICSI following a GnRH antagonist protocol
- regular menstrual cycles of 24-35 days, presumed to be ovulatory
- BMI 17.5 to 32 kg/m^2
- early follicular phase serum FSH between 1 and 15 IU/L.

8.2.1.3. Study treatments

Subjects were screened within 60 days of randomisation for compliance with inclusion and exclusion criteria.

On Day 2-3 of the menstrual cycle, subjects were randomised on a 1:1 basis to receive either Rekovelle or Gonal-F. Randomisation was stratified by centre and age.

Dosing of Rekovelle: The individual dose was determined on the basis of the AMH level at screening and the patient's body weight. The daily dose was fixed during the stimulation period. The maximum dose was 12 µg. The maximum duration for treatment was 20 days.

Dosing of Gonal-F: The starting dose was 150 IU and this was fixed for the first five days of stimulation after which it could be adjusted by 75 IU based on the individual's response. The maximum daily Gonal-F dose allowed was 450 IU. The maximum duration of therapy was 20 days.

During stimulation: Subjects were monitored by transvaginal ultrasound on stimulation Day 1 and 6 and then every second day. When the leading follicle was > 15mm, visits were performed daily. To prevent a premature LH surge, a GnRH antagonist (cetrorelix acetate) was initiated on Day 6 at a dose of 0.25 mg and continued through the gonadotropin stimulation period. Triggering of final follicle maturation was initiated as soon as > 3 follicles with a diameter of > 17 mm were observed. If there were < 25 follicles with a diameter of > 12 mm then 250 µg of hCG was administered. If there were 25-35 follicles of >12 mm a GnRH agonist (triptorelin acetate) could be administered of the cycle cancelled.

The cycle was cancelled if there were excessive follicle development (> 35 follicles with a diameter >12 mm) or poor follicle development (> 3 follicles greater than 17 mm could not be reached by Day 20).

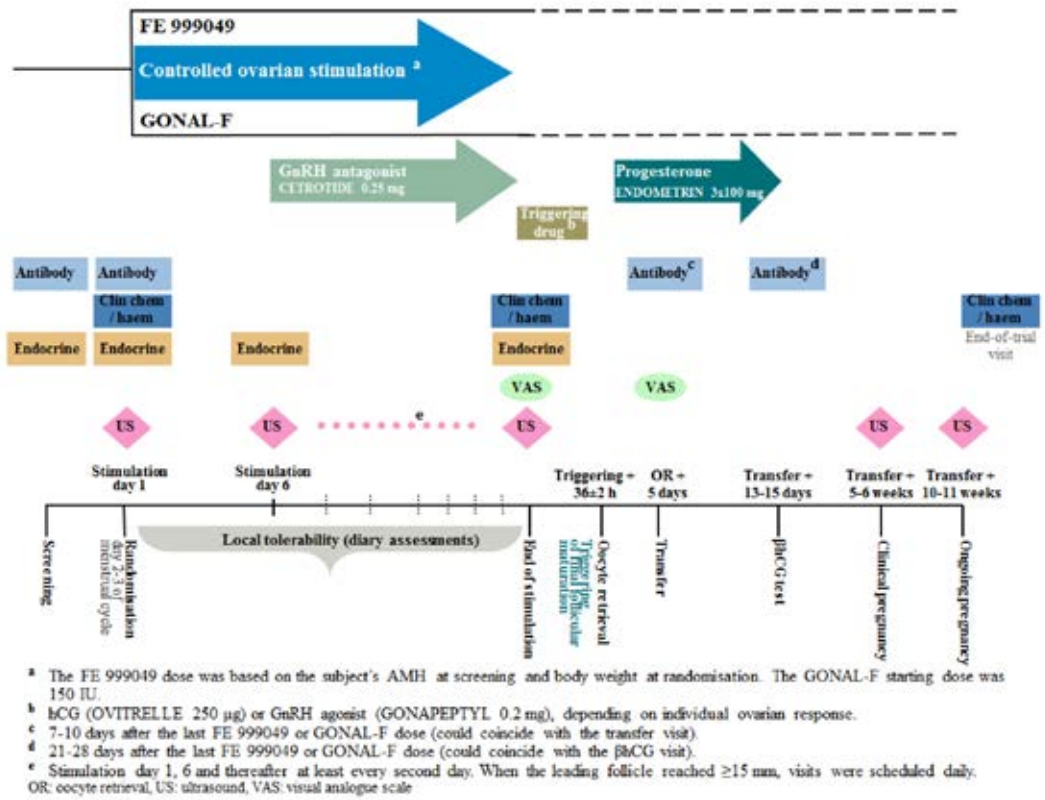
Oocyte retrieval took place 36 h (±2 h) after triggering of final follicular maturation and the oocytes were inseminated by IVF and/or ICSI. Fertilisation and embryo development was assessed from oocyte retrieval to the day of transfer. For subjects who underwent triggering of final follicular maturation with hCG, transfer was performed on Day 5 (blastocyst stage) after oocyte retrieval. Subjects aged ≤37 years at randomisation had single blastocyst transfer. Subjects aged ≥38 years at randomisation had single blastocyst transfer if they had a good-quality blastocyst available, that is, a blastocyst of Grade 3BB or higher; otherwise they had double blastocyst transfer (if two blastocysts were available). Remaining blastocysts could be cryopreserved in accordance with local guidelines and/or regulations. For subjects who underwent triggering of final follicular maturation with GnRH agonist, no transfer took place in the fresh cycle and the blastocysts available on Day 5 were instead cryopreserved. All cryopreserved blastocysts could be used by the subject after completion of the trial, in accordance with local guidelines and/or regulations.

Blood samples were collected throughout the trial for the purpose of evaluating the endocrine profile, clinical chemistry and haematology parameters as well as anti-FSH antibodies. Endocrine parameters were assessed at screening, stimulation Day 1, 6 and end-of-stimulation. Clinical chemistry and haematology parameters were assessed on stimulation Day 1, end-of-stimulation and end-of-trial. Anti-FSH antibodies were assessed at four occasions. The first blood sample was taken at the screening visit. The subsequent three samples were used for analysis of anti-FSH antibodies in the individual subjects in the trial and were taken prior to dosing on stimulation Day 1 and at two occasions post-dosing: 7-10 days and 21-28 days after the last Rekovelle or Gonal-F dose. Subjects with a treatment-induced anti-FSH antibody response were followed until the response had returned to baseline, that is, the pre-dosing level. These subjects were called in for monthly assessments for a period of 3 months after the second post-dosing anti-FSH antibody sampling. Further assessments, if required, were to be made quarterly after the second post-dosing anti-FSH antibody sampling. The assessments were to be terminated when two con secutive assessments indicated that the baseline level had been reached, or after a maximum of 2 years.

Post-trial activities covering pregnancy and neonatal health follow up, as well as the success of cryopreserved cycles with blastocysts obtained in the trial are ongoing.

The dosing of Gonal-F was in line with the product labelling. The doses and regimens of other concomitant fertility medications were in line with the labelling and/or standard clinical practice.

Figure 6: Diagram of Trial Procedures



a The FE 999049 dose was based on the subject's AMH at screening and body weight at randomisation. The GONAL-F starting dose was 150 IU.
b hCG (OVITRELLE 250 µg) or GnRH agonist (GONAPEPTYL 0.2 mg), depending on individual ovarian response.
c 7-10 days after the last FE 999049 or GONAL-F dose (could coincide with the transfer visit).
d 21-28 days after the last FE 999049 or GONAL-F dose (could coincide with the βhCG visit).
e Stimulation day 1, 6 and thereafter at least every second day. When the leading follicle reached ≥15 mm, visits were scheduled daily.
OR: oocyte retrieval, US: ultrasound, VAS: visual analogue scale

8.2.1.4. Efficacy variables and outcomes

Co-primary endpoints

- Ongoing pregnancy rate (at least one intrauterine viable fetus 10-11 weeks after transfer)
- Ongoing implantation rate (number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of blastocysts transferred)

Secondary endpoints

- Positive βhCG rate (positive serum βhCG test 13-15 days after transfer)
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)
- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer)
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by the number of blastocysts transferred)
- Proportion of subjects with extreme ovarian responses (defined as < 4, > 15 or > 20 oocytes retrieved
- Proportion of subjects with early OHSS (including OHSS of moderate/severe grade) and or preventative interventions for early OHSS
- Proportion of subjects with cycle cancellation due to poor ovarian response or excessive ovarian response
- Number and size of follicles on stimulation day 6 and end of stimulation
- Number of oocytes retrieved and proportion of subjects with < 4, 4-7, 8-14, 15-19 and > 20 oocytes retrieved

- Percentage of metaphase II oocytes (ICSI only), fertilisation rate as well as number and quality of embryos on Day 3 and blastocysts on Day 5 after oocyte retrieval
- Circulating concentrations of FSH, LH, oestradiol, progesterone, inhibin A and inhibin B on stimulation Day 6 and end of stimulation
- Total gonadotropin dose and number of stimulation days
- Proportion of subjects with investigator requested gonadotropin dose adjustments
- Frequency and intensity of adverse events
- Changes in circulating levels of clinical chemistry and haematology parameters and proportion of subjects with markedly abnormal changes
- Frequency and intensity of injection site reactions
- Abdominal discomfort related to controlled ovarian stimulation as assessed by a visual analogue scale at end of stimulation and transfer
- Change in body weight and maximum abdominal circumference from stimulation day 1 to end of stimulation and transfer
- Proportion of subjects with treatment induced anti FSH antibodies overall as well as with neutralising capacity
- Frequency and intensity of immune related adverse events
- Proportion of subjects with cycle cancellation due to an adverse event, including immune related adverse events, or due to technical malfunctions of the administration pen
- Proportion of subjects with late OHSS
- Rate of multi-fetal gestation, biochemical pregnancy, spontaneous abortion, ectopic pregnancy and vanishing twins
- Technical malfunctions of the pen (not a medicines issue)

Post-trial Information

- Live birth rate and neonatal health
- Outcomes of cryopreserved cycles

Ongoing pregnancy is considered an appropriate primary endpoint for efficacy trials, as ongoing pregnancy is the best predictor of live birth and it is definable within a time period in which other potential confounding factors are more easily controlled. Ongoing implantation rate was chosen as co-primary endpoint, as it would be supportive of the ongoing pregnancy endpoint and provide reassurance of the efficacy of Rekovelle with respect to treatment outcome. The selection of these two co-primary endpoints was in accordance with the EMA Scientific Advice consultation.

AMH was measured using the Elecsys AMH Plus immunoassay from Roche Diagnostics. This is a homogenous electrochemiluminescence immunoassay employing a quantitative sandwich principal with two antibodies targeting AMH. One antibody is biotinylated whereas the other antibody is covalently linked to a ruthenium complex.

The sponsor developed the following assays for evaluating the immunogenicity of FE999049 and Gonal-F

a. a screening immunoassay, assessing the presence in serum of anti-FSH antibodies using a parametric cut point approach with a 5% false positive rate

b. a confirmatory immunoassay, confirming or disconfirming the specificity of any positive results in assay 1) using a parametric cut off point approach with a < 0.1% false positive rate

c. a titre immunoassay determining the antibody response titre of any anti-FSH antibodies conformed above

d. a cell based assay qualitatively assessing the neutralising capacity of any anti-FSH antibodies confirmed above using a parametric cut off approach with 1% false positive rate

e. a cell based assay determining the neutralising antibody response titre of any positive response above

f. a confirmatory assay based on native FSH in order to assess cross reactivity with native FSH of any anti-FSH antibodies confirmed to be specific towards exogenous FSH, using a parametric cut-point approach of 0.1%

A positive antibody response was defined as one which the post dosing antibody response was positive when the pre dose antibody response was negative or having a greater than 2 fold increase in titre.

Investigator comments: This is a large list of secondary outcomes. Although this runs the risk of finding positive results due to multiplicity, the outcomes measured are all important outcomes to support the primary efficacy endpoint.

8.2.1.5. Randomisation and blinding methods

Assessor-blinded: Included investigators, embryologists and central lab personnel.

Patients were not blinded. This was not possible as the IMP used different devices and dosing algorithms. Subjects were clearly instructed to only discuss their treatment allocation with the trial medication delegate, and to not mention it to the investigator. When an investigator determined that a dose titration was needed, a note was written to the delegate who instructed the patients about the need to change their dosing regimen.

Randomisation was stratified by study centre and age (< 35 years, 35-37 years, and 38-40 years) and allocated by a central electronic system.

Comment: The inability to blind patients is unlikely to have an effect on the measures of efficacy as these were objective. It could however have influenced the reporting of adverse effects.

8.2.1.6. Analysis populations

PP: per protocol set

mITT: modified intention to treat population. This included all randomised and exposed subjects.

Safety set: all patients

Table 7: Analysis Populations

	FE 999049		GONAL-F	
	n	%	n	%
ITT Analysis Set	666	100.0%	663	100.0%
Modified ITT Analysis Set	665	99.8%	661	99.7%
PP Analysis Set	623	93.5%	632	95.3%
Safety Analysis Set	665	99.8%	661	99.7%

As this was a non-inferiority trial, both PP and mITT sets were evaluated.

8.2.1.7. Sample size

The trial was designed to have 90% power to demonstrate non-inferiority with respect to the ongoing pregnancy rate and ongoing implantation rate with a non-inferiority margin of -8%. The non-inferiority margin of -8.0% for ongoing pregnancy had been recommended by the FDA and EMA and followed regulatory precedence for a recent clinical development programme of a new biological entity for controlled ovarian stimulation.

With an anticipated ongoing pregnancy rate was 25-30%, a sample size of 1150 for the mITT was required.

8.2.1.8. Statistical methods

For each co-primary endpoint the null hypothesis (H_0) was tested against the alternative (H_A) by constructing a two-sided 95% CI for the difference in rates. If the lower limit of the two-sided 95% CI was greater than the non-inferiority limit (-8.0%) for both the mITT and the PP analysis sets, the null hypothesis was rejected for the co-primary endpoint analysed. If both null hypotheses were rejected, it would be claimed that Rekovelle was non-inferior to Gonal-F with respect to both co-primary endpoints in the fresh cycle in women undergoing controlled ovarian stimulation. The primary analysis was adjusted for age by the Mantel Haennszel method.

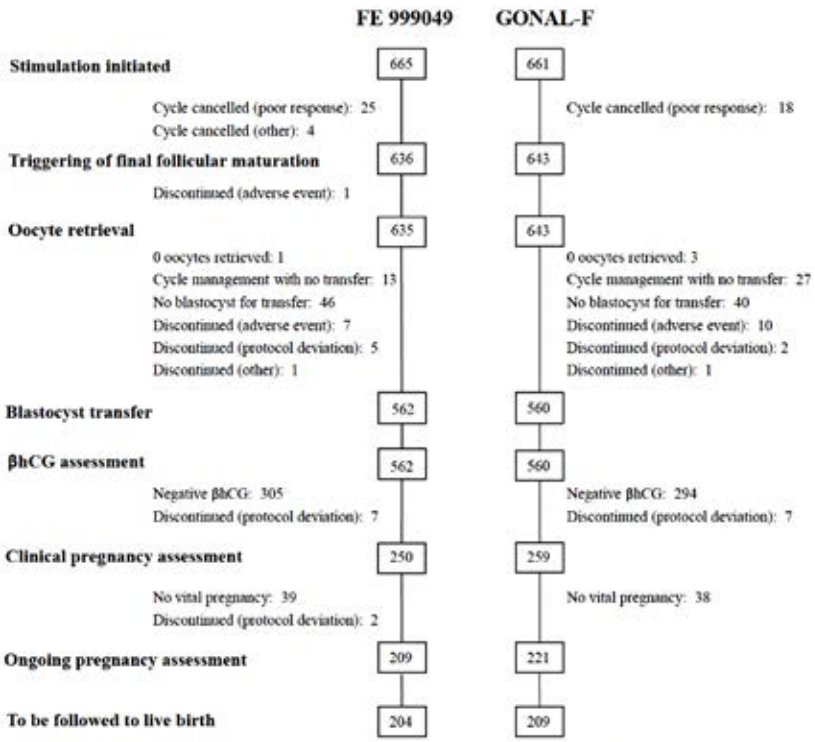
The main co-primary endpoints were ongoing pregnancy rate and ongoing implantation rate. Positive βhCG rate, clinical pregnancy rate, vital pregnancy rate and implantation rate were considered secondary endpoints.
Unless otherwise specified treatment groups were compared using the following tests depending on the type of endpoint. Continuous endpoints were compared between treatment groups using the van Elteren test stratified for age strata while the within age strata comparisons was based on Wilcoxon's test. Categorical endpoints were compared between treatment groups using the chi- square test overall and within age strata. Ordinal endpoints were compared between treatment groups using the Cochran-Mantel-Haenszel test for ordinal data stratified for age strata while the within age strata comparisons were based on Wilcoxon's test for ordinal data.

All statistical tests were performed using a two-sided test at a 5% significance level. Treatment differences were, where appropriate, presented with 95% confidence intervals (CIs) and p-values corresponding to the statistical test of the hypothesis of 'equal effect' against the alternative of 'different effect'. Visual displays were produced as appropriate. All primary and secondary efficacy endpoints were listed. Listings were only produced for the mITT analysis set. Concerning the secondary endpoints*, no formal adjustment for multiplicity was utilised.*

8.2.1.9. Participant flow

In total, 1501 subjects were screened and 1329 randomised. Of those exposed to a study drug, 665 received Rekovelle and 661 Gonal-F. Most patients (95%) completed the trial. More patients in the Rekovelle group discontinued. One of the major reasons related to the protocol deviations were incorrect dosages administered and unblinding due to incorrect use of the pen.

Figure 7: ESTHER-1 Study disposition



Note: Not all discontinuations described in Table 7-1 are directly identifiable as discontinuations in this figure, due to the fact that they are included in other categories in the flow. With regard to the adverse event which is not directly identified, it is included in the category Cycle cancelled (other).

Table 8: Reasons for not completing the trial

	FE 999049		GONAL-F		Total	
	n	%	n	%	n	%
Screened subjects					1501	
Randomised subjects	666		663		1329	
ITT Analysis Set	666	100.0%	663	100.0%	1329	100.0%
mITT Analysis Set	665	99.8%	661	99.7%	1326	99.8%
Completed trial	630	94.6%	639	96.4%	1269	95.5%
Discontinued	36	5.4%	24	3.6%	60	4.5%
Reason for discontinuation:						
Protocol deviation	25	3.8%	11	1.7%	36	2.7%
Adverse event	9	1.4%	10	1.5%	19	1.4%
Randomisation failure	1	0.2%	2	0.3%	3	0.2%
Other	1	0.2%	1	0.2%	2	0.2%

8.2.1.10. Major protocol violations/deviations

There were 42 subjects (6.3%) in the Rekovelle group who experienced a protocol violation compared to 29 subjects (4.4%) in the Gonal-F group. There was an in balance in the number of protocol violations for receiving an incorrect gonadotropin dose, blastocyst available but not transferred and unblinding of the investigator in the Rekovelle group. In relation to the blastocyst transfer policy, the following protocol deviations occurred: 10 subjects consisting of 3 aged < 37 years and 7 aged greater than 38 years but with a good quality blastocyst who should have had a single blastocyst transfer had a double blastocyst transfer, 3 subjects who had blastocysts available and did not undergo transfer; 10 subjects who had no viable blastocysts or compacted morulas available but underwent transfer. The reason for these deviations is not given, presumably due to individual clinicians making a decision. All cases were excluded from the PP analysis, see Table 8.

8.2.1.11. Baseline data

The baseline characteristics of the study group are shown in Table 10 the groups were well balanced.

Table 10: Baseline demographic features

	Rekovelle	Gonal f
Age	33.4 (3.89)	33.2 (3.9)
< 35 years	59.2%	59.3%
35-37	24.2%	25.3%
38-40	16.5%	15.4%
Race White	94.7%	93.2%
BMI (kg/m^2)	23.7 (3.43)	23.3 (3.33)
< 18.5	1.7%	2.3%
18.5-25	68.4%	70.5%
25-30	22.9%	21.2%
>30	7.1%	6.1%

Overall, 71% had primary infertility (no previous pregnancy). The mean duration of infertility was 35.1 ± 23 months. The main reasons for infertility were unexplained (41.8%) and male factor (39.8%).

Table 11: Baseline antral follicle count

	FE 999049 (N=665)	GONAL-F (N=661)
Antral follicles (2-10mm)		
Age Stratum: All age strata	14.7 (6.85)	14.4 (6.75)
Age Stratum: <35 years	16.0 (7.22)	15.8 (7.19)
Age Stratum: 35-37 years	13.2 (5.66)	12.7 (5.86)
Age Stratum: 38-40 years	12.1 (5.94)	11.9 (4.79)

The baseline antral follicle count was similar between treatment groups and decreased with increasing age, see Table 11.

Table 12: Serum AMH concentration at screening

	FE 999049 (N=665)	GONAL-F (N=661)
AMH (pmol/L) at screening		
Mean (SD)	19.4 (14.62)	19.4 (14.79)
Median [IQ-range]	16.3 [9.0;24.8]	16.0 [9.1;25.5]
AMH (pmol/L) at screening, n (%)		
<15	297 44.7%	306 46.3%
15-16	36 5.4%	36 5.4%
17	28 4.2%	18 2.7%
18	24 3.6%	21 3.2%
19-20	45 6.8%	41 6.2%
21-22	35 5.3%	30 4.5%
23-24	28 4.2%	24 3.6%
25-27	26 3.9%	36 5.4%
28-32	41 6.2%	50 7.6%
33-39	53 8.0%	44 6.7%
>=40	52 7.8%	55 8.3%

The mean serum AMH was 19.4 (14.62) pmol/L and approximately 44.7% of patients had an AMH value < 15pmol/L. The mean AMH decreased with increasing age, see Table 12.

Table 13: ESTHER-1 endocrine parameters at baseline

	FE 999049 (N=665)	GONAL-F (N=661)
FSH (IU/L)	7.5 [6.2;9.2]	7.7 [6.5;9.4]
LH (IU/L)	4.5 [3.5;5.8]	4.4 [3.6;5.8]
Estradiol (pmol/L)	158.3 [128.1;198.8]	161.8 [129.9;201.1]
Progesterone (nmol/L)	1.71 [0.80;2.35]	1.69 [0.80;2.32]
Inhibin A (pg/mL)	5.0 [5.0;5.0]	5.0 [5.0;5.0]
Inhibin B (pg/mL)	94.0 [67.5;125.0]	97.0 [72.0;121.0]
TSH (uIU/mL)	1.5 [1.0;2.0]	1.5 [1.1;2.0]
Prolactin (ug/L)	10.3 [7.4;13.9]	9.8 [7.5;13.6]

Data are median [IQ-range]

Endocrine parameters were similar between the two groups, see Table 13.

8.2.1.12. Results for the primary efficacy outcome

Non inferiority for Rekovelle to Gonal-F was demonstrated for the two co-primary endpoints, ongoing pregnancy rate and ongoing implantation rate for both PP and mITT populations. The ongoing pregnancy rate was 30.7% in the Rekovelle group and 31.6% in the GONAL–F group, difference -0.95% 96% CI -5.9-4% (Tables 14 and 15)

Table 14: ESTHER-1 Primary efficacy outcome =ongoing pregnancy rate

	FE 999049			GONAL-F			Comparison*	
Analysis set Age strata	n	N	%	n	N	%	Difference	[95% CI]
PP analysis set	198	623	31.8%	206	632	32.6%	-0.9%	[-6.0%; 4.3%]
<35 years	129	374	34.5%	138	374	36.9%		
35-37 years	39	151	25.8%	49	159	30.8%		
38-40 years	30	98	30.6%	19	99	19.2%		
mITT analysis set	204	665	30.7%	209	661	31.6%	-0.9%	[-5.9%; 4.1%]
<35 years	131	394	33.2%	140	392	35.7%		
35-37 years	41	161	25.5%	50	167	29.9%		
38-40 years	32	110	29.1%	19	102	18.6%		

* The difference and 95% confidence interval is adjusted for age strata

There was a treatment difference in age strata. Those in the 35-37 year age group did better with Gonal–F, where as those 38-40 years do better with Rekovelle.

Sensitivity analysis for treatment differences across trial sites as well as factors potentially impacting pregnancy (implantation method, primary reason for infertility, primary infertility and smoking status) did not influence the outcome.

Table 15: ESTHER-1 Ongoing pregnancy rate by AMH at screening

	FE 999049			GONAL-F		
	n	N	%	n	N	%
PP analysis set						
AMH at screening						
AMH < 15 pmol/L	80	276	29.0%	96	291	33.0%
AMH >= 15 pmol/L	118	347	34.0%	110	341	32.3%
mITT analysis set						
AMH at screening						
AMH < 15 pmol/L	84	297	28.3%	98	306	32.0%
AMH >= 15 pmol/L	120	368	32.6%	111	355	31.3%

Non inferiority for the ongoing implantation rate between Rekovelle and GONAL-f was established. In the mITT analysis, the ongoing implantation rate was 35.2% with Rekovelle and 35.8% with Gonal-f, difference -0.6% 95% CI -6.1%-4.8% (Table 16). Subjects aged 38-40 years had numerically better response in the Rekovelle group. There was homogeneity of treatment differences across sites. There was no difference among implantation rates among the following groups: insemination method, primary reason for infertility, primary infertility and smoking status.

Table 16: ESTHER-1: efficacy endpoint ongoing implantation rate

	FE 999049			GONAL-F			Comparison*	
Analysis set Age strata	n	N	%	n	N	%	Difference	[95% CI]
PP analysis set	200	553	36.2%	206	558	36.9%	-0.9%	[-6.5%; 4.7%]
<35 years	129	329	39.2%	138	321	43.0%		
35-37 years	39	127	30.7%	49	139	35.3%		
38-40 years	32	97	33.0%	19	98	19.4%		
mITT analysis set	206	585	35.2%	209	584	35.8%	-0.6%	[-6.1%; 4.8%]
<35 years	131	342	38.3%	140	333	42.0%		
35-37 years	41	135	30.4%	50	147	34.0%		
38-40 years	34	108	31.5%	19	104	18.3%		

* The difference and 95% confidence interval is adjusted for age strata

8.2.1.13. Results for other efficacy outcomes

The associated secondary pregnancy endpoints of positive βhCG, clinical pregnancy rate, vital pregnancy rate and implantation rate were numerically greater for Gonal-F but there were no statistically significant different between the two groups.

There was no significant difference between the treatment groups in the frequency of cycle cancellations due to poor ovarian response. Oocyte parameters such as fertilisation rate, number of oocytes received, embryo quality on Day 3, blastocyst quality on Day 5 and availability of blastocysts for transfer and cryopreservation were comparable in the two treatment groups.

In relation to the secondary endpoints for pharmacodynamics, the follicular development and advanced endocrine response (oestradiol and inhibin) were higher in the Gonal-F group at the end of stimulation Day 6 (Table 17); however in both groups the levels were well above the threshold of 400pg/ml that predicts ovarian response. This could be explained by the different PK profile of Rekovelle which has a longer T_{max} and $T_{1/2}$.

Table 17: Endocrine profiles on stimulation Day 6-mITT

	FE 999049			GONAL-F			Comparison		
	N	Unadj	Adj	N	Unadj	Adj	Ratio	[95% CI]	P-value
FSH (IU/L)	657	13.5	13.6	647	11.9	11.8	1.15	[1.11; 1.19]	<.001
LH (IU/L)	657	2.9	2.9	646	3.1	3.1	0.94	[0.86; 1.03]	0.158
Estradiol (pmol/L)	657	1885.8	1887.2	645	2061.6	2060.1	0.92	[0.85; 0.99]	0.019
Progesterone (nmol/L)	654	1.7	1.7	645	1.7	1.7	0.97	[0.90; 1.03]	0.327
Inhibin A (pg/mL)	649	98.0	98.2	642	107.5	107.3	0.92	[0.85; 0.99]	0.030
Inhibin B (pg/mL)	654	577.2	580.2	643	611.3	608.1	0.95	[0.89; 1.02]	0.174

N = Number of subjects
Unadj = Unadjusted mean (based on ln-transformed variable)
Adj = Adjusted mean

The size of follicles was similar between treatment groups at the end of the stimulation cycle. At the end of stimulation, FSH remained higher in the Rekovelle group and inhibin A remained lower (Table 18).

Table 18: Endocrine profile at the end of stimulation-mITT

	FE 999049			GONAL-F			Comparison		
	N	Unadj	Adj	N	Unadj	Adj	Ratio	[95% CI]	P-value
FSH (IU/L)	657	13.8	13.9	654	12.6	12.6	1.10	[1.07; 1.14]	<.001
LH (IU/L)	656	1.4	1.4	654	1.4	1.4	0.95	[0.86; 1.04]	0.283
Estradiol (pmol/L)	656	4999.7	5002.0	654	5241.2	5238.7	0.95	[0.89; 1.03]	0.207
Progesterone (nmol/L)	656	2.5	2.5	651	2.6	2.6	0.95	[0.89; 1.01]	0.109
Inhibin A (pg/mL)	648	300.0	300.1	651	325.4	325.3	0.92	[0.86; 0.99]	0.019
Inhibin B (pg/mL)	652	700.9	704.9	652	745.2	741.0	0.95	[0.88; 1.03]	0.220

N = Number of subjects
Unadj = Unadjusted mean (based on ln-transformed variable)
Adj = Adjusted mean

Adjusted treatment means and treatment effect (ratio) are based on a linear model of the ln-transformed variable including treatment group and ln-transformed baseline value.
The P-value corresponds to F-test of treatment effect.

A total of 47 subjects had the cycle cancelled prior to oocyte retrieval. The main reason for cycle cancellation was poor ovarian response (43 subjects). There were no cycle cancellations due to excessive ovarian response. However the trial protocol included an option of administering GnRH for triggering of final follicular maturation in subjects with 25-35 follicles > 12 mm therefore avoiding excessive ovarian response. More patients in the Gonal-F (3.5%) versus Rekovelle (1.5%) received GnRH agonist.

There were no differences in the number of oocytes retrieved in the Rekovelle group (9.6 ± 5.8) versus the Gonal-F group (10.1 ±5.6). More subjects had oocytes retrieved with Rekovelle where the baseline AMH was < 15 pmol/L, whereas more patients had oocytes retrieved with Gonal-F when the AMH was > 15 pmol/L.

Table 19: Oocytes retrieved by AMH-mITT (subjects with triggering)

	FE 999049	GONAL-F	P-value*
Oocytes retrieved			
AMH < 15 pmol/L			
Mean (SD)	8.0 (4.3)	7.0 (3.9)	
Median [IQ-range]	7.0 [5.0;10.0]	6.0 [4.0;9.0]	0.004
AMH >= 15 pmol/L			
Mean (SD)	11.6 (5.9)	13.3 (6.9)	
Median [IQ-range]	11.0 [7.0;15.0]	12.0 [8.0;16.0]	0.002

* P-value based on Wilcoxon's test within AMH at screening

The proportion of subjects with an excessive response leading to GnRH agonist triggering was statistically significantly lower in the Rekovelle group than the Gonal-F group. The proportion of subjects achieving the pre-defined targeted response of 8-14 oocytes retrieved was statistically significantly higher with Rekovelle than Gonal-F despite dose adjustment in 36.8% of the subjects in the Gonal-F group.

Table 20: Oocytes retrieved- distribution of numbers. mITT population

	FE 999049		GONAL-F	
Oocytes retrieved (grouped)	n	%	n	%
<4	76	11.5%	80	12.1%
4-7	191	28.9%	195	29.5%
8-14	275	41.7%	247	37.4%
15-19	77	11.7%	83	12.6%
>=20	41	6.2%	56	8.5%

In the at risk population with AMH < 15 pmol/L, less patients in the Rekovelle group had < 4 oocytes retrieved. In the at risk group with AMH> 15 pmol/L, less patients had an excessive oocyte response with Rekovelle.

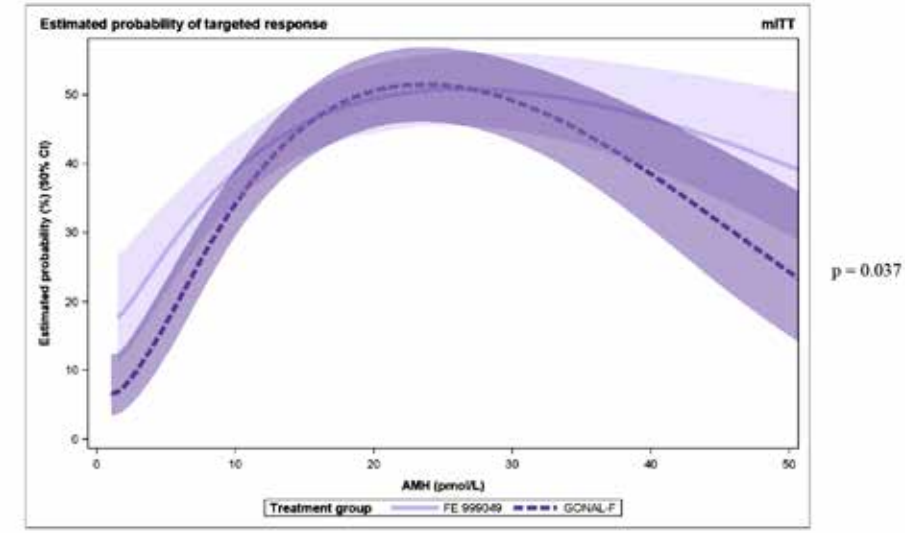
Table 21: ESTHER-1 Extreme ovarian response in risk populations mITT (subjects with triggering)

	FE 999049			GONAL-F			Comparison
	n	N	%	n	N	%	P-value*
AMH < 15 pmol/L							
<4 oocytes retrieved	33	280	11.8%	52	290	17.9%	0.039
AMH >= 15 pmol/L							
>=15 oocytes retrieved	99	355	27.9%	124	353	35.1%	0.038
>=20 oocytes retrieved	36	355	10.1%	55	353	15.6%	0.030

* P-value based on chi-square test

Rekovelle generated better oocyte numbers at the extremes of AMH levels.

Figure 8: Subjects with targeted response by AMH at screening



The most common method of insemination was ICSI. Among patients who had oocytes retrieved, ICSI was used for 531 subjects (83.8%) in the Rekovelle group and 522 (81.6%) in the Gonal-F group.

Those treated with Rekovelle received a lower total dose of gonadotropin than those in the Gonal-F group but similar duration of treatment. The largest difference in doses occurred in patients with high AMH at baseline (Table 22).

Table 22: Duration and total dose of gonadotropin treatment adjusted for age-mITT

	FE 999049	GONAL-F	P-value*
Duration of gonadotropin treatment (days)			
Mean (SD)	8.9 (1.9)	8.6 (1.7)	
Median [IQ-range]	9.0 [8.0;10.0]	8.0 [8.0;10.0]	0.062
Total gonadotropin dose (ug)			
Mean (SD)	90.0 (25.3)	103.7 (33.6)	
Median [IQ-range]	90.0 [72.0;108.0]	99.0 [88.0;115.5]	<.001

* P-value based on van Elteren test adjusted for age strata

8.2.1.14. Evaluator commentary

Non-inferiority of Rekovelle to Gonal-F was demonstrated for the two co-primary endpoints, ongoing pregnancy rate and ongoing implantation rate, for both the PP and mITT populations. The associated secondary pregnancy endpoints of positive hCG rate, clinical pregnancy rate, vital pregnancy rate and oocyte count were supportive.

Regarding the secondary endpoints related to pharmacodynamics, the follicular development was slightly more advanced on stimulation Day 6 in the Gonal-F group compared to the Rekovelle group, which was also reflected as an advanced endocrine response in the Gonal-F group on stimulation Day 6 with statistically significantly higher levels of oestradiol and inhibin A. This could be explained by the different PK profile of Rekovelle and is probably not clinically significant. At end of stimulation, the two treatment groups were comparable in terms of follicular development.

There was no significant difference between treatment groups in the frequency of cycle cancellations due to poor ovarian response, whereas the proportion of subjects with an excessive response leading to GnRH agonist triggering was statistically significantly lower in the Rekovelle group than in the Gonal-F group. The proportion of women achieving the target number of oocytes of 8-14 was slightly higher in the Rekovelle group.

The trial protocol included a number of options to mitigate poor or excessive ovarian response. The outcomes may have differed if these were not performed.

The sponsor will be requested to provide more detailed information about the response where AMH <5 pmol/L and 5-10 pmol/L.

8.3. Other efficacy studies

8.3.1. Trial 000071- ESTHER-II

A controlled, assessor blind, parallel group, multicentre, multinational trial evaluating the immunogenicity of Rekovelle in repeated cycles of controlled ovarian stimulation in women undergoing an assisted reproductive technology programme.

The trial took place in 32 investigational sites: 3 in Belgium, 3 in Brazil, 3 in Canada, 3 in the Czech Republic, 2 in Denmark, 2 in Italy, 2 in Poland, 2 in Russia, 10 in Spain and 2 in the United Kingdom. There were no Australian sites.

The first patient visit was on 26th March 2014. The last patient visit was 26th Jun 2015.

8.3.1.1. Primary objective:

- To evaluate the immunogenicity of Rekovelle and Gonal-F based on the presence of anti-FSH antibodies and their neutralising capacity in women undergoing repeated controlled ovarian stimulation cycles.

8.3.1.2. Secondary objective

- To evaluate the effect of Rekovelle and Gonal-F in repeated controlled ovarian stimulation cycles on ovarian response, including follicular development and endocrine profile as well as on embryo development treatment efficacy and pregnancy rates in the fresh cycles
- To evaluate the safety profile of Rekovelle and Gonal-F including adverse events, routine safety laboratory parameters and local tolerability in repeated controlled ovarian stimulation cycles

8.3.1.3. Patients

Patients were eligible if they had completed ESTHER-1 (COS cycle 1).

Subjects who fail to achieve an ongoing pregnancy in COS Cycle 1 could be offered participation in the trial and thereby start COS Cycle 2. Subjects failing to achieve an ongoing pregnancy in COS Cycle 2 could be offered to start COS Cycle 3 after ensuring that they were still compliant with the eligibility criteria. The treatment allocation in each cycle was the same as in Cycle 1.

Additional exclusion criteria included:

- noncompliance in the previous cycle
- having undergone any stimulation with gonadotropins since the end-of –trial/end of cycle visit
- use of any non-registered investigational drugs since the end of trial/end of visit
- one of more follicles > 10mm observed on the transvaginal ultrasound prior to the start of dosing on stimulation day 1
- pregnancy
- severe OHSS in a previous cycle
- clinically relevant medical history since the previous cycle which precludes gonadotropin stimulation or is associated with a reduced chance of pregnancy

8.3.1.4. Methods

On Day 2-3 of the menstrual cycle, ovarian stimulation was initiated with either Rekovelle or Gonal –F. The Rekovelle daily dose in COS Cycles 2 and 3 was dependent on the ovarian response in the previous cycle. In case of appropriate ovarian response in the previous cycle, that is, 8-14 oocytes retrieved, the same daily dose was repeated in the next cycle. In contrast, if the number of oocytes obtained in the previous cycle was outside the targeted range, the Rekovelle dose was adjusted. Subjects who obtained <4 oocytes or 4-7 oocytes were in the next cycle given a Rekovelle dose which was 50% and 25% higher, respectively, than in the previous cycle. Similarly, subjects who obtained 15-19 oocytes had the Rekovelle dose in the next cycle reduced by 20% and those with ≥20 oocytes had the dose reduced by 33%.

Subjects who had the cycle cancelled prior to oocyte retrieval either due to poor ovarian response or excessive ovarian response were in the next cycle given a Rekovelle dose which was 50% higher or 33% lower, respectively, than in the previous cycle. Subjects who underwent triggering of final follicular maturation with GnRH agonist were in the next cycle given a Rekovelle dose which was 33% lower than in the previous cycle, independent of number of oocytes retrieved. The daily Rekovelle dose for an individual subject was fixed throughout the

cycle. The maximum daily dose in COS Cycles 2 and 3 was 18 µg and 24 µg, respectively. Subjects could be treated with Rekovelle for a maximum of 20 days, and coasting was not allowed.
The Gonal-F starting dose in COS Cycles 2 and 3 was dependent on the ovarian response in the previous cycle. In case of appropriate ovarian response in the previous cycle, that is, 8-14 oocytes retrieved, the same starting dose was repeated in the next cycle. In contrast, if the number of oocytes obtained in the previous cycle was outside the targeted range, the Gonal-F starting dose was adjusted. Subjects who obtained <4 oocytes or 4-7 oocytes were in the next cycle given a Gonal-F starting dose which was 75 IU or 37.5 IU higher, respectively, than in the previous cycle. Similarly, subjects who obtained 15-19 oocytes had the Gonal-F starting dose in the next cycle reduced by 37.5 IU and those with ≥20 oocytes had the dose reduced by 75 IU. Subjects who had the cycle cancelled prior to oocyte retrieval either due to poor ovarian response or excessive ovarian response were in the next cycle given a Gonal-F starting dose which was 75 IU higher or 75 IU lower, respectively, than in the previous cycle. Subjects who underwent triggering of final follicular maturation with GnRH agonist were in the next cycle given a Gonal-F starting dose which was 75 IU lower than in the previous cycle, independent of number of oocytes retrieved. The Gonal-F starting dose was fixed for the first 5 stimulation days after which it could be adjusted by 75 IU based on the individual response. From day 6 the maximum daily Gonal-F dose allowed was 450 IU. Subjects could be treated with Gonal-F for a maximum of 20 days, and coasting was not allowed.

Apart from the following factors, the ART cycle was similar to that described in ESTHER-1. For COS Cycle 2, subjects with a good-quality blastocyst available, that is, a blastocyst of Grade 3BB or higher, had single blastocyst transfer, while subjects with no good-quality blastocyst available had double blastocyst transfer (if two blastocysts were available). For COS Cycle 3, subjects could have single or double blastocyst transfer, independent of age and blastocyst quality. Remaining blastocysts could be cryopreserved in accordance with local guidelines and/or regulations.

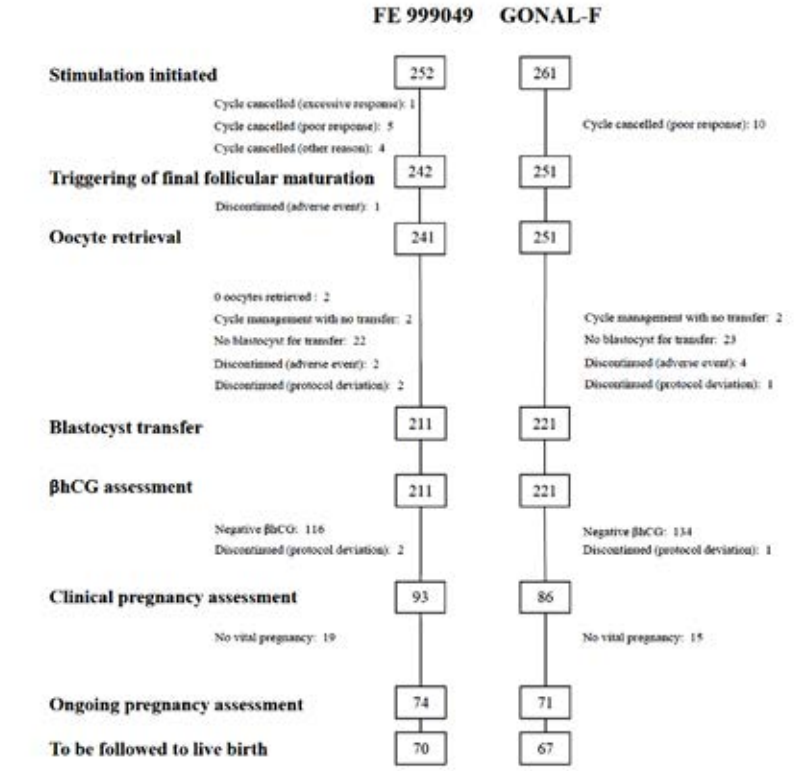
8.3.1.5. Number of subjects

A total of 520 subjects were screened for COS Cycle 2 and 513 subjects were enrolled. All of the 513 subjects enrolled in COS Cycle 2 started stimulation and were exposed to investigational medicinal product: 252 subjects to Rekovelle and 261 subjects to Gonal-F.

A total of 190 subjects were screened for COS Cycle 3 and 189 subjects were enrolled. Of the 189 subjects enrolled in COS Cycle 3, 188 subjects started stimulation and were exposed to investigational medicinal product: 95 subjects to Rekovelle and 93 subjects to Gonal-F.

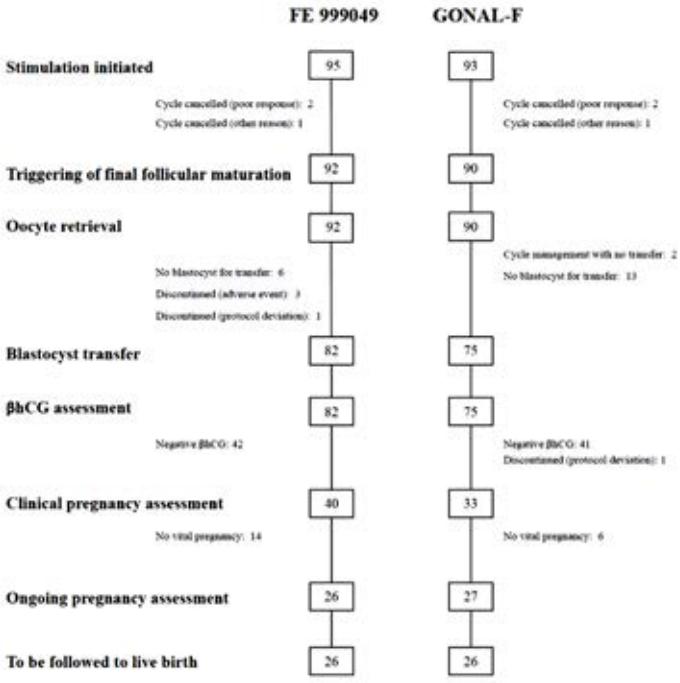
The modified intention-to-treat (mITT) analysis set comprised all enrolled and exposed subjects. In COS Cycle 2, the mITT analysis set comprised 513 subjects, with 252 subjects in the Rekovelle group and 261 subjects in the Gonal-F group. In COS Cycle 3, the mITT analysis set c omprised 188 subjects, with 95 subjects in the Rekovelle group and 93 subjects in the Gonal-F group; Figures 9 and 10.

Figure 9: Subject disposition by main cycle procedure – COS Cycle 2



Note: Not all discontinuations described in Table 7-1 are directly identifiable as discontinuations in this figure, due to the fact that they are included in other categories in the flow.

Figure 10: Subject disposition by main cycle procedure- COS Cycle 3



e: Not all discontinuations described in Table 7-2 are directly identifiable as discontinuations in this figure, due to the fact they are included in other categories in the flow.

8.3.1.6. Demographics

The following table summarises the demographics.

Table 23: Patient demographics

	Rekovelle	Gonal-F
COS 2	252	261
Age- mean and SD < 35years 35-37 38-40	34.2 (3.9) 54.4% 25% 20.6%	34 (3.95) 52.5% 28.4% 19.2%
Race- white	95.2%	92.7%
BMI	24.2 (3.44)	23.9 (3.57)
COS 3	95	93
Age –mean and SD <35years 35-37 38-40	34.7 (4.15) 48.4% 25.3% 26.3%	34.7 (3.99) 47.3% 31.2% 21.5%
Race- white	93.7%	92.5%
BMI	24.1 (3.23)	24.2 (3.75)

There was a greater proportion of subjects in the 38-40 years age bracket in COS 2 and COS 3 than in COS1. In COS3, more patients receiving Rekovelle were 38-40 years than in the Gonal-F group.

The two groups were comparable for endometrial thickness and ovarian volume at baseline, and there was minimal difference in these parameters between COS 2 and COS 3. The mean antral follicle count for Rekovelle and Gonal-F was 13.7 and 14.6 at baseline in COS2 and 13.3 and 14.3 at baseline in COS3. Baseline endocrine parameters were also similar between groups and between COS2 and COS3.

The mean AMH at stimulation day 1 in COS2 16.6 pg/ml and 16.9 pg/ml and for COS3 was 13.8 pg/ml and 16.0 pg/ml respectively, in the FE 99049 and Gonal-F groups.

8.3.1.7. Efficacy results

Efficacy of Rekovelle was maintained over repeated treatment cycles and was comparable to Gonal-F. The ongoing pregnancy rate was 27.8% for Rekovelle and 25.7% for Gonal-F in COS Cycle 2 (Table 24 and Table 25) and 27.4% and 28.0%, respectively, in COS Cycle 3 (Table 26-27). The ongoing implantation rate was also comparable between FE 999049 and Gonal-F in COS 2 and COS 3 (Tables 28-29)

Table 24: Ongoing pregnancy rate- COS Cycle 2

FE 999049				GONAL-F			
n	N	%	[95% CI]	n	N	%	[95% CI]
70	252	27.8%	[22.3%; 33.7%]	67	261	25.7%	[20.5%; 31.4%]

Table 25: Ongoing pregnancy rate by age - COS Cycle 2

	FE 999049			GONAL-F		
Age strata	n	N	%	n	N	%
All observations	70	252	27.8%	67	261	25.7%
<35 years	39	137	28.5%	35	137	25.5%
35-37 years	22	63	34.9%	21	74	28.4%
38-40 years	9	52	17.3%	11	50	22.0%

Table 26: Ongoing pregnancy rate- COS Cycle 3

FE 999049				GONAL-F			
n	N	%	[95% CI]	n	N	%	[95% CI]
26	95	27.4%	[18.7%; 37.5%]	26	93	28.0%	[19.1%; 38.2%]

Table 27: Ongoing pregnancy rate by age- COS Cycle 3

	FE 999049			GONAL-F		
Age strata	n	N	%	n	N	%
All observations	26	95	27.4%	26	93	28.0%
<35 years	12	46	26.1%	14	44	31.8%
35-37 years	9	24	37.5%	8	29	27.6%
38-40 years	5	25	20.0%	4	20	20.0%

Table 28: Ongoing implantation rate- COS Cycle 2

FE 999049				GONAL-F			
n	N	%	[95% CI]	n	N	%	[95% CI]
73	254	28.7%	[23.3%; 34.7%]	69	271	25.5%	[20.4%; 31.1%]

Table 29: Ongoing implantation rate- COS Cycle 3

FE 999049				GONAL-F			
n	N	%	[95% CI]	n	N	%	[95% CI]
33	132	25.0%	[17.9%; 33.3%]	35	121	28.9%	[21.0%; 37.9%]

Serum FSH levels were higher during stimulation and at the end-of-stimulation in the Rekovelle group than in the Gonal-F group in both COS cycles. Follicular development and endocrine profile during and at end of stimulation were comparable in the two treatment groups.

Cycle cancellations due to poor ovarian response in COS Cycle 2 occurred for 5 subjects in the Rekovelle group and 10 subjects in the Gonal-F group, while excessive ovarian response leading to cycle cancellation or triggering with GnRH agonist happened for 2 subjects in each treatment group. In COS Cycle 3, 2 subjects in each treatment group had cycle cancellation due to poor ovarian response and 1 subject in the Gonal-F group experienced excessive ovarian response leading to triggering with GnRH agonist while no subjects in the Rekovelle group had excessive ovarian response.

The mean number of oocytes retrieved among subjects who started stimulation was 8.8 and 8.2 in the Rekovelle and Gonal-F groups, respectively, in COS Cycle 2, and 8.0 and 8.6, respectively, in COS Cycle 3. After adapting the Rekovelle dosing regimen in COS Cycles 2 and 3 based on the subject's ovarian response in the previous COS cycle, the targeted response of 8-14 oocytes retrieved was achieved by 45.3% and 47.9% of the subjects treated with Rekovelle in COS Cycle 2 and COS Cycle 3, respectively, which was comparable to the rates of 45.2% and 48.9%, respectively, in the Gonal-F group.
The total dose of gonadotropin was on average 108 µg Rekovelle and 122 µg Gonal-F in COS Cycle 2, and 130 µg Rekovelle and 133 µg Gonal-F in COS Cycle 3.

Oocyte development parameters such as fertilisation rate, number of fertilised oocytes as well as embryo quality on day 3, blastocyst quality on day 5 and availability of blastocysts for transfer and for cryopreserved on were comparable in the Rekovelle and Gonal-F groups and also in COS Cycle 2 and COS Cycle 3.

8.3.1.8. Response to changes in dose

Oocytes Retrieved in COS Cycle 2 compared to COS Cycle 1

Among the subjects with <4 oocytes retrieved in COS cycle 1 who proceeded to COS Cycle 2 , <4 oocytes retrieved also in COS Cycle 2 was observed for 27.8% (n=10) and 32.4% (n=12) in the Rekovelle and Gonal-F groups, respectively, while 4-7 oocytes retrieved in COS Cycle 2 was observed for 41.7% (n=15) and 43.2% (n=16), respectively, and 8-14 oocytes retrieved in COS Cycle 2 was reached by 13.9% (n=5) and 21.6% (n=8), respectively.

Among the subjects with 4-7 oocytes retrieved in COS cycle 1 who proceeded to COS Cycle 2, 4-7 oocytes retrieved also in COS Cycle 2 was observed for 38.5% (n=30) and 49.0% (n=47) in the Rekovelle and Gonal-F groups, respectively, while 8-14 oocytes retrieved in COS Cycle 2 was reached by 38.5% (n=30) and 33.3% (n=32), respectively.

Among the subjects with 8-14 oocytes retrieved in COS cycle 1 who proceeded to COS Cycle 2, 62.0% (n=62) in the Rekovelle group and 65.9% (n=58) in the Gonal-F group reached 8-14 oocytes retrieved again in COS Cycle 2.

Among the subjects with ≥ 15 oocytes retrieved in COS cycle 1 who proceeded to COS Cycle 2, 8-14 oocytes retrieved in COS Cycle 2 was reached by 50.0% (n=12) and 68.0% (n=17) in the Rekovelle and Gonal-F groups, respectively. Finally, among the subjects with ≥ 20 oocytes retrieved in COS cycle 1 who proceeded to COS Cycle 2, 8-14 oocytes retrieved in COS Cycle 2 was reached by 33.3% (n=3) and 20.0% (n=3) in the Rekovelle and Gonal-F groups, respectively.

Oocytes Retrieved in COS Cycle 3 compared to COS Cycle 2

Among the subjects with <4 oocytes retrieved in COS Cycle 2 who proceeded to COS cycle , <4 oocytes retrieved also in COS Cycle 3 was observed for 40.0% (n=4) and 28.6% (n=4) in the Rekovelle and Gonal-F groups, respectively, while 4-7 oocytes retrieved in COS Cycle 3 was observed for 30.0% (n=3) and 35.7% (n=5), respectively, and 8-14 oocytes retrieved in COS Cycle 3 was reached by 30.0% (n=3) and 28.6% (n=4), respectively. Among the subjects with 4-7

oocytes retrieved in COS Cycle 2 who proceeded to COS cycle 4-7 oocytes retrieved also in COS Cycle 3 was observed for 27.3% (n=9) and 37.5% (n=12) in the Rekovelle and Gonal-F groups, respectively, while 8-14 oocytes retrieved in COS Cycle 3 was reached by 45.5% (n=15) and 40.6% (n=13), respectively.

Among the subjects with 8-14 oocytes retrieved in COS Cycle 2 who proceeded to COS Cycle 3 , 53.7% (n=22) in the Rekovelle group and 64.1% (n=25) in the Gonal-F group reached 8-14 oocytes retrieved again in COS Cycle 3.

Among the subjects with ≥15 oocytes retrieved in COS Cycle 2 who proceeded to COS Cycle 3 , 8-14 oocytes retrieved in COS Cycle 3 was reached by 44.4% (n=4) and 33.3% (n=2) in the Rekovelle and Gonal-F groups, respectively. Finally, among the subjects with ≥20 oocytes retrieved in COS Cycle 2 who proceeded to COS Cycle 3, 8-14 oocytes retrieved in COS Cycle 3 was reached by 100% (n=1) and 100% (n=1) in the Rekovelle and Gonal-F groups, respectively

8.4. Evaluator's conclusions on clinical efficacy

The sponsor has submitted one randomised trial of Rekovelle compared to Gonal-F for controlled ovarian stimulation in IVF/ICSI; and a supportive study for use on repeated cycles.

ESTHER I and II demonstrated that Rekovelle was non inferior to Gonal-F both during the first and subsequent cycles of controlled ovarian stimulation. The secondary endpoints were supportive of the primary endpoints. The response across age stratum was consistent, however FE 999049 was showed a relatively greater response than Gonal-F in the older subgroup, possibly as AMH is a better predictor of ovarian reserve in this age group.

There was a small difference in endocrine parameters on Day 6 between the two treatment groups in ESTHER I. This was probably due to the different half-lives of Rekovelle compared to Gonal-F and is unlikely to be clinically significant.

There was no information about live births.

It is noted that the patients and study nurses were not blinded to the allocation. This was not possible due to the different devices. The sponsor attempted to ensure the investigators and technicians remained blinded- but it is unclear how successful that was. This is not relevant to the efficacy endpoints as there were largely objective.

9. Clinical safety

9.1. Studies providing evaluable safety data

9.1.1. Pivotal 000004- ESTHER-1

The safety population is identical to the mITT population. Thus, 665 subjects exposed to Rekovelle and 661 subjects exposed to Gonal-F contribute with safety data.
The safety evaluation consisted of adverse events (including serious adverse events and adverse events leading to discontinuation) with special emphasis on OHSS and early pregnancy losses, which were identified as adverse events of special interest in the clinical trial protocol. In addition, injection site reactions, anti-FSH antibodies, abdominal discomfort related to controlled ovarian stimulation, changes in body weight and maximum abdominal circumference, potentially immune related adverse events, multi-fetal gestations, potential pen malfunctions, and cycle cancellations due to adverse events or potential pen malfunctions were assessed. Lastly, blood sampling for clinical chemistry and haematology evaluations, vital sign measurements as well as physical and gynaecological examinations was carried out.

9.2. Studies that assessed safety as the main outcome

9.2.1. ESTHER II- 000071

The safety population is identical to the mITT population. Thus, 252 subjects exposed to Rekovelle and 261 subjects exposed to Gonal-F contribute with safety data in COS Cycle 2, while 95 subjects exposed to Rekovelle and 93 subjects exposed to Gonal-F contribute with safety data in COS Cycle 3.

The safety evaluation consisted of adverse events (including serious adverse events and adverse events leading to discontinuation) with special emphasis on OHSS and early pregnancy losses, which were identified as adverse events of special interest in the clinical trial protocol. In addition, injection site reactions, abdominal discomfort related to controlled ovarian stimulation, changes in body weight and maximum abdominal circumference, potentially immune-related adverse events, multi-fetal gestations, potential pen malfunctions and cycle cancellations due to adverse events or potential pen malfunctions were assessed. Lastly, blood sampling for clinical chemistry and haematology evaluation were performed and physical and gynaecological examinations were carried out.

Adverse events were recorded from signed informed consent to the end-of-cycle visit for COS Cycle 2 and again from screening to the end-of-cycle visit for COS Cycle 3, if applicable. Adverse events with onset after start of first administration of IMP and before end of the corresponding COS cycle (that is, end-of-cycle) were considered treatment-emergent. Only treatment-emergent adverse events are described in this section.

9.2.1.1. Study design, objectives, locations and dates

See section 8.2.

9.2.1.2. Inclusion and exclusion criteria

See section 8.2.

9.2.1.3. Safety variables and outcomes

The primary endpoint was the proportion of subjects with treatment induced anti-FSH antibodies after up to 2 repeated controlled ovarian stimulation cycles.

Secondary endpoints related to safety included:

- the proportion of subjects with treatment induced anti-FSH antibodies of neutralising capacity after up to two repeated controlled ovarian stimulation cycles.
- the proportion of subjects with early OHSS and/or interventions to prevent OHSS
- frequency and intensity of adverse events
- clinical chemistry, haematology, vital signs
- injection site reactions
- abdominal discomfort, changes in body weight and abdominal girth
- technical problems with the pen

9.2.1.4. Sample size

There was no sample size set for this study. The number of subjects depended upon the number of subjects requesting a further treatment cycle, who gave consent, and who still met eligibility criteria.

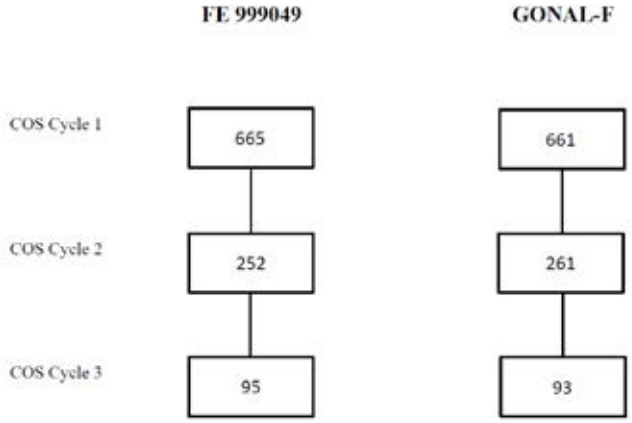
9.3. Patient exposure

Patient exposure and disposition are described in Table 30 and Figure 11 below.

Table 30: Exposure in ESTHER I and ESTHER II

Stimulation cycle		Rekovelle	Gonal-F
COS1	number	665	661
	Duration (days) Median (IQ range)	9 (8,10)	8 (8,10)
	Total dose (µg) (median IQ range)	90 (72,108)	99 (88,115.5)
COS2	number	252	261
	Duration (days) Median (IQ range)	9 (8,10)	9 (8,10)
	Total dose (µg) median (IQ range)	105.0 (80.5, 129.0)	112.8 (96.3, 145.8)
COS3	number	95	93
	Duration (days) Median (IQ range)	9 (8, 10)	9 (8,10)
	Total dose (µg) median (IQ range)	120 (90,153)	132 (99,162.3)

Figure 11: Subject disposition by COS cycle.



9.4. Adverse events

9.4.1. All adverse events (irrespective of relationship to study treatment)

9.4.1.1. Integrated safety analyses

Adverse events occurred in around 50% of patients during the clinical trials. These were generally mild (Tables 31-33).

Table 31: ESTHER-1 adverse events summary

	FE 999049 (N=665)			GONAL-F (N=661)		
	n	%	E	n	%	E
Adverse events	363	54.6%	1063	336	50.8%	961
Adverse events leading to death	0			0		
Serious adverse events	16	2.4%	17	10	1.5%	12
Adverse events leading to discontinuation	9	1.4%	9	10	1.5%	10
Severe adverse events	34	5.1%	38	29	4.4%	44
Adverse drug reactions	113	17.0%	183	91	13.8%	141

Table 32: ESTHER II Adverse events COS Cycle 2

	FE 999049 (N=252)			GONAL-F (N=261)		
	n	%	E	n	%	E
Adverse events	119	47.2%	260	124	47.5%	348
Adverse events leading to death	0			0		
Serious adverse events	4	1.6%	5	4	1.5%	4
Adverse events leading to discontinuation	3	1.2%	3	4	1.5%	4
Severe adverse events	12	4.8%	13	11	4.2%	14
Adverse drug reactions	26	10.3%	31	36	13.8%	58

Table 33: ESTHER II- Adverse events COS Cycle 3

	FE 999049 (N=95)			GONAL-F (N=93)		
	n	%	E	n	%	E
Adverse events	46	48.4%	100	42	45.2%	119
Adverse events leading to death	0			0		
Serious adverse events	0			1	1.1%	1
Adverse events leading to discontinuation	3	3.2%	3	0		
Severe adverse events	1	1.1%	1	3	3.2%	4
Adverse drug reactions	6	6.3%	6	10	10.8%	11

The increased number of adverse events leading to discontinuation was higher in the Rekovelle group, this was largely driven by increased progesterone at the end of stimulation at one site, see below.

9.4.1.2. ESTHER I

The most commonly reported adverse events were seen in similar frequency between Rekovelle and Gonal-F groups : headache (14.6 versus 13.3%), procedural pain (7.4 versus 7.9%), pelvic pain (6.9 versus 6.2%), pelvic discomfort (5.7 versus 3.8%), vomiting in pregnancy (4.5 and 4.5%), spontaneous abortion (3.9 versus 4.5%), nausea (4.4 versus 3.9%), OHSS (3.5 versus 4.8%) and haemorrhage during pregnancy (3.9 versus 4.1%).

The injection site reactions were more commonly associated with the GnRH antagonists or triggering drugs. Most headaches were mild. Most procedural pain was associated with oocyte retrieval.

There were more dosing errors associated with Rekovelle. This was attributed to the users being less familiar with the device.

Table 34: ESTHER-1 Intensity of adverse events

	FE 999049 (N=665)			GONAL-F (N=661)		
	n	%	E	n	%	E
Adverse events	363	54.6%	1063	336	50.8%	961
Mild adverse events	318	47.8%	761	286	43.3%	695
Moderate adverse events	141	21.2%	264	119	18.0%	222
Severe adverse events	34	5.1%	38	29	4.4%	44

9.4.1.3. ESTHER II

In COS Cycle 2, the most commonly observed adverse events (≥4% of subjects in a treatment group) in the Rekovelle and Gonal-F groups respectively were: headache (7.5% and 10.3%), procedural pain (5.2% and 6.5%), pelvic pain (5.6% and 4.2%), haemorrhage in pregnancy (5.6% and 3.8%), biochemical pregnancy (5.2% and 3.1%), pelvic discomfort (2.4% and 5.0%), spontaneous abortion (4.4% and 3.4%), adnexa uteri pain (2.8% and 4.6%) and post procedural discomfort (2.8% and 4.2%).

In COS Cycle 3, the most frequently reported adverse events (≥4% of subjects in a treatment group) in the Rekovelle and Gonal-F groups respectively were: headache (11.6% and 14.0%), procedural pain (5.3% and 8.6%), biochemical pregnancy (9.5% and 4.3%), spontaneous abortion (5.3% and 4.3%), pelvic pain (3.2% and 5.4%), pelvic discomfort (0% and 6.5%), vomiting in pregnancy (3.2% and 4.3%), nausea (1.1% and 4.3%) and fatigue (0% and 4.3%).

Note: more haemorrhage in pregnancy and biochemical pregnancy in ESTHER II than ESTHER I in the Rekovelle group, but this was not seen in ESTHER I. All except 2 patients with haemorrhage in pregnancy had an ongoing pregnancy. More pelvic discomfort was seen in the Gonal-F than the Rekovelle group in ESTER II, this was not observed in ESTHER I.

Most adverse events were mild.

9.4.2. Treatment related adverse events (adverse drug reactions)

Adverse events attributed to the IMP were less frequent in COS 2 and 3 and overall occurred in a similar pattern and frequency between the two groups.

Comment: With IVF, it would be expected that patients experience side effects from the treatment. It would be difficult to differentiate and perhaps subject to reported bias, as to what drug or procedure the adverse events were due to. In addition the patient may experience an adverse event, such as headache or fatigue or pelvic pain, breast tenderness due to the stimulation and subsequent pregnancy- which is actually a positive outcome.

9.4.2.1. ESTHER 1

Table 35: ESTHER-1 Frequent Adverse Drug Reactions

MedDRA system organ class/ preferred term	FE 999049 (N=665)			GONAL-F (N=661)		
	n	%	E	n	%	E
Any adverse drug reactions	113	17.0%	183	91	13.8%	141
Gastrointestinal disorders	21	3.2%	28	13	2.0%	15
Nausea	11	1.7%	12	7	1.1%	8
General disorders and administration site conditions	13	2.0%	13	6	0.9%	6
Fatigue	12	1.8%	12	6	0.9%	6
Nervous system disorders	37	5.6%	46	33	5.0%	40
Headache	35	5.3%	41	30	4.5%	36
Reproductive system and breast disorders	67	10.1%	82	65	9.8%	76
Pelvic discomfort	25	3.8%	29	21	3.2%	22
Ovarian hyperstimulation syndrome	20	3.0%	20	24	3.6%	24
Pelvic pain	13	2.0%	16	17	2.6%	20
Adnexa uteri pain	8	1.2%	8	4	0.6%	4

9.4.2.2. ESTHER II

Table 36: Frequent adverse drug reactions –COS Cycle 2

MedDRA system organ class/ preferred term	FE 999049 (N=252)			GONAL-F (N=261)		
	n	%	E	n	%	E
Any adverse drug reactions	26	10.3%	31	36	13.8%	58
Gastrointestinal disorders	4	1.6%	4	8	3.1%	10
Nausea	3	1.2%	3	6	2.3%	6
Abdominal distension				2	0.8%	2
Diarrhoea				1	0.4%	1
Flatulence	1	0.4%	1			
Vomiting				1	0.4%	1
General disorders and administration site conditions	1	0.4%	1	4	1.5%	5
Fatigue				4	1.5%	5
Chest discomfort	1	0.4%	1			
Injury, poisoning and procedural complications				1	0.4%	1
Post procedural discomfort				1	0.4%	1
Nervous system disorders	9	3.6%	9	13	5.0%	14
Headache	8	3.2%	8	10	3.8%	11
Dysgeusia				2	0.8%	2
Dizziness				1	0.4%	1
Somnolence	1	0.4%	1			
Reproductive system and breast disorders	16	6.3%	17	25	9.6%	27
Pelvic discomfort	5	2.0%	5	6	2.3%	6
Adnexa uteri pain	5	2.0%	5	5	1.9%	5
Ovarian hyperstimulation syndrome	2	0.8%	2	6	2.3%	6
Pelvic pain	4	1.6%	4	4	1.5%	4
Breast pain				2	0.8%	2
Breast discomfort	1	0.4%	1			
Ovarian cyst				1	0.4%	1
Uterine pain				1	0.4%	1
Vaginal discharge				1	0.4%	1
Vaginal haemorrhage				1	0.4%	1
Vascular disorders				1	0.4%	1
Flushing				1	0.4%	1

Table 37: ESTHER II- frequent adverse drug reactions COS Cycle 3

MedDRA system organ class/ preferred term	FE 999049 (N=95) n	%	E	GONAL-F (N=93) n	%	E
Any adverse drug reactions	6	6.3%	6	10	10.8%	11
Gastrointestinal disorders				1	1.1%	1
Constipation				1	1.1%	1
General disorders and administration site conditions				2	2.2%	2
Fatigue				2	2.2%	2
Nervous system disorders	1	1.1%	1	4	4.3%	4
Headache	1	1.1%	1	2	2.2%	2
Dysgeusia				2	2.2%	2
Reproductive system and breast disorders	5	5.3%	5	4	4.3%	4
Adnexa uteri pain	2	2.1%	2	1	1.1%	1
Pelvic discomfort				2	2.2%	2
Nipple pain	1	1.1%	1			
Ovarian cyst				1	1.1%	1
Ovarian hyperstimulation syndrome	1	1.1%	1			
Uterine polyp	1	1.1%	1			

9.4.3. Deaths and other serious adverse events

9.4.3.1. ESTHER I

No deaths occurred in the trial. A total of 26 subjects experienced 29 SAE, 16 patients with 17 events in the Rekovelle group and 10 patients with 12 events in the Gonal-F group. SAE included OHSS, haemorrhage in pregnancy, spontaneous abortion, biochemical pregnancy, threatened abortion, hyperemesis pregnancy, post procedural haemorrhage, adnexal torsion, affect lability and ulcerative colitis.

9.4.3.2. ESTHER II

No deaths occurred during the trial. In COS Cycle 2, there were 4 subjects with 5 serious adverse events in the Rekovelle group and 4 subjects with 4 serious adverse events in the Gonal-F group. Serious adverse events in COS Cycle 2 were mainly related to pregnancy complications, including ectopic pregnancy (1 case for Rekovelle and 2 cases for Gonal-F), haemorrhage in pregnancy (1 case for each), abortion spontaneous (1 case for Rekovelle) and vomiting in pregnancy (1 case for Rekovelle). Other serious adverse events in COS Cycle 2 covered a single case of nephrolithiasis in the Rekovelle group and a single case of OHSS in the Gonal-F group. In COS Cycle 3, there were no seriou s adverse events in the Rekovelle group but 1 serious adverse event of OHSS in the Gonal-F group.

9.4.4. Discontinuations due to adverse events

9.4.4.1. ESTHER-I

Adverse events leading to discontinuation occurred in 1.4% of subjects in the FE 99049 group and 1.5% of subjects in the Gonal-F group.

Table 38: ESTHER-1 adverse events leading to discontinuation

MedDRA system organ class/ preferred term	FE 999049 (N=665)			GONAL-F (N=661)		
	n	%	E	n	%	E
Any adverse events leading to discontinuation	9	1.4%	9	10	1.5%	10
Infections and infestations	1	0.2%	1			
Salpingitis	1	0.2%	1			
Reproductive system and breast disorders	8	1.2%	8	10	1.5%	10
Ovarian hyperstimulation syndrome	6	0.9%	6	7	1.1%	7
Premature ovulation	2	0.3%	2			
Endometrial atrophy				1	0.2%	1
Ovarian hyperfunction				1	0.2%	1
Uterine polyp				1	0.2%	1

9.4.4.2. ESTHER II

Adverse events leading to discontinuation from COS Cycle 2 were recorded for 3 subjects (1.2%) in the Rekovelle group and 4 subjects (1.5%) in the Gonal-F group. In COS Cycle 2, adverse events leading to discontinuation included single cases of premature ovulation, increased progesterone at end-of- stimulation and fractured sacrum due to a fall in the Rekovelle group as well as 2 cases each of OHSS and endometrial disorders in the Gonal-F group. In COS Cycle 3, adverse events led to discontinuation of 3 subjects (3.2%) in the Rekovelle group, with 2 due to increased progesterone at end-of-stimulation and 1 due to early mild OHSS. None of these adverse events led to cycle cancellation in COS Cycle 2 or in COS Cycle 3.

All 3 cases of increased progesterone leading to discontinuation (1 event in COS Cycle 2 and 2 events in COS Cycle 3) were driven by one trial site. At end-of-stimulation, these subjects had a progesterone level of 2.35, 8.03 and 4.16 nmol/L, respectively, according the results from the central laboratory. Blastocyst transfer was cancelled according to local clinical practice and the progesterone results from the local laboratory. However, there appeared to be no consistent cut-off at the trial site, as other subjects with similar progesterone levels, both in the Rekovelle and Gonal-F groups, proceeded to blastocyst transfer. Thus, it is probably misclassified as an adverse event.

9.5. Evaluation of issues with possible regulatory impact

9.5.1. OHSS

9.5.1.1. ESTHER-I

Investigators used Golan's system to Grade (1, 2, 3, 4 and 5) each OHSS cases, see Table 39.

Table 39: ESTHER-1 Classification of mild, moderate and severe OHSS

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

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

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

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

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

Early OHSS occurred within 9 days of triggering, late OHSS occurred with onset > 9 days after triggering.

Preventative interventions of OHSS included cycle cancellation due to excessive ovarian response, triggering of final follicular maturation with GnRH agonist, administration of dopamine agonist.

OHSS was experienced by 55 subjects in the trial; 23 subjects (3.5%) in the Rekovelle group and 32 (4.8%) in the Gonal-F group. In addition, More patients in the Gonal-F group received preventative interventions for OHSS (Table 40).

Table 40: ESTHER-1 Early OHSS and preventative interventions for early OHSS

	FE 999049			GONAL-F			Comparison*
Early OHSS and preventive interventions	n	N	%	n	N	%	P-value
Early OHSS (any grade)	17	665	2.6%	20	661	3.0%	0.291
Early OHSS (moderate/severe)	9	665	1.4%	9	661	1.4%	0.644
Any preventive intervention	15	665	2.3%	30	661	4.5%	0.005
Early OHSS (any grade) and/or preventive interventions	31	665	4.7%	41	661	6.2%	0.046
Early OHSS (moderate/severe) and/or preventive interventions	24	665	3.6%	34	661	5.1%	0.019

* P-value based likelihood ratio test comparing nested logistic regression models including treatment as factor, AMH as covariate and interactions

The most common preventative intervention for early OHSS was triggering of final follicular maturation with GnRH agonist followed by administration of dopamine agonist.

Table 41: ESTHER-1 Late OHSS

	FE 999049			GONAL-F			Comparison*
Late OHSS	n	N	%	n	N	%	P-value
Late OHSS (any grade)	6	665	0.9%	12	661	1.8%	0.320
Late OHSS (moderate/severe)	5	665	0.8%	10	661	1.5%	0.390

* P-value based likelihood ratio test comparing nested logistic regression models including treatment as factor, AMH as covariate and interactions

The number of cases of late OHSS was twice that with Gonal-F than for Rekovelle, however the difference was not statistically significant (Table 41).

9.5.1.2. ESTHER II

In COS Cycle 2, OHSS was experienced by 3 subjects (1.2%) in the Rekovelle group and 8 subjects (3.1%) in the Gonal-F group. Moderate/severe OHSS in COS Cycle 2 did not occur in the Rekovelle group but occurred in 7 subjects in the Gonal-F group, of whom 1 subject in the Gonal-F group was hospitalised for 6 days due to OHSS. Early OHSS was experienced by 2 subjects (0.8%) in the Rekovelle group and 6 subjects (2.3%) in the Gonal-F group, of whom 5 subjects (1.9%) in the Gonal-F group developed early moderate/severe OHSS. Preventive interventions for early OHSS were performed in 4 subjects (1.6%) in the Rekovelle group and 5 subjects (1.9%) in the Gonal-F group in COS Cycle 2. One subject (0.4%) in the Rekovelle group developed late mild OHSS and 2 subjects (0.8%) in the Gonal-F group developed late moderate OHSS (Table 42).

Table 42: ESTHER II- Early OHSS and preventive interventions for early OHSS- COS Cycle 2

	FE 999049			GONAL-F		
	n	N	%	n	N	%
Early OHSS (any grade)	2	252	0.8%	6	261	2.3%
Early OHSS (moderate/severe)	0	252	0.0%	5	261	1.9%
Any preventive intervention	4	252	1.6%	5	261	1.9%
Early OHSS (any grade) and/or preventive interventions	5	252	2.0%	10	261	3.8%
Early OHSS (moderate/severe) and/or preventive interventions	4	252	1.6%	10	261	3.8%

In COS Cycle 3, OHSS was observed in 2 subjects (2.1%) in the Rekovelle group and 1 subject (1.1%) in the Gonal-F group. Moderate/severe OHSS in COS Cycle 3 did not occur in the Rekovelle group but occurred in 1 subject in the Gonal-F group, who was hospitalised for 9 days due to OHSS.

Late OHSS occurred in 1 subject in each treatment group. The subject receiving Rekovelle had mild late OHSS, and the subject in the Gonal-F group had late severe OHSS.

9.5.2. Early pregnancy loss

9.5.2.1. ESTHER-1

Early pregnancy loss occurred in 53 (20.6%) of cases with Rekovelle and 57 (21.4%) of cases with Gonal-F with a positive βhCG. The types of pregnancy loss were similar between the two groups, spontaneous abortion 10.1 and 11.3%, biochemical pregnancy 9.7 and 9.4%, ectopic pregnancy 0.4 and 0.4%, induced abortion 0.4 and 0.4%.

9.5.2.2. ESTHER II

From βhCG to ongoing pregnancy, early pregnancy loss in COS Cycle 2 was experienced by 26.3% and 23.0% of subjects with a positive βhCG in the Rekovelle and Gonal-F groups, respectively. In COS Cycle 3, the frequency of early pregnancy loss among subjects with a positive βhCG was 35.0% for Rekovelle and 23.5% for Gonal-F. The type of pregnancy loss in

COS3 for Rekovelle was biochemical in 22.5% and spontaneous abortion in 12.5%; in the GONAL- f group it was biochemical in 11.8% and spontaneous abortion in 11.8%.

Comment: The higher pregnancy loss in patients who had previously failed IVF is expected. It is noted that at baseline patients in the Rekovelle group had lower AMH and higher proportion of patients in the 38-40 year old age bracket.

9.5.3. Multi-fetal gestations

9.5.3.1. Integrated safety analyses

9.5.3.2. ESTHER-1

There were 4 sets of twins in Rekovelle and 8 with Gonal-F. Of them, 2 subjects in the Rekovelle group and 8 subjects in the Gonal-F group conceived twins after single blastocyst transfer, and the remaining 2 subjects in the Rekovelle group conceived twins after double blastocyst transfer.

9.5.3.3. ESTHER –II

Among subjects with an ongoing pregnancy, multi-fetal gestations, all being twins, were observed in a total of 7 subjects in COS Cycle 2 (5 for Rekovelle and 2 for Gonal-F). Two subjects (in the Rekovelle group) conceived twins after single blastocyst transfer, and the other 5 subjects (3 in the FE99049 group and 2 in the Gonal-F group) conceived twins after double blastocyst transfer.

Twins were observed in 18 subjects in COS Cycle 3 (8 for Rekovelle and 10 for Gonal-F). Of them, 2 subjects (1 in each treatment group) conceived twins after single blastocyst transfer and the other 16 subjects (7 in the Rekovelle group and 9 in the Gonal-F group) conceived twins after double blastocyst transfer.

9.5.4. Injection site reactions

9.5.4.1. Integrated safety analyses

9.5.4.2. ESTHER-1

Injection site reactions occurred in < 3.5% of patients and with a similar frequency between the two groups. Itching and redness occurred immediately after injections but decreased in intensity during the stimulation period. There was less pain with Rekovelle. Swelling occurred about 30 minutes after injection in both groups and persisted during the stimulation period. Bruising occurred after 24 hours and continued over the stimulation period.

9.5.4.3. ESTHER-II

Based on all assessments, the overall injection site reactions with Rekovelle and Gonal-F occurred at an incidence of 3.0% and 2.4% in COS Cycle 2 and of 2.8% and 2.3% in COS Cycle 3, respectively. Severe injection site reactions accounted for <0.1% of all observations in both treatment groups in COS Cycle 2 and COS Cycle 3. On the subject level, about 40-50% of subjects in a treatment group did not have any injection site reactions in COS Cycle 2 or COS Cycle 3, and few subjects (≤3 subjects in a treatment group) experienced severe injection site reactions in COS Cycle 2 and COS Cycle 3.

9.5.5. Anti-FSH antibodies

9.5.5.1. ESTHER-1

Blood samples for analysis of anti-FSH antibodies were collected on stimulation Day 1 prior to dosing, at 7-10 days after the last IMP dose (first post-dosing assessment) and 21-28 days after the last IMP dose (second post-dosing assessment). All blood samples were first analysed in the screening assay: if results indicated absence of anti-FSH antibodies, the samples would be classified as negative for anti-FSH antibodies; if results suggested possible presence of anti-FSH

antibodies, these samples would be further evaluated in the confirmatory assay and only if positive in this assay would be classified as positive for anti-FSH antibodies. Positive samples would subsequently be analysed in an immunoassay for quantification of the anti-FSH antibodies; this assay had a titre quantification limit of 0.30 (titre was expressed as a log10 value and a result of <0.30 means that the titre was not quantifiable). Confirmed positive anti-FSH antibody samples would be assessed in parallel for their neutralising capacity in a cell-based assay.

A treatment-induced anti-FSH antibody response is defined as any post-dosing sample being positive in the confirmatory assay in subjects with a negative pre-dosing sample; or having a ≥2.0 fold increase (pre-determined minimum significant ratio) in titre from the pre-dosing assessment to a post-dosing assessment in subjects with a positive pre-dosing sample.

Before being exposed to gonadotropins, 15 subjects (1.13%) were found to have pre-existing anti-FSH antibodies. In 4 subjects the samples were positive at pre-dosing only. In 11 subjects they were present pre and post dosing, but increased less than 2 fold. None were of neutralising capacity. Two of the 15 subjects had undergone previous ovulation induction (1.5months and 3.6 years previously).

Treatment induced anti-FSH antibodies occurred in 7 of 665 subjects treated with Rekovelle (1.05%) and 5 of 661 subjects treated with Gonal-F (0.76%). These were generally of low titre. These patients had good number of oocytes retrieved and none had a cycle cancellation.

9.5.5.2. ESTHER-II

In COS Cycle 2, treatment-induced anti-FSH antibodies were observed in 2 of the 252 subjects in the Rekovelle group and in 1 of the 261 subjects in the Gonal-F group in COS Cycle 2. There were no new subjects with treatment-induced anti-FSH antibodies in COS Cycle 3. Thus, after up to two repeated COS cycles, the proportion of subjects with treatment-induced anti-FSH antibodies was 0.79% (95% CI [0.10%; 2.84%]) in the Rekovelle group and 0.38% (95% CI [0.01%; 2.12%]) in the Gonal-F group. None of the treatment induced anti-FSH antibodies in COS Cycle 2 or in COS Cycle 3 were of neutralising capacity.

There were 4 subjects who had anti-FSH antibodies in treatment Cycle 2 who proceeded to a second round of COS. The pregnancy outcomes of these women were comparable to other women in the group. There was one subject with antibodies of neutralising capacity pre-dosing, however post dosing her antibodies were not neutralising.

One 1 subject in the [information redacted] Rekovelle group had treatment-induced anti-FSH antibodies in COS Cycle 3. The proportion of subjects with treatment-induced anti-FSH antibodies was 1.05% (95% CI [0.03%; 5.73%]) in the Rekovelle group [information redacted]. This subject had also had treatment-induced anti-FSH antibodies in COS Cycle 2 and the anti-FSH antibodies were below the titre quantification limit both in COS Cycle 2 and in COS Cycle 3.

The proportion of subjects with treatment-induced anti-FSH antibodies did not increase after two repeated COS cycles for Rekovelle or Gonal-F. [information redacted]

9.5.6. Potentially immune related adverse events

9.5.6.1. ESTHER-1

Both a narrow and broad scope searches on the SMQ 'anaphylactic reactions', 'angioedema' and 'severe cutaneous adverse reactions' were carried out for adverse events that were potentially immune related.

A narrow scope search on the SMQ anaphylactic reactions did not identify any adverse events. A broad scope search on the SMQ anaphylactic reactions found 20 subjects (3%) in the Rekovelle group and 11 subjects (1.7%) in the Gonal-F group.

A narrow-scope search on the SMQ Angioedema identified only 1 adverse event of urticaria, which was reported in the Rekovelle group but was assessed as having no reasonable possible causality to the IMP by the investigator. A broad-scope search on the SMQ 'Angioedema' found 2 subjects (0.3%) in the Rekovelle group and 4 subjects (0.6%) in the Gonal-F group who experienced at least 1 adverse event. None of these adverse events were regarded as having reasonable possible causality to the IMP by the investigator.

No adverse events were identified by a narrow-scope search or a broad scope search on the SMQ 'severe cutaneous adverse reactions'.

A narrow scope search on the SMQ 'hypersensitivity' found that 5 subjects (0.8%) in the Rekovelle group and 8 subjects in the Gonal-F group reported at least 1 AE which covered the event of urticaria. A broad scope search identified 15 subjects in the Rekovelle group and 12 subjects in the Gonal-F group.

9.5.6.2. ESTHER II

A narrow-scope search on the SMQs 'Anaphylactic reactions', 'Angioedema' and 'Severe cutaneous adverse reactions' did not identify any adverse events in COS Cycle 2 or COS Cycle 3. A narrow-scope search on the SMQ 'Hypersensitivity' in COS Cycle 2 found that 2 subjects in the Rekovelle group and 4 subjects in the Gonal-F group reported at least 1 adverse event but none of the adverse events identified were assessed as having reasonable possible causality to Rekovelle or Gonal-F by the investigator. A narrow-scope search on the SMQ 'Hypersensitivity' in COS Cycle 3 did not identify any adverse events in the Rekovelle group but identified a single event of atopic dermatitis in the Gonal-F group, which was judged to have no reasonable possible causality to the IMP by the investigator.

9.5.7. Technical malfunction and other problems with the pen

9.5.7.1. ESTHER-1

A total of 10 subjects reported 11 events of malfunctions of 10 pens, all in the Rekovelle group. There was a technical problem with the pen confirmed on one occasion. A technical problem was not identified in 4 events and 6 events were attributed to human errors associated with inadequate instructions or misunderstanding.

9.5.7.2. ESTHER II

There were no cycle cancellations due to technical malfunction with the pens. There were a total of 3 subjects who reported pen malfunctions (2 in COS Cycle 2 and 1 in COS Cycle 3), all in the Rekovelle group. After examination, all the 3 cases were human errors associated with inadequate instructions or misunderstanding of instructions.

There were 2 patients in the Rekovelle group who omitted more than 5 days of gonadotropins due to incorrect use of the pen.

9.6. Other safety issues

In the ESTHER-1 study, there were no significant changes in chemistry, haemoglobin or vital signs. Clinically significant changes in gynaecological examination from normal at baseline to abnormal at the end of trial occurred in 7 subjects, 3 for Rekovelle and 4 for Gonal-F. This included 1 subject with a right fallopian tube hydrosalphinx, 1 subject with a right breast abscess and 2 with a pelvic infection in the Rekovelle group, and 1 subject with erythema cervix and erythema vagina, 1 with a cervix abnormality due to ectopic pregnancy, 1 subject with an enlarged uterus and 1 subject with an unstructured gestational sac in the Gonal-F group.

In ESTHER-II, there was no significant difference between the groups in terms of abdominal discomfort, changes in body weight or waist circumference. There were no significant changes in biochemistry or haematology.

9.7. Post marketing experience

Not relevant

9.8. Evaluator's overall conclusions on clinical safety

There were no major safety concerns. The adverse events with Rekovelle were consistent with those with Gonal-F and/or related to the IVF procedure and/or pregnancy. There were more dosing and administration errors with the Rekovelle device in ESTHER-I. This may be explained by health care providers not being familiar with the device.

The most commonly observed adverse events in the Rekovelle and Gonal-F groups respectively were headache (14.6% versus 13.3%), procedural pain (7.4% and 7.9%), pelvic pain (6.9% and 6.2%), pelvic discomfort (5.7% and 3.8%), vomiting in pregnancy (4.5% and 4.5%) and haemorrhage in pregnancy (3.9% and 4.1%).

The most frequent SAE was OHSS. Early, late and measures to prevent OHSS were more common in the Gonal-F group. OHSS occurred in 23 subjects, 17 early and 6 late in the Rekovelle group and 32 subjects, 20 early and 12 late, in the Gonal–F group. More patients in the Gonal-F group received interventions to prevent OHSS. The duration of hospitalisation for OHSS in the Rekovelle group was shorter than in the Gonal-F group.

Injection site reactions occurred at a low rate.

Treatment induced FSH antibodies occurred in 1.05% of the Rekovelle group[information redacted]. None of these were neutralising. The presence of antibodies was not associated with any difference in efficacy or safety outcomes. There was no significant increase in antibody response after repeated dosing.

The rate of multiple gestations was similar in both treatment groups.

It is not known who reported the safety outcomes. The evaluator notes that the nurses who administered the dose changes were not blinded as to the treatment allocation, thus if they were reporting adverse events there may be a reporting bias.

Patients with OHSS were excluded from COS 2 and 3. This may underestimate the true rate of OHSS in the real world setting.

10. First round benefit-risk assessment

10.1. First round assessment of benefits

The following table describes the benefit of Rekovelle compared to Gonal-F for the management of controlled ovarian stimulation.

Table 43: Benefit of Rekovelle compared to Gonal-F for the management of controlled ovarian stimulation

Indication: Controlled Ovarian Stimulation	
Benefits	Strengths and Uncertainties
-Demonstrated non inferiority to Gonal-F for ongoing pregnancy and ongoing implantation rates	*STRENGTH:* *The use of a fixed dosing regime was proposed to lead to a greater benefit in*

Indication: Controlled Ovarian Stimulation	
Benefits	Strengths and Uncertainties
	achieving optimal ovarian response. This was seen in preventing hyperstimulation and OHSS related events, but not in achieving better results in patients with low AMH to start with. *UNCERTAINTIES:* *if there will be a reduced need for blood tests and ultrasound with this FSH product compared to other products* *Use before or after other FSH products* *Use in the Australian setting- particularly in view of the need for the specific AMH assay.* *There was no information given about the live birth rate* *It is unknown how this would compare using an adjusted fixed dosing algorithm like Gonal-F*

10.2. First round assessment of risks

The following table describes the risks of Rekovelle compared to Gonal-F for the management of controlled ovarian stimulation.

Table 44: Risks of Rekovelle compared to Gonal-F for the management of controlled ovarian stimulation

Risks	Strengths and Uncertainties
- *more problems with using the pen device (at least initially). This could be resolved with education.* - *potential dosing errors with weight based as opposed to unit based dosing* -	STRENGTH -possibly less OHSS UNCERTAINTY - is the reduced risk of OHSS preventative endpoints a valid measure of benefit? - If the use of the AMH assay is better than the current methods of dosing FSH.

10.3. First round assessment of benefit-risk balance

The clinical trials submitted demonstrated Rekovelle, when used according to the recommended dosing algorithm, was non inferior to Gonal-F in the endpoints of ongoing pregnancy and implantation rates as well as most of the secondary endpoints.

There may be some limitations in the external validity of this trial as different IVF centres and clinicians have different practices. Variability in the success of IVF among treatment centres is a well-known phenomenon.

However, the major concern about the approval of this medicine is the need for it to be used with an accurate AMH assay in order to give the appropriate dose. It is unclear if this medicine can be used with other AMH assays other than the Elecsys and what the status of the recommended assay is in the Australian setting. This is critical to the approval of this medicine.

It is uncertain if the reduction in OHSS and interventions to prevent OHSS are clinically significant.

10.4. First round recommendation regarding authorisation

At this time, the sponsor will need to respond to further questions before a recommendation is made.

11. Clinical questions

11.1. Clinical questions

In Study 000009 there were exploratory endpoints for FSH receptor gene single nucleotide polymorphisms, and the gene expression profile of granulosa and cumulus cells. Are these relevant to Rekovelle or part on another research question?

11.1.1. Pharmacokinetics and Pharmacodynamics

2. Please provide further information in support of the use of high dose OCP to suppress endogenous FSH.
3. Please provide the justification for the covariates used in the PK-PD model, and other covariates that may also affect the response
4. Justify the use of this model at the extremes of AMH that is, < 5 and >40pmol/L
5. Please explain the intra and inter-individual variability in PK and PD

11.1.2. AMH assay

1. What is the sensitivity and specificity of AMH for ovarian reserve? How does it compare with ultrasound?
2. Can the dosing algorithm for Rekovelle be used with other AMH assays?

11.1.3. Efficacy

1. In ESTHER II was all of COS cycles consecutive?
2. In ESTHER II, was the baseline AMH the only AMH value used to titrate the dose of Rekovelle?
3. Could you describe the differences in the pens used for Gonal-F and Rekovelle?
4. Were all injections in the abdomen?

5. Please describe the primary efficacy in patients with AMH < 5pmol/L and 5-10pmol/L.
6. What was the live birth rate?

11.1.4. Safety

1. Please describe who reported the AE in the trial- were they blinded as to the treatment allocation.
2. The small percentage of women with anti-FSH antibodies at baseline is noted. The sponsor has stated in the conclusion of the main body of the report that anti-FSH antibodies had been previously described in infertile patients with anti-ovarian antibodies cross reacting with the FSH β chain. Is there any information about the prevalence of anti-FSH antibodies in healthy women? Could this be due cross reactivity with other proteins or the assay lacking sensitivity?

11.2. First round evaluation errata

The sponsor did not identify any errata.

12. Second round evaluation

12.1. Clinical questions

In Study 000009 there were exploratory endpoints for FSH receptor gene single nucleotide polymorphisms, and the gene expression profile of granulosa and cumulus cells. Are these relevant to Rekovelle or part on another research question?

12.1.1.1. Sponsor response:

The original intention of the exploratory endpoints in trial 000009 was to investigate additional potential differentiating features between Rekovelle and Gonal-F. However due to the small sample size, the exploratory analyses focused on studying the dose-response characteristics of Rekovelle.

12.1.1.2. Evaluator comment:

The response is adequate

Please provide further information in support of the use of high dose OCP to suppress endogenous FSH.

12.1.1.3. Sponsor's response:

The use of high dose COC results in inhibition of the hypothalamic-pituitary-ovarian axis, thereby blocking the gonadotropin production and secretion, FSH as well as LH. However, a number of investigators have demonstrated that down regulation is not 100% even with high dose oral contraceptives and FSH levels are often observed in the range of 2–5 mIU/mL, with single values of up to 15 mIU/mL found in individual subjects. Since oestradiol was not assessed as a PD endpoint in the trials CS01 and 000020, high dose COC was preferred for FSH down-regulation rather than down regulation with a gonadotropin agonist, as in the trials CS02 and CS03, which causes a greater burden to the trial subjects than shifting from their regular COC to a high dose COC. The subjects in trials CS01 and 000020 were tested for being down-regulated (that is, FSH < 5 mIU/mL) on Day -3 and Day -1, Pre-dose FSH measurements on the day of dosing were above lower limit of quantification, but still below 5 mIU/mL, in 7 out of 30 subjects receiving Rekovelle in trial CS01. A sensitivity analysis evaluating the exclusion of 5 of

these subjects, with the highest FSH concentrations, from the PK model indicated that exclusion did not affect the structural model estimates to a great extent.

12.1.1.4. Evaluator comment:

The response is adequate

Please provide the justification for the covariates used in the PK-PD model, and other co-variates that may also affect the response.

12.1.1.5. Sponsor's response:

The covariates used in the PK-PD model were those most frequently proposed to predict ovarian reserve. AMH is a better predictor of ovarian response to controlled ovarian stimulation than the age of the patient, basal FSH, basal oestradiol, basal inhibin B and ovarian volume. AMH is an objective measurement with a well characterised reference range for female patients in the reproductive age and has less individual intra- and inter-cycle variation than AFC and is therefore considered more reliable and robust.

Data from the Phase II dose response study FE999049 were explored for the impact of well-known biomarkers on ovarian reserve. This is described in a table below.

Table 45: Impact of baseline parameters on number of oocyte retrieved

Covariate	Explained variation
FE 999049 dose by body weight +	
AMH	35%
Basal FSH	23%
Inhibin B	17%
AFC	26%
Age	15%
FE 999049 dose by body weight + AMH +	
Basal FSH	38%
Inhibin B	35%
AFC	38%
Age	35%

12.1.1.6. Evaluator comment:

The response is acceptable. AMH would appear to be the best marker of ovarian reserve.

Justify the use of this model at the extremes of AMH that is, < 5 and >40pmol/L.

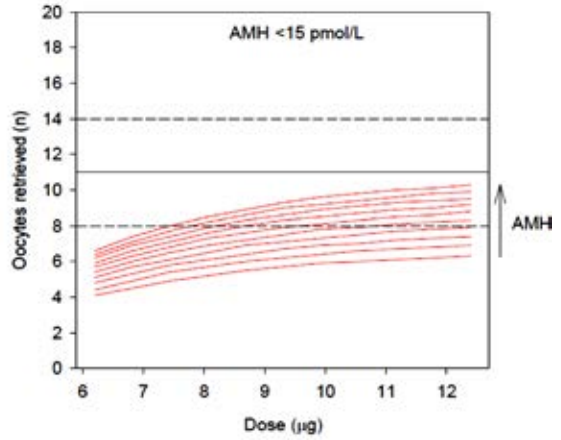
12.1.1.7. Sponsor response

The dose response model was based on Phase II trial 000009 was estimated on data from subjects with serum AMH levels ranging from 5.0-44.9 pmol/L. In the Phase III study, 9.4% has AMH levels < 5 pmol/L and 4.8% had levels > 44.9 pmol/L.

For patients with AMH<15pmol/L the dose of Rekovelle for the first treatment cycle is 12 µg.

Figure 14: Estimated number of oocytes retrieved by FE999049 dose for increasing AMH

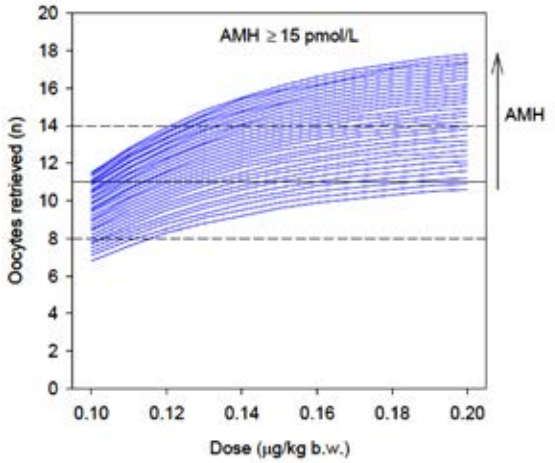
AMH levels between 5 and 14 pmol/L. The horizontal dotted lines and the horizontal solid line illustrate the range of 8-14 oocytes retrieved and the target of 11 oocytes retrieved, respectively.



For patients with an AMH ≥ 40pmol/L, the estimated dose is 0.1ug/kg.

Figure 15: Estimated number of oocytes retrieved by FE999049 dose for increasing AMH

AMH levels between 15 and 45 pmol/L. The horizontal dotted lines and the horizontal solid line illustrate the range of 8-14 oocytes retrieved and the target of 11 oocytes retrieved, respectively.



In the Phase III trials, the FE999049 individualised dosing regimen resulted in significantly fewer excessive responders in those with high baseline AMH levels.

Table 46: Ovarian response in subjects with AHM >40 pmol/L ESTHER-1

	FE 999049 N=45	GONAL-F N=50	P-value
AMH >40 pmol/L			
Number of oocytes retrieved	9.9 (7.1)	19.3 (9.0)	<0.001
≥15 oocytes retrieved	24%	66%	<0.001
≥20 oocytes retrieved	11%	42%	<0.001

Data are mean (SD) or %

12.1.1.8. Evaluator comment

The sponsor's response is acceptable. It is noted there is a paucity of data in patients with AMH < 5pmol/L or > 40pmol/L

Figure 14 demonstrates a non-linear dose response curve which flattens after a dose of around 10µg. In patients with an AMH level < 5 pmol/L, and increase in Rekovelle dose from 6 to 12 µm increases the oocyte response from 4 to 6. For patients given a Rekovelle dose of 12 µg, the expected oocyte response is around 6 where the AMH is < 5pmol/L and 10 where the AMH is 14 pmol/L. Thus, AMH < 5 pmol/L levels it is likely that insufficient oocytes (less than the target number of 8) will be retrieved.

Figure 15 shows an increasing slope of the dose response curve as the AMH dose increases. Patients with an AMH level > 40 pmol/L are shown in the top 6 blue lines. At a dose of approximately 0.1 µg/kg the number of oocytes retrieves is approximately 11.

Please explain the intra and inter-individual variability in PK and PD.

12.1.1.9. Sponsor response

There was no data to explain the intra-individual variability.

The inter individual variability was not experimentally investigated but considered to be due to FSH, body weight and AMH.

12.1.1.10. Evaluator comment

The response is acceptable

What is the sensitivity and specificity of AMH for ovarian reserve? How does it compare with ultrasound?

12.1.1.11. Sponsor response

It is not possible to estimate the sensitivity and specificity of AMH for ovarian reserve as there is no gold standard measure. For the Roche Elecsys AMH assay, a prospective study of 451 women was conducted to determine the correlation between AMH and AFC. There was a significant negative correlation between age and AMH (spearmen correlation coefficient -0.47), and positive correlation between AMH and AFC (spearmen correlation coefficient 0.68). There was variability of AFC results by site and sonographer.

Table 47: Correlation between AMH and AFC

	AFC 0-7	AFC 8-15	AFC > 15	N
AMH ≤ 4.86 pmol/L (0.681 ng/mL)	43 (63.2 %)	22 (32.4 %)	3 (4.4 %)	68
4.86 pmol/L (0.681 ng/mL) < AMH ≤ 16.2 pmol/L (2.27 ng/mL)	20 (12.0 %)	95 (56.9 %)	52 (31.1 %)	167
AMH > 16.2 pmol/L (2.27 ng/mL)	3 (1.4 %)	52 (24.1 %)	161 (74.5 %)	216
N	66	169	216	451

A table of studies by La Marca in 2010 showed that the sensitivity and specificity of AMH for predicting ovarian reserve ranged between 44-97% and 41-100% respectively. The cut off for AMH ranged from 0.7-11.8pmol/L.

The performance of AMH versus AFC at individual clinics has been evaluated in a retrospective analysis of data from two multicentre trials sponsored by Ferring; one conducted with the long GnRH agonist protocol and one conducted with the GnRH antagonist protocol. AMH was more strongly correlated with oocyte yield than AFC with correlation coefficients of 0.56 versus 0.28 in the long GnRH agonist trial and 0.55 versus 0.34 in the GnRH antagonist trial.

12.1.1.12. Evaluator comment

There seems to be good correlation between AMH and ovarian reserve. AMH is a better predictor of ovarian response than AFC. AMH levels of < 10 pmol/L are predictive of low ovarian reserve. There is large variability in the correlation between studies and it is unclear of this relates to patient characteristics, IVF protocols, ultrasonographer differences or other factors*. The evaluator is uncertain if the correlation between AMH and ovarian reserve and ovarian response found in this study can be generalised to other clinics.*

Can the dosing algorithm for Rekovelle be used with other AMH assays?

12.1.1.13. Sponsor's response

The manual assays are associated with operator variation. The automated assays are highly sensitive and precise, both are registered in Australia. Both the Beckman Coulter ACCESS and Roche Elecsys assays are using the same antibodies (Gen II antibody pair) but with different calibrators (human rAMH versus bovine AMH, respectively). No international standard of AMH assays is available.

High correlations (r ≥ 0.95) between manual and automated AMH assays have been reported, but the values provided with the manual assays are 20-30% higher compared to those from an automated AMH assay. There is high inter-laboratory variability of the manual AMH assay.

There have been reports comparing the automated AMH assays (Beckman Coulter ACCESS and Roche Elecsys) with the manual Beckman Coulter Gen II ELISA assay concluding that they are not interchangeable with differences of around 20%.

Table 48: Overview of AMH assays (35)

Competitor assays	Beckman Coulter AMH Gen II (Kumar et al., 2010; Beckman Coulter AMH Gen II ELISA package insert, 2013)	Beckman Coulter Immunotech AMH (Immunotech AMH (Beckman Coulter) package insert, 2012)	AnshLabs Ultrasensitive (AnshLabs UltraSensitive AMH/ MIS ELISA package insert, 2014)	AnshLabs picoAMH (AnshLabs picoAMH ELISA package insert, 2014)	Roche Assay Elecsys® AMH (Gassner and Jung, 2014)	Beckman Coulter Access 2 IA AMH (Beckman Coulter, 2014)
Assay type	Manual	Manual	Manual	Manual	Automated	Automated
Imprecision	<8%	<14%	<6%	<6%	1.8–2.0%	2.87–4.34%
Sample type	Serum, plasma	Serum, plasma	Serum, plasma	Serum, plasma	Serum, Li-heparin plasma	Serum, Li-heparin plasma
Minimum sample volume	20 µl	25 µl	50 µl	100 µl	50 µl	20 µl
Incubation time	<3 h	3 h	2.5 h	4.5 h	18 min	39 min
Limit of detection (LoD)	0.08 ng/ml	0.14 ng/ml	0.023 ng/ml	0.0012 ng/ml	0.01 ng/ml	≤0.02 ng/ml
Limit of Quantification (LoQ)	0.16 ng/ml	0.35 ng/ml (Decanter et al., 2014)	0.06 ng/ml	0.0039 ng/ml	0.03 ng/ml	≤0.08 ng/ml
Measurement range	0.16–22.5 ng/ml	0.42–21.0 ng/ml	0.06–11.6 ng/ml	0.003–0.75 ng/ml	0.01–23.0 ng/ml	0.02–24.0 ng/ml

Note that the Beckman Coulter Immunotech AMH assay is no longer available in Australia and Europe, and that the AnshLabs Ultrasensitive AMH assay is at present not available in Australia and Europe (the AnshLabs picoAMH assay is available in Europe but the measurement range is not applicable for use in Assisted Reproductive Technologies).

There are currently two reports comparing the performance of the two new Beckman Coulter ACCESS and Roche Elecsys assays. The publication by Nelson et al suggested a relatively good consistency between the Roche Elecsys and Beckman Coulter ACCESS assays with a systematic difference of 6% (slope 1.06). Van Helden and Weiskirchen have also showed an excellent correlation between the Elecsys and ACCESS AMH assays with a systematic difference of 3% (slope 0.97)

Figure 16: Roche Elecsys AMH assay versus Beckmn Coulter ACCESS AMH assay (37)

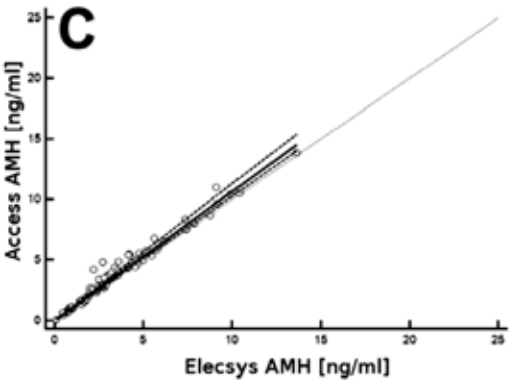
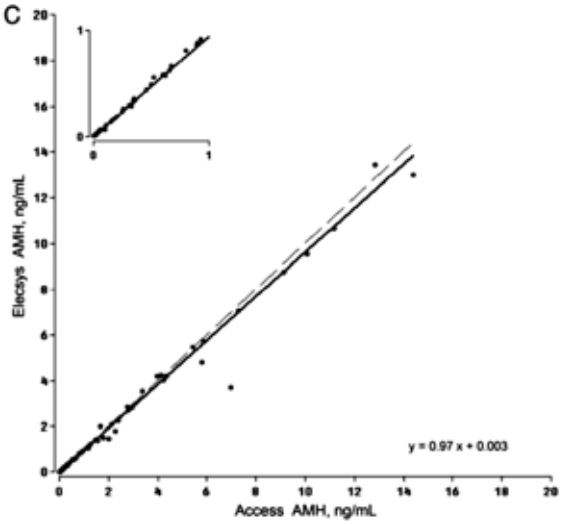


Figure 17: Roche Elecsys AMH assay versus Beckman Coulter ACCESS assay



The sponsor recommends caution if using AMH levels from other assays for the dosing of Rekovelle.

12.1.1.14. Evaluator response

The response is acceptable. The use of only the one AMH assay may limit the use of this product to those centres with access to AMH levels with the Roche assay.

In ESTHER II, were all of the COS cycles consecutive?

12.1.1.15. Sponsor response

Patients were not allowed to undergo non-trial COS cycles between COS 1, COS 2 and COS 3 cycles in ESTHER 1 and ESTHER 2, however it was acceptable to undergo cycles with cryopreserved blastocysts between the fresh COS cycles.

Table 49: Proportion of patients using blastocysts and days between stimulated cycles COS 1-COS 2 and COS 2-COS 3 for FE999049 and Gonal-F

		FE999049	Gonal-F
COS 1-COS 2	Proportion of patients using blastocyst	18%	19%

		FE999049	Gonal-F
	Days between stimulated cycles	102.5 (80-140)	107 (80-147)
COS 2-COS 3	Proportion of patients using blastocyst	14%	11%
	Days between stimulated cycles	98 (71-132)	97 (63-127)

12.1.1.16. Evaluator comment

The response is acceptable. This is unlikely to have a significant effect on the results; however an expert opinion will be requested to check this.

In ESTHER II, was the baseline AMH the only AMH level used to titrate the dose of Rekovelle?

12.1.1.17. Sponsor response

The AMH value from the screening visit in ESTHER-1 was only used to determine the Rekovelle dose in that first cycle. In ESTHER-2, the daily dose of Rekovelle as well as the starting dose of Gonal-F was based on the ovarian response in the previous cycle.

12.1.1.18. Evaluator response

The response is acceptable

Can you describe the difference in the pens used for Gonal-F and Rekovelle?

12.1.1.19. Sponsor response

The Rekovelle injection pen is reusable and can be reloaded with a new cartridge when empty, while the Gonal-F pre-filled pen is a disposable pen and is discarded when empty (Figure 18). The mechanism that drives the drug from the cartridge through the injection needle is different for the two pens. The Rekovelle injection pen is spring assisted and the activation button is situated at the side of the pen. The Gonal-F pre-filled pen is driven by manual force applied to the end of the pen. Both pens differ in the visual appearance.

Figure 18: Rekovelle injection pen versus Gonal-F pre-filled pen

		GONAL-F pre-filled pen	FE999049 injection pen
			
Similarities	Intended User	Patient Healthcare professional to demonstrate the use	Patient Healthcare professional to demonstrate the use
	Injection sites	Abdominal wall	Abdominal wall
	Depth of Needle Insertion	Determined by the needle length	Determined by the needle length
	Pen needles used in the phase 3 program	29G, 12mm Sterile, provided separately	29G, 12mm Sterile, provided separately
Differences	Durability	Disposable (variable multi-dose)	Reusable (variable multi-dose)
	Intended Use	Subcutaneous injection of Gonal-f®	Subcutaneous injection of FE 999049
	Dosing Unit	International Units (IU)	microgram
	Dose Resolution	12.5 IU (= 20µL) per increment (click)	0.33 µg (= 10µL) per increment (click)
	Dose Range	12.5 IU – 450 IU	0.33 µg – 24.0 µg
	Operating Force	Manual top activation	Spring assisted side activation
	Overall Dimensions	Length: app. 155 mm Diameter: app. 17 mm	Length: app. 175 mm Diameter: app. 19 mm

Were all injections in the abdomen?

Yes.

Please describe the primary efficacy endpoint in patients with AMH < 5pmol/L and 5-10pmol/L.

12.1.1.20. Sponsor's response

There were 104 patients (7.8%) with AMH < 5 pmol/L and 249 (18.8%) with AMH 5-10 pmol/L.

Table 50: Ongoing pregnancy and ongoing implantation for AMH <5 pmol/L and AMH 5-10 pmol/L ESTHER-1

	FE 999049			GONAL-F		
	n	N	%	n	N	%
Ongoing pregnancy						
AMH 0-<5 pmol/L	11	50	22.0%	15	54	27.8%
AMH 5-<10 pmol/L	44	131	33.6%	36	118	30.5%
Ongoing implantation						
AMH 0-<5 pmol/L	11	36	30.6%	15	46	32.6%
AMH 5-<10 pmol/	44	120	36.7%	36	102	35.3%

12.1.1.21. Evaluator comment

The overall pregnancy rate in the mITT population was 30.7% for FE999049 and 31.6 % for Gonal-f. The ongoing implantation rate in the entire mITT population was 32.2% for FE999049 and 35.8% for Gonal-F. As expected, the efficacy of both FE999049 and Gonal-F is reduced in patients with AMH< 5pmol/L at levels of around 28% and 12% respectively for overall pregnancy rate and 5% and 9% respectively for ongoing implantation rate.

What was the live birth rate?

12.1.1.22. Sponsor response

Table 51: Live birth rate at 4 weeks after birth ESTHER-1 and ESTHER-2

	COS 1		COS 2		COS 3	
	FE 999049	GONAL-F	FE 999049	GONAL-F	FE 999049	GONAL-F
Live birth	29.8% (198/665)	30.7% (203/661)	27.4% (69/252)	25.3% (66/261)	26.3% (25/95)	26.9% (25/93)
Live rate at 4 weeks after birth	29.8% (198/665)	30.4% (201/661)	27.4% (69/252)	25.3% (66/261)	26.3% (25/95)	26.9% (25/93)

12.1.1.23. Evaluator's response

The live birth rate is similar in the FE999049 and Gonal-F groups.

Please describe who reported AE at in the trial- were they blinded.

12.1.1.24. Sponsor response

The investigator who was blinded to the treatment allocation reported AE. If the patient told a trial nurse who was unblinded to the treatment allocation, this was subsequently assessed by the investigator who was blinded.

Anti-FSH antibodies at baseline?

12.1.1.25. Sponsor response

There is little information about the prevalence of anti-FSH antibodies in healthy women. Anti-gonadotrophic antibodies have been associated with PCOS, endometriosis and treatment with GnRH agonists.

For the Phase II and III trials of Rekovelle, validated electrochemiluminescence immunoassays where used for the detection of anti-FSH antibodies in pre-treatment and post-treatment samples. The assays were of the bridging type, that is, only molecules capable of binding at least two FSH molecules are detected and consisted of a screening step (5% false positives), a confirmatory step (0.1% false positives) and additional characterisation steps (titre, cross-reactivity) for confirmed positive samples. Screen positive samples underwent confirmatory analysis and were confirmed positive if the percent signal inhibition seen after addition of Rekovelle was above the confirmatory cut-point. Confirmed positive samples were then reported with titre as quantitative output. In all Phase II and III trials, assay cut-points were statistically established prior to sample analysis using drug naïve samples from the respective trial populations. The anti-drug antibody assays exhibited a high sensitivity of 30 ng/mL anti-FSH in serum and a low background. In conclusion, the assay is very specific and sensitive, thus positive pre-treatment samples are unlikely caused due to cross-reactivity with other proteins or due to the lack of assay sensitivity. Overall, the low incidence of pre-existing anti-FSH antibodies in patients undergoing their first IVF cycle in the ESTHER-1 trial was as expected. The fact that repeated treatment with Rekovelle of patients with pre-existing anti-FSH antibodies did not increase the antibody titre is also in agreement with the current literature.

12.1.1.26. Evaluator response

The response is adequate.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

The benefits of Rekovelle in ovarian stimulation remain unchanged. Non-inferiority with Gonal-F for the co-primary end-points for ongoing pregnancy rate and ongoing implantation rate was established in the pivotal studies. In addition, the sponsor has provided new information demonstrating similar outcomes in live birth rate.

The proposed benefit in terms of dosing algorithm to optimise ovarian response is uncertain for a number of reasons. These include uncertainty about the ability to extrapolate the dosing algorithm in a population that is different to the clinical study, based on 1) local variability in endpoints with AMH levels; 2) the need for the specific Elecsys AMH assay that may not be available to clinicians.

13.2. Second round assessment of risks

The risks of Rekovelle are consistent with the risks for other FSH products. In the clinical trials, patients treated with the Rekovelle dosing algorithm had less OHSS related events than those treated with Gonal-F and the usual treatment algorithm. It is unknown if this is the effect of the drug or the dosing algorithm.

13.3. Second round assessment of benefit-risk balance

The clinical trials demonstrated non-inferiority of Rekovelle compared to Gonal-F on the primary efficacy endpoints ongoing pregnancy rate and ongoing implantation rate. Secondary endpoints were consistent, including live birth rate. The risk of OHSS was less with Rekovelle than Gonal-F.

However, the clinical trials used a dosing algorithm which relied upon a specific assay, specimens were collected and processed using strict criteria, there is a wide range of strength of association between AMH levels and oocyte counts and pregnancy outcomes in different centres and therefore the validity of the doing algorithm in the Australian setting is unknown. This is a major problem with the submission.

14. Second round recommendation regarding authorisation

At this stage, the evaluator could not recommend approval of Rekovelle due to concerns about the dosing algorithm. The sponsor is requested to provide further evidence of the ability of the AMH assay to predict pregnancy outcome in the Australian setting.

15. References

La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC, Stabile G, Volpe A. Anti-Müllerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010; 16: 113-130.

Nelson SM, Pastuszek E, Kloss G, Malinowska I, Liss J, Lukaszuk A, Plociennik L, Lukaszuk K. Two new automated, compared with two enzyme-linked immunosorbent, antimüllerian hormone assays. Fertil Steril 2015; 104: 1016-1021.

Van Helden J, Weiskirchen R. Performance of the two new fully automated anti-Müllerian hormone immunoassays compared with the clinical standard assay. Hum Reprod 2015; 30: 1918-1926.

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