Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Follitropin delta (rhu)

Proprietary Product Name: Rekovelle

Sponsor: Ferring Pharmaceuticals Pty Ltd

October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of common 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
PER.C6®	Host cell line of human origin

Abbreviation	Meaning
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
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New Biological Entity
Decision:	Approved
Date of decision:	24 March 2017
Date of entry onto ARTG	31 March 2017
Active ingredient(s):	Follitropin delta (rhu)
Product name(s):	Rekovelle
Sponsor's name and address:	Ferring Pharmaceuticals Pty Ltd PO Box 315, North Ryde, NSW 1670
Dose form(s):	Solution for injection
Strength(s):	33.3 micrograms/mL [12 micrograms in 0.36 mL; 36 micrograms in 1.08 mL; 72 micrograms in 2.16 mL]
Container(s):	Glass cartridge
Pack size(s):	Rekovelle 12 micrograms/mL - Pack of 1 cartridge and 3 needles to be used with the Rekovelle injection pen Rekovelle 36 micrograms/mL - Pack of 1 cartridge and 6 needles to be used with the Rekovelle injection pen Rekovelle 72 micrograms/mL - Pack of 1 cartridge and 9 needles to be used with the Rekovelle injection
Approved therapeutic use:	*Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle.*
Route(s) of administration:	Subcutaneous (SC) injection in abdominal wall
Dosage:	Individual based on the patient's body weight and AMH
ARTG number (s):	271653, 271652 and 270336

Product background

This AusPAR describes the application by the sponsor, Ferring Pharmaceuticals Pty Ltd, to register a new biological entity, follitropin delta as Rekovelle (Rekovelle).

Rekovelle is proposed to be used for controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle.

The proposed dosing regimen involves once daily subcutaneous (SC) administration with an individualised dose based on the patient's serum anti-Müllerian hormone (AMH) concentration and body weight, up to a maximum of 12 µg (first treatment round) or 24 µg (subsequent treatment rounds) per day. The draft Product Information (PI) document describes an average treatment cycle of 9 days duration (range, 5 to 20 days).

Rekovelle is dosed in micrograms (µg) and not in international units (IU) of biological activity. The dosing regimen is specific for Rekovelle and the µg dose cannot be applied to other gonadotropins.

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 µg to 24.0 µg in increments of 0.33 µg.

The active substance of Rekovelle is follitropin delta, a recombinant human follicle stimulating hormone (rFSH), which is manufactured via a human fetal retinal cell line. This differs from follitropin alpha (Gonal-F) and follitropin beta (Puregon) which are manufactured via Chinese hamster ovary (CHO) cell lines. FSH from human menopausal urine is also marketed in Australia.

Due to differences in glycosylation profile, follitropin delta has lower clearance and induces a higher ovarian response than follitropin alpha when administered at equal doses of biological activity (IU).

The manufacturer has therefore developed an individualised dosing algorithm, based on AMH levels and body weight. This was based on a Pharmacokinetic (PK)/Pharmacodynamic (PD) simulation.

AMH is a dimeric glycoprotein produced by granulosa cells of prenatal and early antral follicles. After an initial increase until early adulthood, levels decrease, becoming undetectable about 5 years before menopause. There is individual variation in the rate of the decrease.

Indication and dosing information for other exogenous FSH products marketed in Australia are shown below (Table 1).

Table 1: Exogenous FSH products marketed in Australia

Drug name	Indication	Dosage information as per PI
Bemfola Recombinant human follicle stimulating hormone (follitropin alfa (rch)) Made in CHO cells	Controlled ovarian hyperstimulation in women undergoing assisted reproductive Technologies*	*Women undergoing Assisted Reproductive Technologies*: A commonly used regimen for superovulation involves the administration of 150 IU (11 microgram) to 225 IU (16.5 microgram) of Bemfola daily, commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum oestrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU (33 microgram) daily. Down-regulation with either a GnRH agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. Dosage regimes should be customised in order to achieve the

Drug name	Indication	Dosage information as per PI
		desired result. In a commonly used protocol Bemfola is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks treatment with an agonist, 225 IU (16.5 microgram) Bemfola is administered (subcutaneously) for the first 7 days. The dose is then adjusted according to the ovarian response.
Gonal-F Recombinant human follicle stimulating hormone (follitropin alfa (rch) Made in CHO cells	For controlled ovarian hyperstimulation in women undergoing assisted reproductive technologies*	*Women undergoing Assisted Reproductive Technologies:* A commonly used regimen for superovulation involves the administration of 150 IU (10.92 microgram) to 225 IU (16.5 microgram) of Gonal-F daily, commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum oestrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450 IU (32.76 microgram) daily. A single injection of 250 microgram r-hCG or 5000 IU up to 10,000 IU u-hCG is administered 24 – 48 hours after the last Gonal-F injection to induce final follicular maturation. In clinical trials, final follicular maturation was judged to be when at least two follicles were > 16 mm mean diameter and when E2 levels were within the physician's acceptable range for the number of follicles present. Down-regulation with either a GnRH agonist or antagonist is now commonly used in order to suppress the endogenous LH surge and to control tonic levels of LH. Dosage regimes should be customised in order to achieve the desired result. In a commonly used protocol Gonal-F is started approximately 2 weeks after the start of agonist treatment, both being continued until adequate follicular development is achieved. For example, following two weeks treatment with an agonist, 225 IU (16.5 microgram) Gonal-F is administered (subcutaneously) for the first 7 days. The dose is then adjusted according to the ovarian response.
Puregon Follitropin beta Recombinant	Controlled ovarian hyperstimulation to induce the	*Controlled ovarian hyperstimulation in medically assisted reproduction programs*: Various stimulation protocols are applied. Stimulation of follicular growth is generally

Drug name	Indication	Dosage information as per PI
human follicle stimulating hormone Made in CHO cells	development of multiple follicles in medically assisted reproduction programs (e.g. in vitro fertilisation and related procedures).	achieved by daily administration of 75-300 IU FSH. Puregon can be given either alone, or in combination with clomiphene citrate to stimulate the endogenous production of gonadotrophins, or in combination with a GnRH agonist, in particular to prevent premature luteinisation. Maturation of follicles is monitored by ultrasound assessment. The concurrent determination of serum oestradiol levels may also be useful. When ultrasound assessment indicates the presence of at least three follicles of 16-20 mm, and there is evidence of a good oestradiol response (plasma levels of about 300-400 picogram/mL (1000-1300 pmol/L) for each follicle with a diameter greater than 18 mm), the final phase of maturation of the follicles is induced 30-40 hours after the last administration of Puregon by administration of hCG in a dose of 5000-10000 IU oocyte retrieval is performed 34-35 hours later. After embryo transfer, up to three repeat injections of 1000 to 3000 IU hCG each may be given within the following 9 days to provide luteal phase support.
Elonva	Controlled Ovarian Stimulation (COS) for the development of multiple follicles and pregnancy in women undergoing in-vitro fertilisation techniques.	In the treatment of women of reproductive age, the dose of Elonva is based on weight and age. A single 100-microgram dose is recommended in women who weigh less than or equal to 60 kilograms and who are 36 years of age or younger. A single 150-microgram dose is recommended in women: Who weigh more than 60 kilograms, regardless of age. Who weigh 50 kilograms or more and who are older than 36 years of age. Women older than 36 years of age who weighed less than 50 kilograms were not studied.

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 to 10% whereas in couples where the women is > 40years it is in the order of 17 to 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.

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 reserve could result in low efficacy but the same dose in someone with high ovarian reserve could result in OHSS. The National Institute for Health and Excellence (NICE) guidelines from the United Kingdom (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.

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.

Regulatory status

The current product is a new biological entity and was first registered on the Australian Register of Therapeutic Goods on the 31 March 2017.

It was approved in the European Union (EU) in December 2016 for *Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle. There is no clinical trial experience with Rekovelle in the long GnRH agonist protocol*.

A similar submission has also been made to HealthCanada.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Rekovelle 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.

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

Drug substance (active ingredient)

The drug substance is a clear or slightly turbid colourless solution.

All manufacturing steps have been fully validated.

Structure

The amino acid sequences for both α and β subunits of Rekovelle drug substance (DS), follitropin delta are identical to those for endogenous human FSH and to those of existing CHO derived recombinant FSH products. The glycosylation profile of recombinant proteins is dependent on the expressing cell line and the cell culture conditions.

Rekovelle contains both α2,3 and α 2,6 sialylation patterns while CHO-derived rFSH products exclusively carry α2,3 linked sialic acid. This difference contributes to the observed differences in glycosylation profiles between Rekovelle and CHO derived rFSH products. Because of these differences some of the pharmacopoeial specifications in the follitropin monograph (European Pharmacopeia (Ph.Eur.)) cannot be applied to Rekovelle (see more under Specifications below).

Rekovelle is a heterodimer composed of one α and one β subunit. The molecular weights (determined by mass spectrometry as monoisotopic mass) of the de-glycosylated amino acid alkylated backbones of α and β subunits are 10,779 and 13,173 Daltons (Da), respectively. Expected molecular weight (MW) values are inclusive of an additional 57 Da per alkylated cysteine residue in subunit α (10 cysteines) and subunit β (12 cysteines). The average molecular weights of the glycosylated α and β subunits determined by MALDI-ToF-MS are approximately 15,200 and 18,500 Daltons, respectively. Thus, approximately 40 % of the total molecular weight of the molecule is due to glycosylation.

The molecular formula and average formula weight of the protein backbone (reduced, non-alkylated) for α and β subunits are shown below:

α subunit: $C_{437}H_{682}N_{122}O_{134}S_{13}$; 10,206 Da

β subunit: $C_{538}H_{833}N_{145}O_{171}S_{13}$; 12,485 Da

Drug product

All analytical procedures are fully validated.

All excipients are approved for SC 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.

Stability

Stability studies have been conducted in accordance with relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. Stability data have been generated under stressed and real time.

Approved shelf life (include temperature excursion during shipping if necessary) a shelf-life of 36 months at 5 ±3°C is proposed for the drug product.

For product related impurities no significant changes were observed after storage at the intended temperature of 5 ±3°C. DP content and L –methionine content show no significant changes over time at 5 ±3°C. A decrease in phenol content was observed. However, phenol content is still within the lower limit of acceptance criteria after 36 months at the intended storage temperature of 5 ±3°C.

The product is photo-sensitive in the primary package. However, each secondary package, injection pen and carton separately provides sufficient protection from light.

The product is sensitive to freezing and thawing. The product label must include 'do not freeze'. The following is recommended:

Store in a refrigerator (2°C–8°C). Do not freeze.

Within its shelf life, Rekovelle may be removed from the refrigerator, without being refrigerated again and stored at or below 25°C for up to 3 months and must be discarded afterwards.

Before use: store in the original package in order to protect from light.

After the first injection: the cartridge can be stored at or below 25°C and it must be discarded after 28 days

Specifications

The product is not able to meet the specifications outlined in the Ph. Eur. There is a requirement under section 14/14A of the Therapeutic Goods Act 1989 for the sponsor to apply for exemption from the requirement to meet the applicable standard, in this case the Ph.Eur. monograph for follitropin concentrated solution (2286) which became effective on January2014.

The Ph. Eur. monograph refers to follitropin produced in mammalian cells by recombinant DNA technology. The currently marketed follitropin products are CHO derived follitropin alfa and follitropin beta. It is therefore considered that the EDQM Chemical Reference Standard (CRS) that accompanies this monograph is also CHO derived. The amino acid sequence of Rekovelle is identical to the endogenous human FSH sequence for both α and β subunits and to that in existing CHO derived recombinant FSH products.

However, the glycosylation profile of recombinant proteins is dependent on the expressing cell line and the cell culture conditions. Rekovelle contains both α2,3 and α2,6 sialylation patterns, while CHO-derived rFSH products exclusively carry 2,3 linked sialic acid, giving it a different glycosylation profile.

Comparison between the analytical methods and specifications described in the monograph for follitropin concentrated solution and those used for release of the DS is provided by the sponsor and discussed in different parts of the sponsor's dossier. All quality attributes specified in the monograph are also defined as critical quality attributes (CQAs) and included in the specification for Rekovelle. However, Rekovelle does not conform to some of the pharmacopoeial specifications due to the distinct glycosylation profile. The test methods used for some of the parameters are different to those described in the monograph. This may necessitate an application for Section 14/14A exemption. A recommendation to this effect has been put to the sponsor.

Biopharmaceutics

Not applicable.

Quality summary and conclusions

Summary of issues

There is a requirement under section 14/14A of the Therapeutic Goods Act 1989 for the sponsor to apply for exemption from the requirement to meet the applicable standard, in this case the Ph.Eur. monograph for follitropin concentrated solution (2286) which became effective on January 2014.

With respect to Quality matters, the PI, Consumer Medicine Information (CMI) and labels as detailed in the table above are acceptable.

Proposed Conditions of registration

Batch release testing & compliance with certified product details (CPD)

1. It is a condition of registration that all batches of Rekovelle imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Rekovelle imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

III. Nonclinical findings

Introduction

The nonclinical dossier was generally of high quality. All pivotal safety-related studies were Good Laboratory Compliant (GLP) compliant.

Pharmacology

Primary pharmacology

FSH is produced by the anterior pituitary gland. In women, binding of circulating FSH to the cognate receptor (FSH-R) on granulosa cells in the ovary stimulates follicular growth, maturation and development. The use of recombinant human FSH to stimulate follicle maturation in women undergoing ART is well established.

Follitropin delta was shown to bind to the FSH-R in a cell-free in vitro assay with sub-nanomolar affinity (affinity constant (Ki) 0.10 nM) equivalent to follitropin alfa. In cell-based functional assays, it was shown to act as an agonist of the FSH-R, triggering intracellular cyclic adenosine monophosphate (cAMP) accumulation in transfected Human Embryonic Kidney (HEK) 293 cells and downstream receptor signalling in cultured human granulosa cells, acting with comparable potency to follitropin alfa.

Development batches of follitropin delta were shown to promote ovarian enlargement in rats in the Steelman-Pohley bioassay (conducted according to Ph. Eur.) with similar potency to follitropin alfa. However, in Phase I clinical trials, equivalent IU doses of follitropin delta and follitropin alfa based on the Steelman-Pohley bioassay reportedly exhibited different pharmacokinetic properties. The sponsor attributes this effect to the

differential glycosylation patterns of follitropin delta and alfa due to species differences in the cell lines used for their production. The potency of post-development batches of follitropin delta was solely characterised in vitro (in a cell based functional assay).

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamic studies were performed with follitropin delta. This is acceptable given that FSH is known to bind specifically to FSH-R, the expression of which is restricted to the gonads in vivo.

Safety pharmacology studies covered the core battery of systems. There were no adverse effects of follitropin delta on the central nervous or respiratory systems in rats or on the cardiovascular system of cynomolgus monkeys at ≤ 52.2 µg/kg SC, with peak serum concentrations in animals estimated to be 24 (rats) and 67 (monkeys) times higher than in patients at the maximum recommended human dose (2.58 ng/mL, based on extrapolation of steady-state data from Clinical Study CS02). Follitropin delta did not inhibit the hERG potassium (K+) channel in vitro (tested at 313 ng/mL, approximately 120 times the clinical peak plasma concentration (C_{max})).

Pharmacokinetics

Follitropin delta was absorbed slowly following SC administration in both laboratory animal species tested (time to C_{max} (T_{max}), 4 to 8 h in rats and monkeys), and in humans (approximately 13 h). The serum half-life was shown to be long in rats (approximately 7 to 9 h) and humans (approximately 30 h). The volume of distribution was low in rats, as anticipated for a large recombinant protein. Peak and overall serum drug exposure (C_{max} and area under the concentration versus time curve (AUC)) were proportional to dose in monkeys and humans, while greater than dose-proportional in rats, and were increased with repeat dosing.

The different glycosylation pattern of follitropin delta and follitropin alfa are attributed to their production in human (PER.C6) and hamster (CHO) cell lines, respectively. CHO cells, unlike human cells, are incapable of sialylating glycoproteins in the α2,6 [information redacted] In mice and rats (but not humans), α2,6-sialylation is associated with an increased rate of elimination by the liver. Knock-out of the asialo-glycoprotein receptor in mice and pharmacological antagonism on the receptor in rats were shown to increase follitropin delta exposure, while exposure to follitropin alfa was unaffected. The faster clearance of follitropin delta as compared to follitropin alfa in rats will translate to lower apparent potency in the Steelman-Pohley bioassay. With α2,6-sialylation not known to aid protein elimination in humans, equivalent IU doses (derived from activity in rats) can be expected to result in higher exposure (and greater activity) for follitropin delta compared to follitropin alfa in patients. [information redacted] In vitro data showed equivalent FSH R affinity and potency for follitropin delta to that of follitropin alfa.

No distribution, metabolism or excretion studies were performed with follitropin delta. This is acceptable based on ICH S6 (R1) and considering these are anticipated to parallel the pathways for endogenous FSH, including elimination primarily in the urine.

The pharmacokinetic profiles of follitropin delta in rats, monkeys and humans were shown to be sufficiently similar to allow the laboratory animal species to serve as appropriate models for assessing the toxicity profile of the drug.

Pharmacokinetic drug interactions

No drug interaction studies were performed. This is acceptable given the nature of the drug.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted with follitropin delta in mice and rats by the SC (clinical) and intravenous (IV) routes. A maximum non-lethal dose of 290 µg/kg (the highest dose tested) was established in all instances, and is 55 (mice) and 110 (rats) times higher than the maximum recommended human dose on a body surface area basis. Follitropin delta is therefore seen to have a low order of acute toxicity.

Repeat-dose toxicity

Repeat-dose toxicity studies of up to 4 weeks duration were conducted in rats and cynomolgus monkeys. Follitropin delta was administered once daily by SC injection, matching the clinical route and dosing regimen. Species selection, group size and dose selection were appropriate. Animals of both sexes were used. Study duration was short but acceptable, with longer studies not feasible in either species due to the development of anti-drug antibodies.

Relative exposure

Exposure ratios have been calculated based on animal: human serum $AUC_{0-24\,h}$ values (Table 2). Very large multiples of the human exposure at the maximum recommended clinical dose was obtained at the highest dose levels tested. Disappointingly, the pivotal 4 week rat study did not include adequate toxicokinetic sampling to determine AUC; exposure in that study is estimated from the 2 week rat study.

Table 2: Relative exposure in repeat-dose toxicity studies

Species	Study duration [Study no.]	Dose (µg/kg/day)	$AUC_{0-24\,h}$^ (ng·h/mL)	Exposure ratio†
Rat (Wister Han)	2 weeks [Study ADR0055]	1.45	Below LLoQ#	NC
		14.5	135	3.2
		145	4296	103
	4 weeks [Study ADR0060]	1.04	Below LLoQ#*	NC
		7.3	68*	1.6
		52.2	1016*	24
Monkey (Cynomolgus)	7 days [Study 1475-099]	290	29218	698
	4 weeks [Study 1475-101]	0.52	60	1.4
		5.22	499	12
		52.2	7726	185
Human (patients)	PK/PD modelling report [on Study 000009]	[24 µg/day] (MRHD)	41.8‡	–

^, data are for the sexes combined at the last sampling occasion; #, LLoQ (lower limit of quantification) = 1 ng/mL; NC, not calculated;
*, estimate based on extrapolation of data from Study ADR0055; ‡, AUC calculated from dose/CL for dosing at 12 µg, then doubled (see Section 6.2.3); †, animal: human plasma AUC_{0-24h}

Major findings

Effects on the female reproductive organs were the most prominent finding in treated animals, with effects on mammary gland, pituitary, hormone levels, and male reproductive tissues also seen.

Notable changes in the female reproductive tract of follitropin delta-treated animals comprised:

- increased ovary size/weight, ovarian follicular cysts and follicular haemorrhages in both species, and increased number and prominence of corpora lutea in rats, observed at all dose levels tested
- vaginal/cervical epithelial mucification in rats (at ≥1.04 µg/kg/day in the pivotal 4 week study)
- uterine epithelial hypertrophy (at ≥ 7.3 µg/kg/day in the pivotal 4-week study) and endometrial proliferation/folding (at ≥ 52.2 µg/kg/day) in rats, and movement to proliferation phase in monkeys (at all doses in the pivotal 4-week study), with endometrial stromal hyalinisation (at 0.52 µg/kg/day) and cyst formation (at 5.22 µg/kg/day) also observed in the monkey uterus.
- oviduct enlargement/dilatation in monkeys at ≥0.52 µg/kg/day in the pivotal 4 week study.

Mammary gland acinar proliferation was increased in incidence/severity in female rats at all doses in the pivotal 4 week study (≥ 1.04 µg/kg/day) and with treatment at 14.5 µg/kg/day for 2 weeks. Increased pituitary weight was evident in rats dosed at 52.2 µg/kg/day for 4 weeks, and hyperplasia/hypertrophy of acidophilic cells of the pituitary gland occurred in monkeys at all dose levels in the pivotal 4 week study (≥0.52 µg/kg/day).

These findings are consistent with the primary pharmacology of the drug, with FSH activity and resultant ovarian stimulation causing hormonal changes that affect sensitive tissues. Oestradiol was shown to be increased and luteinising hormone decreased several fold in monkeys, and multi-fold increases in inhibin-B were shown in both species. Most of the histological changes in rats and monkeys were reversed or partly reversed by the end of a 4 week treatment-free period.

Remarkably, the vagina was not subjected to microscopic examination in either monkey study. This is considered to be a serious deviation from the relevant TGA-adopted EU guideline on repeat-dose toxicity[1], which includes it as a core tissue to be studied histologically. However, it is not judged to be a critical deficiency overall given the examination in rats, existing experience with the pharmacological class and the absence of other observed off-target effects.

Although follitropin delta is proposed to be indicated solely for use in females, male animals were included in the repeat-dose toxicity studies. Treatment was associated with feminisation of the mammary gland in male rats (seen at ≥1.45 µg/kg/day in the 2-week study) and testes atrophy in monkeys (at ≥0.52 µg/kg/day for 4 weeks), accompanied by degeneration of the germinal epithelium and decreased sperm in the epididymis with treatment at 290 µg/kg/day for 2 weeks. These findings are also consistent with the

[1] CPMP/SWP/1042/99 Rev 1 Corr Guideline on repeated dose toxicity

primary pharmacological activity of the drug. Together with the female data, they support an absence of systemic off-target toxicity for follitropin delta.

Genotoxicity

Genotoxicity studies were not performed. As a large molecular weight protein, follitropin delta is not anticipated to interact with DNA or other chromosomal material, and genotoxicity studies are not required under the relevant ICH guideline.[2] Follitropin alfa and follitropin beta were both previously found not to exhibit genotoxic activity.

Carcinogenicity

No carcinogenicity studies were submitted. This is considered to be acceptable given the nature of the drug, in accordance with the relevant guideline[2], with rodent carcinogenicity studies not feasible due to the development of anti-drug antibodies.

Reproductive toxicity

Reproductive toxicity studies with follitropin delta covered fertility and early embryonic development only (examined in rats). The main study was appropriately conducted (in terms of the species used, group size, timing/duration of treatment, end points examined), and consistent with the relevant TGA-adopted guideline[3]. Administration was once daily by the clinical route (SC).

Impairment of fertility was observed in female rats at ≥ 0.84 µg/kg/day, with disruption of oestrus cycling seen at 2.61 µg/kg/day. Exposure at these doses is presumed to be subclinical, based on AUC data obtained in the general repeat-dose toxicity studies in rats (used due to very limited toxicokinetic sampling in the reproductive toxicity studies). Pre-implantation loss was doubled at 2.61 µg/kg/day; reflecting a marked increase in the number of corpora lutea with no change in the number of implantations. Pre-implantation loss was unaffected at 0.84 µg/kg/day but the number of live embryos per female was doubled, in line with an increase in the number of corpora lutea.

Potential effects on male fertility were examined in a pilot rat study, with decreased sperm count and an increase in abnormal sperm observed at 36.3 µg/kg/day. This study featured only a limited number of animals, involved treatment of males for only 2 weeks prior to mating (rather than the 4 week period recommended in the guideline[3]) and involved pairing of treated males with treated females confounding determination of a sex-specific fertility index. There was no examination of male fertility in a definitive study, which is acceptable given the indication.

These findings are consistent with exaggerated pharmacology of follitropin delta, and in line with effects on reproductive tissues seen in the general repeat-dose toxicity program.

Embryofetal and pre/postnatal development studies were not conducted and placental transfer and excretion in milk were not investigated. This is acceptable. Follitropin alfa was found to cause dystocia and marked post-implantation loss in rats and rabbits previously, without being teratogenic. The sponsor proposes contraindication in pregnancy and lactation.

[2]ICH S6 (R1) Preclinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals.
[3] ICH S5(R2) Detection Of Toxicity To Reproduction For Medicinal Products & Toxicity To Male Fertility

Pregnancy classification

The sponsor initially proposed Pregnancy Category B3[4], then Category C[5] after receiving the TGA's first round evaluation. Findings of embryofetal lethality with the closely related agent, follitropin alfa, warrant placement in Pregnancy Category D[6] instead. This is appropriate even in the absence of observed teratogenicity and though pharmacologically mediated, and matches the categorisation of Gonal-F. Category B3 and C are both inappropriate given the serious and irreversible nature of the adverse effects on embryofetal development.

Local tolerance

Follitropin delta was well tolerated locally following single SC injection in a specialised study in rabbits conducted with various formulations containing 37 µg/mL of the active ingredient (11% higher than the clinical strength). In the repeat-dose toxicity studies where the tested formulation more closely matched the clinical formulation in terms of the excipient profile, injection site reactions were consistent with injection trauma only in rats (tested up to 72.5 µg/mL follitropin delta; more than twice the clinical strength) and were mild in monkeys (tested up to 208.8 µg/mL; >6 times the clinical strength).

Paediatric use

Follitropin delta is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- The nonclinical submission contained no critical deficiencies. The set of submitted nonclinical studies was in accordance with ICH guideline S6 (R1)[2] on the preclinical safety evaluation of biotechnology-derived pharmaceuticals. All pivotal safety-related studies were GLP-compliant.
- Follitropin delta has a distinct glycosylation profile compared to existing recombinant human FSH products (follitropin alfa and follitropin beta) owing to its production in a human cell line rather than Chinese hamster ovary cells.
- In vitro, follitropin delta was shown to bind to the FSH receptor with sub-nanomolar affinity and activate the downstream signalling cascade with similar potency to follitropin alfa. FSH activity was demonstrated for follitropin delta in vivo in rats (ovarian enlargement in the Steelman-Pohley bioassay) and was also evident in rats and monkeys in general repeat-dose toxicity studies.
- No adverse effects on the cardiovascular, respiratory and central nervous systems were observed with follitropin delta in safety pharmacology studies.

[4] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
[5] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
[6] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

- Follitropin delta was slowly absorbed following SC injection in laboratory animal species (rats and cynomolgus monkeys), as in humans, with a long serum half-life. The distinct glycosylation profile was shown to influence pharmacokinetics in rodents, but is not expected to do so in humans. More rapid clearance in rats underestimates potency determination in the Steelman-Pohley bioassay. For this reason, the sponsor proposes dosing by mass rather than IU.
- Follitropin delta displayed a low order of acute toxicity by the SC (clinical) and IV routes in mice and rats.
- Repeat-dose toxicity studies by the SC route of up to 4 weeks duration were conducted with follitropin delta in rats and cynomolgus monkeys. Although short, study duration is acceptable, with longer studies not feasible due to the development of anti-drug antibodies. Very large multiples of the human exposure was obtained at the upper dose levels tested in animals. Major target organs were the ovary, vagina, uterus, mammary gland and pituitary, with changes in these tissues reflecting exaggerated effects related to the drug's primary pharmacology (FSH activity and resultant ovarian stimulation causing hormonal changes that affect sensitive tissues). No toxicity due to off-target effects was seen. SC injection was well tolerated locally in laboratory animal species (examined in rats, rabbits and monkeys).
- Consistent with ICH S6 (R1)[2], no genotoxicity or carcinogenicity studies were conducted with follitropin delta.
- Follitropin delta impaired fertility, disrupted oestrus cycling and adversely affected early embryonic development (increased pre-implantation loss) in rats, consistent with exaggerated pharmacology. No embryofetal development studies were performed but adverse effects (embryofetal lethality) are expected based on previous findings for follitropin alfa.
- There are no nonclinical objections to the registration of Rekovelle.
- It was recommended that the sponsor revise some nonclinical sections of the proposed Product Information document. In particular, the pregnancy category should be changed to Category D.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

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 CHO cell lines. Rekovelle is derived from a human cell line. The relevance of this is uncertain.

Guidance

Early in the scientific development programme, National Scientific Advices were obtained from the Medicines and Healthcare products Regulatory Agency (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.

Contents of the clinical dossier

Scope of the clinical dossier

The submitted clinical studies are listed in Table 3 below.

Table 3: 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 3 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 3 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

Also included were separate reports on the immunogenicity and PK-PD modelling.

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

Paediatric data

This medication is not proposed for use in children.

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 summarises the PK studies submitted.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*	Objective
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

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

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of the product has been well described and is similar to other FSH products. One major difference is the slower clearance, higher exposure and longer half-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.

Pharmacodynamics

Studies providing pharmacodynamic data

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.

Studies providing pharmacodynamic information

Submitted pharmacodynamic studies:

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

Evaluator's conclusions on pharmacodynamics

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

Medical device issues

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 to 44 years but not in women aged 20 to 35 years. There are a number of problems with the available AMH assays. Firstly, different methods will produce different results (such as 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 doing 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.

Summary of AMH assay

More details of this assay are given in Attachment 2 under the same heading.

1. It shows good correlation for the lower range of AMH, although at higher levels of AMH there was considerable disagreement between the two assays.
2. The PK-PD 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 a 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 (for example, 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.
3. 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.

   Results showed that 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.

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 µg to 24.0 µg in increments of 0.33 µg. The injection pen will be registered in Australia following granting of the CE mark[7] in Europe.

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

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.

Dosage selection for the pivotal studies

Evaluator's conclusions on dose finding for the pivotal studies

The ability to extrapolate the doses to AMH levels < 5 pmol/L or > 40 pmol/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.

[7] 'Conformité Européene' which literally means 'European Conformity".

Efficacy

Studies providing efficacy data

- ESTHER-1 (Evidence based stimulation trial with Human rFSH in Europe and Rest of World Trial) 00004: use of Rekovelle at the initial COS cycle.8.2.1
- ESTHER II Trial 00071: use of Rekovelle with repeated COS cycles.8.3.1

Evaluator's conclusions on 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 Rekovelle 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.

Safety

Studies providing safety data

Studies providing evaluable safety data

- Pivotal 000004- ESTHER-1 as well as ESTHER-2.

Patient exposure

The table below outlines the patient exposure in ESTHER-1 and ESTHER-2.

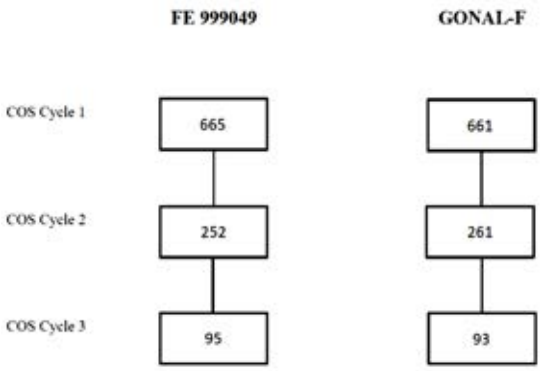
Table 6: Exposure in ESTHER I and ESTHER II

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)

Stimulation cycle		Rekovelle	Gonal-F
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 1 describes the subject disposition by COS cycle.

Figure 1: Subject disposition by COS cycle.



Safety issues with the potential for major regulatory impact

OHSS

ESTHER-I

Investigators used Golan's system to grade (1, 2, 3, 4 and 5) each OHSS case see Table 7.

Table 7: 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 and 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 8)

Table 8: 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 9: 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.

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 10)

Table 10: 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.

Early pregnancy loss

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% and induced abortion 0.4% and 0.4%.

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%.

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 a higher proportion of patients in the 38 to 40 year old age bracket.

Multi-fetal gestations

Integrated safety analyses

ESTHER-1

There were 4 sets of twins in the Rekovelle group and 8 in the Gonal-F group. 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.

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.

Injection site reactions

Integrated safety analyses

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 administration. 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.

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 to 50% of subjects in a treatment group did not have any injection site reactions in COS Cycle 2 or COS Cycle 3. Few subjects (≤3 subjects in a treatment group) experienced severe injection site reactions in COS Cycle 2 and COS Cycle 3.

Anti-FSH antibodies

ESTHER-1

Blood samples for analysis of anti-FSH antibodies were collected on stimulation Day 1 prior to dosing, at 7 to 10 days after the last IMP dose (first post-dosing assessment) and

21 to 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 were 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 (1.5 months 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.

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 subject in the Rekovelle group had treatment-induced anti-FSH antibodies in COS Cycle 3 giving the proportion of subjects with treatment-induced anti-FSH antibodies as 1.05% (95% CI [0.03%; 5.73%]) in the Rekovelle group in COS Cycle 3. 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.

Potentially immune related adverse events

ESTHER-1

Both narrow and broad scope searches on the Standardised MedDRA Queries (SMQ) 'anaphylactic reactions' 'angioedema' and 'severe cutaneous adverse reactions' were carried out for adverse events that were considered 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 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.

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.

Technical malfunction and other problems with the pen

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.

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.

Postmarketing data

Not applicable.

Evaluator's conclusions on 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 (AE) 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 serious AE (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 and 0.76% of the Gonal f group. 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.

First round benefit-risk assessment

First round assessment of benefits

The following table describes the 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 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

Indication: Controlled Ovarian Stimulation	
	· It is unknown how this would compare using an adjusted fixed dosing algorithm like Gonal-F

First round assessment of risks

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.

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.

First round recommendation regarding authorisation

At this time, the sponsor will need to respond to further questions before a recommendation is made (see Attachment 2 Clinical questions).

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

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.

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.

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- thus the validity of the doing algorithm in the Australian setting is unknown. This is a major problem with the submission.

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.

Population pharmacokinetics

Summary of findings

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 T_{max} 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 may result in an optimised 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. Risk-benefit assessment of the proposed dosing algorithm remains to be evaluated.

A minor consideration with regard to the proposed Australian draft PI is as follows:

Pharmacokinetics and 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.

V. Pharmacovigilance findings

Summary

- Ferring Pharmaceuticals Pty Ltd has submitted EU-RMP version 3.0 (6 September 2016; DLP 2 July 2015) and ASA version 4.0 (24 November 2016) in support of this application.
- The sponsor proposed the following Summary of Safety Concerns and their associated risk monitoring and mitigation strategies (Table 11):

Table 11: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Ovarian hyperstimulation syndrome	ü	–	ü	–
Important potential risks	Hypersensitivity/immunogenicity	ü	–	ü	–
	Thromboembolic events	ü	-	ü	-
	Ovarian torsion	ü	-	ü	-
	Multiple pregnancy	ü	-	ü	-
	Pregnancy loss	ü	-	ü	-
	Ectopic pregnancy	ü	-	ü	-
	Reproductive system neoplasms	ü	-	ü	-
	Congenital malformations	ü	-	ü	-
Missing information	Use in patients with renal and hepatic impairment	ü	–	ü	–
	Experience in anovulatory patients with polycystic ovarian syndrome	ü	–	ü	–
	Experience with Rekovelle in the GnRH agonist protocol	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
	Limited experience in women >40 years of age	ü	-	ü	-

R=routine and A=Additional[8]

- No additional pharmacovigilance or risk minimisation activities are proposed, however:
  - A Dear Health Care Provider (DHCP) letter addressing the need to use the specified Roche ElecSys AMH Assay for dose selection should be implemented
  - The Rekovelle injection pen will be supplied with an 'instructions for use' leaflet, which is considered part of the routine risk minimisation activities. It must be supplied, along with the CMI, with the product.

Conclusions

The recommendations made in the Round 1 and Round 2 RMP evaluations have been addressed satisfactorily by sponsor.

Two additional recommendations are made, following the meeting of the Advisory Committee on Medicines (Table 12):

Table 12: Post-Advisory committee update

Post ACM update
Outstanding (Post-ACM) RMP issues The Delegate has requested that additional risk minimisation, in the form of a DHCP letter to all fertility specialists/clinics, to inform HCPs of the need to use the recommended Roche ElecSys AMH assay be implemented. This should be distributed prior to supply of the product and this activity, including the proposed distribution method should be documented in the ASA. The sponsor should submit a draft of the DHCP letter prior to approval. The ASA should be revised and agreed with TGA prior with launch, including the DHCP letter as an additional risk minimisation activity. **Wording for conditions of registration**

[8] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Post ACM update

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Rekovelle EU-RMP version 3.0 (dated 6 September 2016; data lock point 2 July 2015) with Australian Specific Annex version 4.0 (dated 24 November 2016), included in submission PM-20165-04337-1-5), which must be revised to be consistent with pregnancy category D and including distribution of a Dear Health Care Professional letter (as below), and any future revisions as agreed with the TGA must be implemented.

A DHCP letter addressing the need to use the specified Roche ElecSys AMH Assay for dose selection must be distributed to fertility specialists/clinics prior to supply.

The Consumer Medicines Information and Instructions for Use must be supplied to the patient with the product.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator did not have any objections to the registration of Rekovelle for the proposed indication.

Nonclinical

The nonclinical evaluator did not have any objections to the registration of Rekovelle for the proposed indication.

Clinical

Premarket clinical development program

The following data was submitted:

- 4 Phase I studies
- 1 Phase II study
- 2 Phase III studies (as outlined below)

ESTHER-1

- pivotal efficacy trial
- designed to assess non-inferiority to Gonal-F
- co-primary endpoints: ongoing pregnancy rate, ongoing implantation rate

ESTHER-2

- Safety/immunogenicity trial
- up to two repeated treatment cycles in women who did not achieve an ongoing pregnancy in ESTHER-1.

Pharmacodynamics and pharmacokinetics

The pharmacodynamics was as expected for a recombinant FSH product.

Follitropin delta has slower clearance, higher exposure, and longer $T_{1/2}$ than follitropin alpha. As a result, the sponsor developed a dosing algorithm based on AMH and body weight.

In-vitro diagnostic test

Roche's Elecsys AMH assay was included on the ARTG (174907 GMDN CT850) in August 2010 (intended use: determination of AMH). There are other AMH assays included on the ARTG.

Efficacy

ESTHER-1

Randomised, assessor-blinded (investigators, embryologists, central laboratory personnel were blinded; patients were not blinded), multicentre, non-inferiority study at 37 sites in 11 countries (Belgium, Brazil, Canada, Czech Republic, Denmark, France, Italy, Poland, Russia, Spain, and United Kingdom).

Recruitment was between October 2013 and May 2015 with a follow-up for livebirths completed in January 2016. The following table summarises the study:

Table 13: Summary of ESTHER-1 study

	Details
Patients	Women aged 18-40 years First IVF/ICSI cycle Unexplained infertility, tubal infertility, endometriosis stage I/II, or partners with male infertility BMI: 17.5-32.0 kg/m^2 Regular, presumed ovulatory, menstrual cycles of 24-35 days Presence of both ovaries Early follicular phase FSH serum concentration: 1-15 IU/L Main exclusion criteria were: – Endometriosis stage III-IV – Recurrent miscarriage – Anovulatory polycystic ovarian syndrome
Intervention	SC follitropin delta (Rekovelle) Fixed daily dose determined by serum AMH level, by a central laboratory using the automated Elecsys AMH immunoassay (Roche), and body weight

	Details
	(as per the dosing instructions in the proposed PI): AMH < 15 pmol/L: 12 µg (regardless of weight) AMH 15+ pmol/L: 0.10-0.19 µg/kg (maximum: 12 µg)
Comparator	SC follitropin alpha (Gonal-F) 150 IU (11 µg) for the 1st 5 days Dose could then be adjusted up or down according to follicular response (to a maximum of 450 IU)
Endpoints	Co-primary (measured 10-11 weeks after blastocyst transfer) Ongoing pregnancy rate: at least one viable fetus 10-11 weeks after transfer Ongoing implantation rate: number of viable foetuses divided by the number of blastocysts transferred Selected pre-specified secondary outcomes – Livebirth rates – Targeted ovarian response (8-14 oocytes) – Extreme ovarian response (<4 or >14 oocytes) – Early/late OHSS

GnRH antagonist (cetrorelix) was started on stimulation day-6

Sample size; non-inferiority margin

The primary aim of ESTHER-1 was to show non-inferiority of follitropin delta (fixed dose determined by AMH and body weight) to follitropin alpha (conventional dosing) on the co-primary endpoints of pregnancy rate and implantation rate.

As originally agreed with the EMA, the non-inferiority margin was specified as - 8.0%; although the subsequent EMA Rapporteur's assessment report did question this.

The pre-specified sample size was 1300. This allowed for blinded assessment for 1150 women, which gave 80% power to detect non-inferiority, off a pregnancy/implantation rate of 25-30%. This meant that the point estimate of the difference between the two arms was assumed to be about 2.7%.

Selected baseline characteristics are shown in Table 14 below.

Table 14: Baseline characteristics

Age	Rekovelle n=665	Gonal-F n=661
Age (mean)	33.4 years	33.2 years
Age years (%) <35 35-37 38+	 59% 24% 17%	 59% 25% 15%

Age	Rekovelle n=665	Gonal-F n=661
BMI kg/m^2	24	23
Duration of infertility (months)	35	35
Primary infertility (%)	71	71
Primary reason for infertility (%) Unexplained Tubal Male factor Endometriosis (I/II) Other	 42 14 40 3 <1	 41 15 39 4 <1
Endocrine profile AMH (pmol/L) FSH (IU/L) LH (IU/L)	 16.3 7.5 4.5	 16.0 7.7 4.4

The following tables summarise the results (mITT and PP were similar).

Table 15: Results from ESTHER-1

	Rekovelle n=665	Gonal-F n=661	Difference (95% CI)
Co-primary endpoints Ongoing pregnancy Ongoing implantation	 204 (30.7%) 206/585 (35.2%)	 209 (31.6%) 209/584 (35.8%)	 -0.9% (-5.9%, 4.1%) -0.6% (-6.1%, 4.8%)
Selected secondary endpoints Women with a livebirth Women with a live neonate Birthweight Gestational age Multiple pregnancy	 198 (29.8%) 198 (29.8%) 3186 g 272 days 4 (2.0%)	 203 (30.7%) 201 (30.4%) 3168 g 272 days 8 (3.8%)	 -0.9% (-5.8%, 4.0%) -0.6% (-5.5%, 4.3%) 22.8 g (-97.2 g, 142.8 g) 0.1 days (-3.1, 3.3) -2.0% (-5.0%, 1.1%)

Co-primary endpoints by age are shown in Table 16 below.

Table 16: Co-primary endpoints by age (Per Protocol (PP))

	Rekovelle n=665	Gonal-F n=661	Difference (95% CI)
Co-primary endpoints Ongoing pregnancy Ongoing implantation	204 (30.7%) 206/585 (35.2%)	209 (31.6%) 209/584 (35.8%)	-0.9% (-5.9%, 4.1%) -0.6% (-6.1%, 4.8%)
Selected secondary endpoints Women with a livebirth Women with a live neonate Birthweight Gestational age Multiple pregnancy	198 (29.8%) 198 (29.8%) 3186 g 272 days 4 (2.0%)	203 (30.7%) 201 (30.4%) 3168 g 272 days 8 (3.8%)	-0.9% (-5.8%, 4.0%) -0.6% (-5.5%, 4.3%) 22.8 g (-97.2 g, 142.8 g) 0.1 days (-3.1, 3.3) -2.0% (-5.0%, 1.1%)

ESTHER-2 evaluated two subsequent controlled ovarian stimulation (COS) cycles of women who did not achieve on-going pregnancy in ESTHER-1.

The dosing regimen used in ESTHER-2 was not directly based on any modelling or estimation, but was dependent on the ovarian response in the previous cycle (Cycle 1 in ESTHER-1). Women who had an adequate response in the first cycle were started on the same dose. Women who obtained <4 oocytes or 4-7 oocytes were in the next cycle given a follitropin delta dose which was 50% and 25% higher, respectively, than in the previous cycle. Follitropin doses up to 24 µg could be administered in ESTHER-2. Women who had an excessive oocyte response had a dose lower.

Ongoing pregnancy rate:

COS2: follitropin delta: 28%; follitropin alpha: 26%

COS3: follitropin delta: 27%; follitropin alpha: 28%

Safety

Results from ESTHER-I are shown in the table below.

Table 17: Safety results from ESTHER-1

	Follitropin delta n=665	Follitropin alpha n=661
Preventive interventions Early OHSS (< 10 days after triggering final	15 (2.3%)	30 (4.5%)

	Follitropin delta n=665	Follitropin alpha n=661
follicular maturation)	17 (2.6%)	20 (3.0%)
Any grade	9 (1.4%)	9 (1.4%)
Moderate/severe	31 (4.7%)	41 (6.2%)
Any grade or preventive intervention	24 (3.6%)	34 (5.1%)
Moderate/severe or preventive intervention		
All OHSS	23 (3.5%)	32 (4.8%)
Any grade	14 (2.1%)	19 (2.9%)
Moderate/severe	37 (5.6%)	53 (8.0%)
Any grade or preventive intervention	29 (4.4%)	44 (6.7%)
Moderate/severe or preventive intervention		
	2 (0.3%)	6 (0.9%)
Hospitalisation due to OHSS	4.0	8.7
Mean duration (days)	8	52
Total duration (days)		

As in the above table, rates of OHSS were higher in the follitropin alpha group and interventions to prevent OHSS were higher in the follitropin alpha arm (with the obvious caveat that the statistical significance of the difference is difficult to interpret because of the problem of multipole comparisons). Commonly reported adverse events occurred with similar frequency in the follitropin delta and follitropin alpha groups: 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%).

Early and late pregnancy loss and multiple pregnancies were similar for follitropin delta and alpha as were injection site reactions.

Results obtained from ESTHER-2 study showed that Rekovelle has limited immunogenicity (of no clinical relevance).

Medication errors were more common with Rekovelle which the sponsor put down to the learning curve for the injection pen.

Risk management plan

Routine pharmacovigilance is proposed in Australia. The EMA considered that routine pharmacovigilance was sufficient in the EU.

Summary of safety concerns are shown in the table below.

Table 18: Summary of safety concerns

Important identified risk	OHSS
Important potential risks	Immunogenicity, hypersensitivity

	Thromboembolic events Ovarian torsion Multiple pregnancy Pregnancy loss Ectopic pregnancy Reproductive system neoplasms Congenital malformations
Missing information	Experience in women older than 40 Experience in anovulatory women with POCS Experience in the long GnRH agonist protocol Experience in women with hepatic or renal impairment

The following should be added to missing information:

- Use with AMH assays besides the Roche assay.
- Use with same-cycle-variable dosing.

Risk-benefit analysis

Delegate's considerations

There were no particular concerns with the comparison, internal to ESTHER-1/ and ESTHER-2, or the endpoints used. (A minor point is that cumulative livebirth rates accounting for the transfer of all fresh and frozen embryos were not available because some women proceeded directly to a further fresh cycle.)

Comments on external validity, that is, applicability and relevance to Australian clinical practice:

- As per the EMA Summary of Product Characteristics (SmPC): There is no clinical trial experience with Rekovelle in the long GnRH agonist protocol.
- Women older than 40 years of age were excluded (similar to the pre-market studies for other exogenous FSH products). Based on the most recently published data, 25.5% of women undergoing an autologous cycle in Australia were 40 years or older.[9]
- Women with anovulatory polycystic ovarian syndrome (PCOS) were not part of ESTHER-1/-2; presumably because of the inclusion criterion: Patients were to have regular menstrual cycles, presumed to be ovulatory. PCOS is a common anovulatory disorder and IVF is an effective treatment for PCOS patients, who typically have high AMH levels. The proposed PI includes the statement: anovulatory patients with polycystic ovarian syndrome have not been studied (this is also included in the PIs of other exogenous FSH products).
- The Roche Elecsys automated AMH analysis in the Phase III premarket study was at a central laboratory. It is uncertain how well the dosing algorithm will work in routine clinical practice in Australia, where the assay will be done at multiple laboratories.

[9] NPESU, Assisted Reproductive Technology in Australia and New Zealand, 2014. University of NSW, 2016.

- In Australia, starting doses of follitropin alpha tend to be individualised based on, among other factors, the antral follicle count and age. It is not uncommon in Australia for women to be started on doses of follitropin alpha greater than 150 IU.
- Rates of OHSS in Australia tend to be low due to close surveillance by IVF specialists. thus, external validity of the difference in OHSS between Rekovelle and FSH is unknown
- There were no Australian sites in the clinical development program.
- Off-label dosing (for example, a same-cycle-variable dose or use of AMH assays other than the Roche assay) could introduce uncertainty around the comparative effectiveness and safety in everyday clinical practice.

A technical/methodological point is the comparison. The interventions compared in the pivotal pre-market Phase III study (ESTHER-1) were compound (rather than simple) interventions (medicine plus individualised same-cycle-fixed dosing versus a different medicine plus same cycle-variable dosing).

- Follitropin delta plus fixed dosing based on AMH levels and body weight.
- Follitropin alpha plus flexible dosing, 150 IU for the first 5 days, then adjustment by the treating doctor based on ovarian response.

Whether follitropin delta plus same-cycle-flexible dosing is more or less efficacious and safe than follitropin delta plus same-cycle-fixed dosing based on the algorithm was not tested.

Summary of issues

Pending further advice, at this point in time, based on the available pre-marketing data, efficacy and safety have been satisfactorily established.

Conditions of registration

Standard conditions as well as implementation of the RMP.

Proposed action

The Delegate had no reason to say, at this time, that Rekovelle should not be approved for registration.

Request for ACPM advice

1. Please comment on the applicability/relevance of the pre-market studies to Australian clinical practice.
2. Is routine pharmacovigilance adequate? Or should uptake, usage (for example, off-label dosing), and outcomes be actively monitored in routine clinical practice in Australia?
3. The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application

Questions for sponsor

1. What is the current wording of the intended use of the Roche Elecsys AMH assay in the EU? (please provide the Instructions for Use)
2. What is the registration status of Rekovelle in Canada?

3. What is the status of the Roche Elecsys AMH assay in Canada and the USA? (please provide the Instructions for Use)

Response from sponsor

Presented here is the sponsor's response to the TGA Delegate's Request for ACPM's Advice on the application to register Rekovelle (follitropin delta; Rekovelle) solution for injection (12 µg/0.36 mL, 36 µg/1.08 mL and 72 µg/2.16 mL) for controlled ovarian stimulation (COS) for the development of multiple follicles in women undergoing assisted reproductive technologies (ART).

The Delegate has raised two questions for ACPM and three questions for the sponsor. These will be addressed in turn in this pre-ACPM response.

Applicability/relevance of the pre-market studies to Australian clinical practice

The Delegate has included a series of discussion points related to the applicability and relevance of the Rekovelle clinical development programme to Australian clinical practice and has asked ACPM to comment specifically on this matter.

The Rekovelle clinical development programme included a large, multi-centre, randomised comparator-controlled Phase III trial (ESTHER-1) in first-cycle patients and a Phase III trial in repeat COS cycles (ESTHER-2). As with trials used to support the registration of current gonadotropin products, the ESTHER trials involved a population which, while broadly reflective of the population of women in developed countries commonly seeking ART, by necessity was controlled for a number of factors that could potentially influence the trials' ability to answer the research question at hand, namely to assess the comparability of Rekovelle and the control exogenous follicle stimulating hormone (FSH) product follitropin alfa (Gonal-F). Importantly, the comparator arm of the ESTHER trials was designed to be consistent with the product label for follitropin alfa, as well as to take into account patient safety considerations and routine clinical practice. In addition, the eligibility criteria for the ESTHER trials were quite broad, with the studies accommodating wide ranges in patient age and body mass index and allowing for most of the common reasons for infertility.

The specific issues raised in Delegate's discussion are addressed below.

- *As per the EMA SmPC: There is no clinical trial experience with Rekovelle in the long GnRH agonist protocol.*

While the Rekovelle development programme did not explore the use of the product in a GnRH agonist protocol, it should be noted that that the vast majority of COS cycles undertaken in Australia involve GnRH antagonist down-regulation (approximately 75 to 90% of cycles), consistent with the ESTHER trial design.

However, to emphasise this limitation of the ESTHER trials, the sponsor proposes that the EU SmPC statement:

> *There is no clinical trial experience with Rekovelle in the long GnRH agonist protocol.*

be included in the Precautions section of the Rekovelle Product Information (PI).

- *Women older than 40 years of age were excluded (similar to the pre-market studies for other exogenous FSH products). Based on the most recently published data, 25.5% of women undergoing an autologous cycle in Australia were 40 years or older. [NPESU, Assisted Reproductive Technology in Australia and New Zealand, 2014. University of NSW, 2016.]*

The response rate in older women is well-recognised to be lower than in younger women and in this respect it is unlikely that Rekovelle would be any different from other FSH

products which also lacked pre-market evidence in this population, as acknowledged by the TGA Delegate.

The fertility problems seen in women in this age group are commonly a result of diminished oocyte quality or ovarian reserve or a combination of both factors. As such, most women >40 years of age would be expected to have serum AMH levels <15 pmol/L. With this in mind, it is worth noting that approximately 45% of women in the ESTHER-1 trial had baseline AMH level in this category (corresponding to a maximum daily dose of Rekovelle of 12 µg). Hence, while trial experience with Rekovelle is lacking in women >40 years of age, as acknowledged in the proposed PI, there is nevertheless ample experience with Rekovelle in women with low ovarian reserve, which would to serve as a guide to physicians choosing to use the product in women in this age group. Basing the dose of Rekovelle in an >40 year old woman on her baseline AMH level (and weight) is expected to give a reasonable ovarian response (that is, number of oocyte retrieved). But, due to possible deficits in oocyte quality in women in this age group, her likelihood of a pregnancy might be less than for a younger woman having the same baseline AMH value.

- *Women with anovulatory polycystic ovarian syndrome (PCOS) were not part of ESTHER-1/-2; presumably because of the inclusion criterion: Patients were to have regular menstrual cycles, presumed to be ovulatory. PCOS is a common anovulatory disorder and IVF is an effective treatment for PCOS patients, who typically have high AMH levels. The proposed PI includes the statement: anovulatory patients with polycystic ovarian syndrome have not been studied (this is also included in the PIs of other exogenous FSH products).*

As noted by the TGA Delegate, the sponsor has acknowledged the limited experience in anovulatory patients with polycystic ovarian syndrome (PCOS) in the proposed PI by the inclusion of the following statement:

> *Polycystic ovarian syndrome patients with anovulatory disorders have not been studied.*

Similar statements are included in the PI documents for other FSH products. The clinical community in Australia is experienced in the use of gonadotropins in this population and is aware of the challenges and risks associated with COS in patients with PCOS, including the risk of OHSS.

While patients with anovulatory PCOS were not included the ESTHER-1 trial, the study did include ovulatory patients with polycystic ovaries, a far more common form of PCOS than the anovulatory form and these patients displayed in ESTHER-1 a significantly lower risk of OHSS on Rekovelle than on follitropin alfa, without a compromise in efficacy.

- *The Roche Elecsys automated AMH analysis in the Phase III premarket study was at a central laboratory. It is uncertain how well the dosing algorithm will work in routine clinical practice in Australia where the assay will be done at multiple laboratories*.

The sponsor undertook a rigorous evaluation of the technical performance and global accessibility of a number of AMH assays prior to adopting the Roche AMH assay for Rekovelle dose determination. A number of criteria were evaluated for the available AMH assays, including precision, sensitivity, calibration time, analysis time, and published evidence of performance, geographical presence and platform reliability. On the basis of these technical criteria, the Roche Elecsys AMH assay was considered to be the only option at the time of evaluation that met the standards required of a companion diagnostic.

The Roche Elecsys AMH assay includes rigorous calibration and quality control procedures that are standardised across laboratories to ensure the high degrees of accuracy and precision. Furthermore, it has been established from analyses performed on samples from different matrices, collected in different types of tubes, stored under different conditions for different time periods that the assay results remain highly stable

and reliable, with a very strong correlation around unity across a wide range of clinically-relevant concentrations.[10]

For these reasons, TGA can be assured that the Roche Elecsys AMH assay is expected to perform in the same manner in routine Australian clinical practice to the way it performed in the ESTHER programme.

- *In Australia, starting doses of follitropin alpha tend to be individualised based on, among other factors, the antral follicle count and age. It is not uncommon in Australia for women to be started on doses of follitropin alpha greater than 150 IU.*

The sponsor accepts that, based on personal experience, and in view of inter-individual variability in ovarian response, clinicians may choose to individualise the starting dose of follitropin alfa based on factors such as level of ovarian reserve and age and as a consequence, start with doses other than 150 IU in some patients in order to achieve a desired ovarian response. However, the evidence base for this practice is lacking, with no published guidelines available to assist in the practice. In contrast, the individualised dosing approach for Rekovelle has been developed and established prospectively in a well conducted clinical programme.

The ESTHER-1 trial compared Rekovelle, given in a fixed-dose regimen throughout the first cycle, with follitropin alfa, given in a flexible-dose regimen starting with 150 IU for 5 days, then allowing dose adjustments based on ovarian response, consistent with recommendations in the follitropin alfa PI. With these strategies, the study produced very favourable outcomes for efficacy for both interventions. For example, live birth rates of 29.8% and 30.7% were reported for Rekovelle and follitropin alfa respectively in ESTHER-1 (mean age of patients approximately 33.3 years but with approximately 40% of patients aged between 36 to 40 years). These live birth rates overall are comparable to those reported most recently (2014) for women in the Australian population aged between 30 to 34 years who underwent their first ART cycle (30.0%) and are more favourable than the first-cycle live birth rates reported for women aged between 35 to 39 years (21.8%)[11] noting that endogenous FSH products such as follitropin alfa are by far the most commonly used agents for first-cycle COS in Australia.

Hence, the sponsor maintains that the follitropin alfa dose-strategy employed in ESTHER-1 and the efficacy outcomes observed in the trial for the comparator appear reasonably representative of Australian clinical practice.

- *Rates of OHSS in Australia tend to be low due to close surveillance by IVF specialists. Thus, external validity of the difference in OHSS between Rekovelle and FSH is unknown*

While individual clinicians may report low rates of ovarian hyperstimulation syndrome (OHSS) in Australia, the true overall rates remain unknown, primarily because the reporting of OHSS in the clinical setting is mainly restricted to those cases resulting in hospitalisation of the patient. By contrast, surveillance for and the reporting of OHSS is comprehensive in a controlled clinical trial setting and therefore a well-conducted trial, such as the ESTHER-1 trial, is expected to provide an accurate reflection of the difference in the true rates of this adverse event between the interventions at the dosages employed in the trial. In addition, ESTHER-1 provided an opportunity to rigorously assess the need for preventive intervention for OHSS, a related safety outcome that would not be easily assessable outside of a controlled trial. ESTHER-1 not only showed fewer cases of OHSS

[10] Gassner D, Jung R. First fully automated immunoassay for anti-mullerian hormone. Clin Chem Lab Med. 2014;52:1143-1152.
[11] Harris K, Fitzgerald O, Paul R, et al. Assisted reproductive technology in Australia and New Zealand 2014 (September 2016: https://npesu.unsw.edu.au/data-collection/australian-new-zealand-assisted-reproduction-database-anzard)

overall for Rekovelle than for follitropin alfa but also fewer cases of OHSS and/or women requiring preventive intervention.

In the ESTHER-1 trial, follitropin alfa was commenced at 150 IU daily, the lowest recommended starting dose and therefore the dose carrying the least risk of OHSS for this product. However, in view of the TGA Delegate's previous comment above, that Australia fertility centres not uncommonly start COS with follitropin alfa doses higher than the 150 IU used in ESTHER-1, there may in fact be more scope for overstimulation with follitropin alfa in clinical practice than seen in ESTHER-1.

- *There were no Australian sites in the clinical development program.*

It is not unusual for drug development programmes not to involve Australian sites. Like many other development programmes, the ESTHER trials were conducted in sites primarily in Europe and North America and there is no reason to expect that the outcomes for Rekovelle when following the proposed dosage protocol would be different in the Australian clinical setting to those seen in the registration trials.

- *Off-label dosing (such as a same-cycle-variable dose or use of AMH assays other than the Roche assay) could introduce uncertainty around the comparative effectiveness and safety in everyday clinical practice.*

The risks associated with off-label use apply to all registered products. In terms of within-cycle adjustments in Rekovelle dose, there remains an absence of evidence to suggest that this improves outcomes, remembering that the use of Rekovelle in a fixed-dose regimen has been shown to be non-inferior in terms of efficacy to follitropin alfa and with less risk of OHSS.

On the uncertainty of using an AMH assay other than the Roche Elecsys AMH assay, the sponsor is aware that in Australia AMH testing is routinely performed as part of ART programmes. This is usually either with the Roche Elecsys AMH assay or the Beckman Coulter Access AMH assay, both of which are automated. In the sponsor's response to the clinical evaluator's comments, two studies were referred to in which the performance of these assays has been compared.[12] These publications established that a strong correlation exists between the two automated assays, with the slopes of the lines of best fit varying by only 3% to 6% from the unity line. A strong correlation between the two assays was most recently confirmed by Pigny and co-workers.[13] This evidence suggests that the influence on Rekovelle dose-determination would be minimal if the Beckman Coulter Access AMH assay were to be used for this purpose instead of the Roche Elecsys AMH assay.

As for the development of any new product (including other gonadotropin products), the ESTHER trials have not covered all possible ART settings, populations and circumstances in which Rekovelle may be used in future. To address this, statements in the proposed Rekovelle PI highlight not just the representativeness of the ESTHER trial results but also the limitations in extrapolating to patients or protocols not included in these studies. New trials designed to address these limitations are underway or in planning, with a view to including their findings in the Rekovelle PI.

- *Adequacy of routine pharmacovigilance with Rekovelle*

The Delegate has asked ACPM about the adequacy of routine pharmacovigilance with Rekovelle and whether there is a need for uptake, usage (for example, off-label dosing) and outcomes to be actively monitored should the product become available in Australia.

[12] van Helden J, Weiskirchen R. Performance of the two new fully automated anti-mullerian hormone immunoassays compared with the clinical standard assay. Hum Reprod. 2015;30:1918-1926.
Nelson SM, Pastuszek E, Kloss G, et al. Two new automated, compared with two enzyme-linked immunosorbent, antimullerian hormone assays. Fertil Steril. 2015;104:1016-1021.e6.
[13] Pigny P, Gorisse E, Ghulam A, et al. Comparative assessment of five serum antimullerian hormone assays for the diagnosis of polycystic ovary syndrome. Fertil Steril. 2016;105:1063-1069.e3.

The sponsor's position is that routine monitoring is sufficient for Rekovelle, as is the case in the EU. ART in Australia is a well monitored discipline for which treatments and outcomes are thoroughly captured in databases, most notably the Australian & New Zealand Assisted Reproduction Database (ANZARD). Also, as discussed above, 'off-label' starting doses that lack a rigorous evidence base are not uncommonly used for current gonadotropins yet there has never been a need to actively monitor outcomes specifically for this practice.

Also on the matter of pharmacovigilance, the TGA Delegate has requested that two items be added the RMP proposed for Australia. The sponsor will discuss the appropriateness of this request with the Delegate should Rekovelle be recommended for approval by ACPM.

Questions for sponsor

1. *What is the current wording of the intended use of the Roche Elecsys AMH assay in the EU? (please provide the Instructions for Use)*

The wording of the intended use of the assay in the EU is

> *Immunoassay for the in vitro quantitative determination of AMH in human serum and plasma. The determination of AMH is used for the assessment of the ovarian reserve and the prediction of response to COS in conjunction with other clinical and laboratory findings. In addition, the determination of AMH (in pmol/L) in combination with body weight is used for the establishment of the individual daily dose of the human recombinant follicle-stimulating hormone (rFSH) follitropin delta of Ferring (in accordance with the current prescribing information of the Ferring follitropin delta) in controlled ovarian stimulation for the development of multiple follicles in women undergoing an assisted reproductive technology program. The electrochemiluminescence immunoassay 'ECLIA' is intended for use on Elecsys and cobas e immunoassay analyzers.*

The instructions for use document for this assay was provided.

2. *What is the registration status of Rekovelle in Canada?*

The marketing authorisation procedure of Rekovelle in Canada is ongoing.

3. *What is the status of the Roche Elecsys AMH assay in Canada? And the US? (please provide the Instructions for Use)*

The Roche Elecsys AMH assay is currently approved in Canada with the following intended use:

> *Immunoassay for the in vitro quantitative determination of AMH in human serum and plasma. The determination of AMH is used for the assessment of the ovarian reserve and the prediction of response to COS in conjunction with other clinical and laboratory findings. The electrochemiluminescence immunoassay 'ECLIA' is intended for use on Elecsys and cobas e immunoassay analyzers.*

An extension of the intended use to include use for the determination of Rekovelle dose is currently under review by Health Canada, with approval expected in February 2017. When the extension for use is approved, the instructions for use document will be the same as that available in the EU.

The Elecsys AMH assay is approved in the USA but only for the determination of ovarian reserve in women presenting to fertility clinics. As the sponsor has not yet sought to register Rekovelle in the USA there is no immediate plan to extend the intended use of the assay in that country to include the determination of Rekovelle dose.

Conclusion

The primary evidence supporting the registration of Rekovelle comes from the ESTHER trials. While it would be unreasonable to expect these trials to accommodate all possible

ART protocols and patient types, the sponsor maintains that the main design elements of the trials and the clinical trial outcomes align well with Australian clinical practice and that the Roche Elecsys AMH assay can be expected to perform in a similar manner in Australian facilities as it did in the ESTHER trials

In the first-cycle of use, the dose of Rekovelle is individualised according to women's ovarian reserve, as measured by a serum AMH concentration and body weight. The ESTHER-1 programme established that, with this fixed-dose regimen, Rekovelle provides similar efficacy to follitropin alfa but is associated with less risk of OHSS than the existing product. The sponsor contends that the clinical outcomes of the ESTHER programme, including the relative efficacy and safety of Rekovelle to follitropin alfa is generalisable to the majority of women undergoing ART in Australia.

The registration and availability of Rekovelle in Australia would provide local fertility specialists access to a novel recombinant FSH product derived from a human cell line. Rekovelle use with a personalised dosage regimen is supported by a rigorous evidence-base, unlike the situation with current gonadotrophins, for which doses may be based on age and a measure of ovarian reserve but without evidence to support such practice and in contravention to the PI documents for these products.

Advisory Committee Considerations

The ACM, taking into account the submitted evidence of efficacy, safety and quality, considered Rekovelle solution for injection containing 12 µg/0.36 mL; 36 µg/1.08 mL; 72 µg/2.16 mL of follitropin delta are of the opinion that there is an overall positive benefit–risk profile for the indication**;**

> *Rekovelle is indicated for controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies such as IVF or ICSI.*

Specific advice

The ACM advised the following in response to the Delegate's specific questions on this submission:

Please comment on the applicability/relevance of the pre-market studies to Australian clinical practice

The ACM advised that in the Australian context most IVF specialists have several options in their choice of medication and dose. The applicability or relevance of the pre –market studies to Australian clinical practice is difficult to predict because of these options. The ACM noted that the sponsor wishes to refer to a specific assay to determine AMH levels. The ACM considered care should be taken to ensure practitioners are aware of the assay(s) that the Rekovelle dosing algorithm has been validated with.

Is routine pharmacovigilance adequate? Or should uptake, usage (for example, off-label dosing), and outcomes be actively monitored in routine clinical practice in Australia

The ACM advised that in Australia, individualised dosing algorithms based on advice from the PI and clinician's judgements (which may include age, AMH and previous treatments) are used. The ACM also advised that Assisted Reproductive Technology (ART) in Australia is a well monitored discipline, for which treatments are thoroughly captured in notable databases including 'off–label' starting doses commonly used for current gonadotropins, and subsequently, there was little need for further active monitoring.

The ACM noted the comments from the non-clinical evaluator that the sponsor had not changed the Pregnancy Category from C to D nor made other revisions to the PI around use in pregnancy. The ACM recommended that the Pregnancy Category and advice for Rekovelle should be Category D and in line with other recombinant FSH products.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Rekovelle follitropin delta (rhu) 12 µg/0.36 mL solution for injection glass cartridge with rubber plunger; Rekovelle follitropin delta (rhu) 36 µg /1.08 mL solution for injection glass cartridge with rubber plunger and Rekovelle follitropin delta (rhu) 72 µg /2.16 mL solution for injection glass cartridge with rubber plunger indicated for:

> *Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle.*

Specific conditions of registration applying to these goods

- The Rekovelle follitropin delta (rhu) EU Risk Management Plan (RMP), version 3.0, dated 6 September 2016 (data lock point 2 July 2015) with Australian Specific Annex, version 4.0, dated 24 November 2016, which must be revised to be consistent with pregnancy category D and including distribution of a Dear Health Care Professional letter (as below), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- A Dear Health Care Professional (DHCP) letter addressing the need to use the specified Roche ElecSys AMH Assay for dose selection must be distributed to fertility specialists/clinics prior to supply.
- The Consumer Medicines Information and Instructions for Use must be supplied to the patient with the product.
- Batch Release Testing:

  All batches of Rekovelle imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

Attachment 1. Product Information

The PI for Rekovelle approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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