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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ovaleap

International non-proprietary name: follitropin alfa

Procedure No. EMEA/H/C/002608

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

A ₂₇₇	Absorption at 277 nm
AA	Amino acid(s)
AC	Affinity chromatography (step)
AE	Adverse event
AI	Antennarity index
AIEC	Anion exchange chromatography
AIEX	Anion exchange chromatography step
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
Anti-hTSH	Anti human thyroid stimulating hormone
API	Active plasma ingredient
ART	Assisted reproductive technologies
Asn	Asparagine
ATC	Anatomical Therapeutic Chemical
ATCC	Atypical Type Culture Collection
ATP	According-to-protocol
AUC	Area under the concentration-time curve
AUC _{0-24h}	Area under the concentration-time curve from zero to 24 hours post-dose
BMI	Body mass index
BpyV	Bovine polyomavirus
BSA	Bovine spongiform encephalopathy
cAMP	Cyclic adenosine monophosphate
CDSF-1	CHO dhfr-serum free cell line no. 1
CFR	Code of Federal Regulations
CFU	Colony forming units
CL _{obs}	Clearance
C _{max}	Maximum serum concentration
CHMP	Committee for medicinal products for human use
CHO	Chinese hamster ovary
CHOSI	Chinese hamster ovary SI cell line
CI	Confidence interval

CIP	Clearing in place
CMV	Cytomegalovirus
CL/f	Apparent clearance
Cmax	Maximum plasma concentration
CNS	Central nervous system
Da	Dalton
DF	Diafiltration
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECL	Electrochemiluminescence
EMA	European Medicines Agency
ELISA	Enzyme linked immunoabsorbent assay
EPAR	European public assessment report
FSH	Follicle stimulating hormone
GLP	Good laboratory practice
GMP	Good manufacturing practice
GnRH	Gonadotropin releasing hormone
h	Hour
hCG	Human chorionic gonadotropin
hFSH	Human follicle stimulating hormone
HIC	Hydrophobic interaction chromatography step
HRP	Horseradish peroxidase
ICH	International conference on harmonisation
ICSI	Intracytoplasmic sperm injection
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INN	International Non-proprietary Name
ITT	Intent-to-treat
IU	International Unit
IVF	In vitro fertilisation
LH	Luteinising hormone
MCB	Master Cell Bank

MedDRA	Medical Dictionary for Regulatory Activities
M	Metre
mg	Milligram
min	Minute
mL	Millilitre
Mm	Millimetre
mmol	Milimole
N	Number of subjects / patients
Neu5Ac	N-acetylneuraminic acid
Neu5Gc	N-glycolylneuraminic acid
ng	Nanogram
nm	nanometre
NIBSC	National Institute for Biological Standards and Control
NOAEL	No observed adverse effect level
OHSS	Ovarian hyperstimulation syndrome
Pg	Picogram
PhEur	European pharmacopeia
PK	Pharmacokinetic(s)
Pmol	Picomole
PN	Pronucleus
PT	Preferred term
r hFSH	Recombinant human follicle stimulating hormone
s.c.	Subcutaneous
SD	Standard deviation
SEC	Size exclusion chromatography step
SmPC	Summary of product characteristics
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TEADR	Treatment-emergent adverse drug reaction
$t_{1/2}$	Half-life
Tmax	Time at which Cmax occurred

V_{z_obs}

Volume of distribution

ZIP

Zero-inflated Poisson

1. Background information on the procedure

1.1. Submission of the dossier

The applicant, Teva Pharma B.V., submitted on 28 February 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ovaleap, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2011.

The applicant applied for the following indication:

In adult women

- *Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomifene citrate.*
- *Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra fallopian transfer.*
- *Ovaleap in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/l.*

In adult men

- *Ovaleap is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.*

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible

similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice on 25 June 2009 (EMA/CHMP/SAWP/357275/2009) from the CHMP. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Merckle Biotec GmbH
Dornierstraße 10
D-89079 Ulm
Germany

Manufacturers responsible for batch release

Merckle Biotec GmbH
Dornierstraße 10
D-89079 Ulm
Germany

Teva Pharmaceuticals Europe B.V.
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff

Co-Rapporteur: János Borvendég

- The application was received by the EMA on 28 February 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 June 2012.
- During the meeting on 19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to

the applicant on 25 July 2012.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 20 February 2013.
- During the CHMP meeting on 21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 June 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 03 July 2013 and 19 July 2013.
- On 31 July 2013, the CHMP, in the light of the overall data submitted issued a positive opinion for granting a Marketing Authorisation to Ovaleap.

2. Scientific discussion

2.1. Introduction

Follicle stimulating hormone (FSH) is a gonadotropic hormone produced by the anterior lobe of the mammalian pituitary gland. It is indispensable for normal female and male gamete growth and maturation, and normal gonadal steroid production. Deficient endogenous production of FSH is a known cause of infertility and administration of exogenous gonadotropins is used to treat this condition. Naturally derived FSH, manufactured from the urine of post-menopausal women, has been available for over 30 years. The availability of recombinant DNA technology allows the manufacture of FSH independently of the collection of large volumes of urine and provides a highly pure product devoid of infectious or pharmacological contaminants such as luteinising hormone (LH), proteinacious or potentially allergenic materials.

About the product

Ovaleap is presented as a sterile, clear solution for subcutaneous injection. The concentration of the formulation is 600 IU follitropin alfa (equivalent to 44 µg). The solution contains mannitol, L-methionine and polysorbate 20 as stabilisers, benzyl alcohol and benzalkonium chloride as preservatives and sodium phosphate buffer for adjustment of pH 7.0.

The Applicant claims Ovaleap to be a biosimilar medicinal product to Gonal-f, 75 IU (5.5 micrograms), powder and solvent for solution for injection, for which Merck Serono Europe Ltd., United Kingdom is Marketing Authorisation Holder since 20 October 1995. The active substance of Ovaleap is recombinant human follicle stimulating hormone (rhFSH). Throughout the dossier and in this AR the code name XM17 has been used for the r-hFSH used for the production of Ovaleap.

There are currently two recombinant human follicle stimulating hormone (rhFSH) preparations marketed in Europe; Gonal-f, which contains follitropin alfa as active substance (EMA, 1995), and

Puregon, which contains follitropin beta as active substance (EMA, 1996). The amino acid sequence of follitropins alfa and beta are indistinguishable both from each other and from human FSH (hFSH) derived from urine; follitropin alfa and beta differ in their glycosylation patterns.

XM17 is an rhFSH which has been developed as a biosimilar medicinal product with Gonal-f as reference product. It is expressed in genetically modified Chinese hamster ovary (CHO) cells and produced through a large-scale cell culture process. The rhFSH is a heterodimeric glycoprotein hormone weighing approximately 22,690 Da, the sum of the non-covalently bound alfa (10,205 Da) and beta (12,485 Da) subunits. The alfa subunit (92 amino acids) is common to the other gonadotropins, LH and human chorionic gonadotropin (hCG), whilst the beta subunit (111 amino acids) confers specificity. The Applicant claims XM17 and Gonal-f have a high degree of similarity in terms of glycosylation profile.

Currently approved recFSH

The currently approved recombinant follicle stimulating hormones (FSH) in Europe are:

- Gonal-f (EU/1/95/001/001-035, MAH: Serono Europe Ltd.), the reference product in this biosimilar application.

Three pre-filled multidose preparations are available: 300 IU/0.5 ml (EU/1/95/001/033), 450 IU/0.75 ml (EU/1/95/001/034) and 900 IU/1.5 ml (EU/1/95/001/035).

- Puregon (EU/1/96/008/001-041, MAH: N.V. Organon). Puregon has the same indications as Gonal-f, except for the following indication "*stimulation of follicular development in women with severe LH and FSH deficiency in association with a luteinising hormone (LH) preparation*", which is only approved for Gonal-f.

Background on mechanism of action FSH within the Assisted Reproduction Techniques (ART)

Secretion of gonadotropins (LH and FSH) is controlled by GnRH (gonadotropin releasing hormone) produced in the hypothalamus.

FSH, like LH, is synthesized and secreted by the anterior pituitary gland. It is a heterodimeric glycoprotein consisting of two non-covalently bound subunits; alfa and beta. All glycopeptides (FSH, LH, TSH, and hCG) share a common α -chain, an identical structure containing 92 amino acids. It has two N-glycosylation sites. The β -subunit, which is specific for r-hFSH, consists of 111 amino acids, and has also two N-glycosylation sites. Due to extensive post-translational glycosylation the hormone exists in a variety of isoforms.

FSH is essential for normal female gamete growth and maturation, and induction of normal gonadal steroid production. In the first protocols used in ART (standard "long" protocol), a GnRH agonist was used to suppress the hypothalamic-pituitary ovarian axis (pituitary down regulation) for controlled ovarian stimulation and additionally to prevent a premature LH surge. When desensibilisation has been achieved, controlled (= exogenous) ovarian stimulation with gonadotropins (FSH alone or FSH + LH) is started, while the use of the GnRH agonist is continued until the time when hCG will be administered. HCG is administered for final follicular maturation and triggering of ovulation after confirmation of adequate follicular development.

Another option to achieve desensibilisation is the use of a GnRH antagonist. In contrast to the long-acting GnRH-agonists which after an initial stimulation (flare-up effect), inhibit pituitary gonadotropin secretion by desensitizing gonadotrophins to GnRH via receptor down-regulation, the antagonists block GnRH receptor in a dose-dependent competitive fashion and have no flare effect¹; gonadotropin suppression is almost immediate.

FSH is available as recombinant peptide produced by cultured cells (Gonal-f, Puregon). FSH derived from human menopausal urine is also available on the European market in combination with LH (hMG = human menopausal gonadotropin (e.g. Menopur)), or in purified forms derived from human menopausal urine. These different formulations are equally effective in achieving pregnancy^{2,3}.

2.2. Quality aspects

2.2.1. Introduction

The active substance in Ovaleap, referred to as XM17, is a recombinant human follicle stimulating hormone (rhFSH) claimed to be biosimilar to the reference product Gonal-f (follitropin alfa) authorised in the EU (EMA/H/C/71).

FSH is a glycoprotein hormone that is produced in the anterior lobe of the pituitary gland. FSH is indispensable for normal female and male gamete growth and maturation and normal gonadal steroid production. Deficient endogenous production of FSH is a known cause of infertility and administration of exogenous gonadotropins is used to treat this condition.

FSH is a glycoprotein consisting of two non-covalently bound subunits:

- The alfa chain is common to other heterodimeric glycoprotein hormones (FSH, luteinising hormone (LH), thyroid stimulating hormone and chorionic gonadotropin). It has 92 amino acids with 10 cysteine residues resulting in five disulfide bridges. It has two N-glycosylation sites (Asn 52 and Asn 78) and contains three methionine residues.
- The beta chain, which is specific for FSH, consists of 111 amino acids with 12 cysteine residues resulting in six disulfide bridges. It also has two N-glycosylation sites (Asn 7 and Asn 24) and contains one methionine residue.

2.2.2. Active Substance

Manufacture

The active substance is manufactured at Merckle Biotec GmbH, Dornierstrasse 10, D-89079 Ulm, Germany.

¹ Matikainen T, Ding YQ, Vergara M et al. Differing responses of plasma bioactive and immunoreactive follicle-stimulating hormone and luteinizing hormone to gonadotropin-releasing hormone antagonist and agonist treatments in postmenopausal women. *J Clin Endocrinol Metab* 1992; 75:820.

² Nugent D, Vandekerckhove P, Hughes E, et al. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2000; (4):CD000410.

³ Bayram N, van Wely M, van Der Veen F. Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2001; (2):CD002121.

XM17 is being expressed in a CHO derived cell line after adaptation to serum free conditions. A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed and maintained in accordance with current Good Manufacturing Practices (cGMP) and ICH guidelines. An extensive range of tests was performed for their characterisation, in accordance with ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Manufacturing process

The manufacturing process XM17 active substance incorporates the maintenance of recombinant CHO cells in serum free cell culture media. The CHO cells secrete the active substance into the medium.

The process includes the following main steps:

- Thawing of cells and expansion in flasks;
- Main culture in bioreactor;
- Harvest with filtration;
- Purification with a series of chromatography, viral inactivation and filtration and ultrafiltration/diafiltration steps.

Process validation

The process validation program was conducted at commercial scale and was supplemented by a set of small scale validation studies. Acceptance criteria applied during process validation were based on data obtained during XM17 development. The refined and proposed acceptance criteria for the control of the validated and final manufacturing process were presented.

Manufacturing process development

Several changes were introduced during development, including changes to the fermentation and purification process and site transfers. A comparability exercise was performed to support these changes.

Characterisation

1. Elucidation of structure and other characteristics:

1.1. Physicochemical characterisation:

XM17 active substance was extensively characterised using orthogonal state-of-the-art methods. The parameters determined included molecular mass, N-terminal sequencing, peptide mapping, secondary structure, isoform distribution and extensive glycosylation analysis. Some of the methods are also in use as routine batch release tests.

The majority of glycans exhibited by XM17 are sialylated, with relatively high amounts of di-, tri- and tetra-sialylated glycans, a smaller amount of monosialylated glycans and lower amounts of the other studied forms of sialylated glycans. Glycans with Neu5Gc were detected in XM17.

1.2. Biological characterisation:

Potency was established with the Ph. Eur. *in vivo* rat bioassay (routine control method) and with an *in vitro* cell-based receptor binding assay (only for characterisation).

2. Variants and impurities:

Product-related impurities include non-monomeric rhFSH (aggregates and multimers), truncated forms, oxidised forms, and deamidated species.

The main potential process-related impurities include residual host cell proteins (HCP), residual DNA, insulin and isopropanol.

Specification

The proposed release and stability specifications for XM17 comprise test attributes for appearance (visual inspection), pH (Ph. Eur.), identity, glycosylation and isoform analysis, content, potency, purity, specified impurities and bioburden, (Ph. Eur.), endotoxins (Ph. Eur.).

The current specifications, including the acceptance limits, are considered as justified and acceptable.

Stability

The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance with current guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.

The stability data provided were within the specifications and support a shelf life for the active substance of 24 months when stored at less than -70°C.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The active substance is formulated with sodium dihydrogen phosphate dihydrate, sodium hydroxide, mannitol, L-methionine, polysorbate 20, benzyl alcohol, benzalkonium chloride and water for injections. These excipients are commonly used for biopharmaceutical preparations. The Ovaleap formulation is based on the reference product Gonal-f and another FSH-containing product Puregon (EMA/H/C/86).

Ovaleap is presented as a solution for injection in a cartridge with the following dosage forms (600 IU follitropin alfa per mL): 300 IU/0.5 mL, 450 IU/0.75 mL and 900 IU/1.5 mL. One pack of Ovaleap contains 1 cartridge and 10 or 20 injection needles. It should be administered by subcutaneous injection with a re-usable CE-marked pen provided separately.

The container closure system consists of an uncoloured 1.5 mL Type 1 glass cartridge, a bromobutyl stopper, an aluminium crimp caps with rubber liner (bromobutyl rubber on product side).

Adventitious agents

Non-viral adventitious agents:

Tests of raw materials of non-animal origin including excipients

Except the cell banks, all raw materials and excipients used in the production process are of non-animal source. The serum-free cell culture medium contains no animal-derived components and is manufactured using non-animal derived materials only. The medium includes recombinant human insulin produced in an animal component-free process.

Raw materials, solutions and buffers and excipients are tested for endotoxins.

In addition, testing for bioburden (bacteria, fungi) is performed on the purified water, water for injections, phosphate buffered saline solution, buffers and solutions used for the chromatography step up to and including the final virus filtration, and all excipients.

The cell culture medium is tested for sterility according to Ph. Eur.

Tests of raw materials of animal origin

The MCB and WCB are the only animal-derived materials employed in the manufacturing process. Raw materials of biological origin were employed during the development of the cell lines or the generation of cell banks only. There are no concerns regarding TSE in relation to the use of these raw materials.

Tallow derivatives

The supplier for the raw materials of the stopper formulation uses tallow derivatives during manufacture. They are manufactured from tallow by rigorous processes as stated in the Note for Guidance EMA/410/01, as revised and do not present a quantifiable BSE risk.

Testing of microbial contamination

MCB and WCB are tested for microorganisms (bacteria, fungi, yeasts) according to Ph. Eur. and by examination using transmission electron microscopy. Mycoplasma tests were performed according to Ph. Eur. Both cell banks were found to be free from any contaminants.

In-process controls during production

Appropriate testing is conducted to ensure that the cell cultures do not show signs of microbial contamination. All concentrates are tested for bioburden.

In relation to the finished product manufacturing process, integrity of the filters is confirmed. Environmental monitoring is conducted throughout the process.

Viral adventitious agents:

Three complementary approaches are used to control the potential viral contamination of the product:

Testing of cell banks and other raw materials of biological origin

Extensive tests for viral contamination were performed on the MCB in accordance with ICH Q5A. No viral contamination was detected.

No evidence for viral contamination was found in the two post-production cell banks.

Viral testing of unprocessed bulk

The unprocessed harvest is tested for viral adventitious agents using a 14-day *in vitro* assay. No viral contamination was detected.

Viral clearance studies

Two of the downstream manufacturing steps were specifically designed for virus reduction and a third step was also validated for viral reduction capacity. Viral reduction studies in validated down-scaled models were performed, using adequate model viruses.

Manufacture of the product

The manufacturing process includes the following steps:

- Preparation of the stock solutions and buffers;
- Mixing of appropriate volumes;
- Filtration and aseptic filling into glass cartridges;
- Visual inspection;
- Labelling, blistering and packaging.

Product specification

The batch release specifications for the medicinal product are based on results from batch consistency testing and are considered acceptable. Appropriate tests (including tests for identity, purity, content, pharmaceutical tests and microbiological tests) and limits are in place.

Stability of the product

Real-time and accelerated stability studies were initiated in accordance to ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of finished product. On the basis of the data provided, the approvable shelf life for the finished product is two years at 2-8°C, with the additional option of storage at room temperature (not above 25°C) for up to three months. The in-use shelf life is 28 days at 25°C.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to EMA.

Comparability Exercise for Finished Medicinal Product

A comprehensive and state-of-the-art comparability exercise with the reference medicinal product Gonal-f was performed to demonstrate biosimilarity. The programme covered:

- Molecular mass;
- Primary structure;
- Secondary structure;
- Isoform distribution;
- Glycosylation profile (including composition of N-linked glycans, sialic acid content, site-specific glycosylation analysis);

- Multimers and aggregates;
- Truncated forms;
- Oxidised forms;
- Deamidated forms;
- Biological activity (*in vivo* rat bioassay and *in vitro* cell-based receptor binding assay)

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

Manufacture

The process is well described. The CHO host cell line, the construction and characterisation of the expression plasmid and the transfection, clonal selection and isolation of the production cell line, followed by the final generation and storage of MCB and WCB are well described. Characterisation and stability data of both MCB and WCB are sufficient after supplementary data were provided in response to the Day 120 and Day 180 questions.

The monitoring of manufacturing steps was sufficiently described. The operating and critical ranges of the in-process parameters and tests were derived from data collected during the development of the upstream and downstream process, data collected in down-scaled validation studies (in particular with regard to purification capacity of a number of impurities in relation to load, column life-time studies and viral reduction validation) and data from the manufacture at commercial scale of three validation batches and several transfer and conformance batches. Critical in-process controls (IPCs) are clearly defined and deemed acceptable.

Process validation/evaluation is considered satisfactory.

Characterisation

XM17 active substance was extensively characterised using orthogonal state-of-the-art methods. Since most characterisation studies included comparison to the reference product, dependent on the techniques, studies were done with active substance as manufactured with the commercial scale upstream and downstream process, active substance isolated from finished product, finished product or active substance formulated as the reference product Gonal-f.

The molecular mass of XM17 was confirmed. Comparative results were shown for XM17 active substance reference standard and XM17 finished product.

Identity of rhFSH was confirmed by immunoblotting. Mass spectrometry of the native separated alfa- and beta-subunits of XM17 finished product and active substance confirmed the molecular masses of the two subunits.

The primary structure was studied for all manufactured XM17 active substance batches with N-terminal sequencing and peptide mapping. Results of sequencing of the N-terminal amino acids by means of Edman degradation and peptide mapping confirmed the sequences predicted on the basis of literature. In addition, peptide mapping results were shown as part of the comparative studies with the reference product. The two glycosylation sites on each subunit were confirmed

by the detection of the expected decrease of 1 Da in mass due to deglycosylation of the respective glycosylated peptides.

Results of secondary structure analyses of XM17 showed high homogeneity for different XM17 batches and were comparable with results from literature.

Analysis of isoform distribution supported batch-to-batch consistency within different active substance batches and to active substance extracted from finished product.

The distribution was similar for XM17 extracted from finished product and active substance batches, indicating batch-to-batch consistency with regard to charged species.

N-linked glycan distribution in XM17 was determined using intact heterodimeric rhFSH, as well as the alpha and beta subunits. The distribution of the native (sialylated) as well as the neutral (desialylated) oligosaccharides was determined by means of HPAEC-PAD. Based on the results, the total sialic acid content, the ratio Neu5Gc/Neu5Ac, and the antennarity index (AI) were determined both for XM17 and Gonal-f.

Glycans with N-glycolyl neuraminic acid (Neu5Gc) were detected in XM17 at both glycosylation sites studied for both subunits, which was considered as a Major Objection at Day 120: for XM17, actual batch analysis results of total sialic acid are higher compared to values measured for Gonal-f and to values reported for Puregon.

A small shift in sialylation was observed, compared to Gonal-f.

Reference is made to guideline EMEA/CHMP/BWP/49348/2005, where it is stated:

"It is not expected that the quality attributes in the similar biological and reference medicinal products will be identical. For example, minor structural differences in the active substance, such as variability in post-translational modifications may be acceptable, however, must be justified. Likewise, differences between the impurity profiles of the similar biological medicinal product and the reference medicinal product should be justified and would be considered on a case-by-case basis, and supported by the comparability exercise for quality attributes in relation to safety and efficacy.

Therefore, differences in impurity profiles and significant differences in product related substances may have consequences with regard to the amount of non-clinical and clinical data which may be required in order to make satisfactory justification of the safety and efficacy of the similar biological medicinal product".

Based on this guidance, the presence of the higher amount of Neu5Gc in XM17 active substance had to be justified with appropriate non-clinical and clinical data and biosimilarity had to be justified based on quality, pre-clinical and clinical data. The applicant provided additional comparative data confirming the already identified difference with the reference product as described above. From a quality perspective, this difference is acceptable and is sufficiently justified by non-clinical and clinical data.

Impurities

All relevant (product- and process-related) impurities have been studied in the characterisation studies. In general, impurities were undetectable or occurred at low concentrations.

Aggregates were characterised using suitable methods. It was considered at Day 120 that characterisation and comparability studies should be extended with an orthogonal method for (non-covalent) aggregates, for example analytical ultracentrifugation (AUC). This method should also be used to assess specificity and accuracy/trueness. The requested data were submitted; these data did not give rise to specific comments or concerns.

Potency was established with the Ph. Eur. *in vivo* rat bioassay (routine control method) and with an *in vitro* cell-based receptor binding assay (only for characterisation). A question was asked concerning the validation of the *in vitro* method. The justification provided, including reference to the validation report, was considered sufficient.

Viral safety

Two of the downstream manufacturing steps were specifically designed for virus reduction and a third step was also validated for viral reduction capacity. Viral reduction studies in validated down-scaled models were performed, showing sufficient viral reduction capacity.

Specifications

The specifications, method descriptions and summary validation data gave rise to a number of points for clarification. Most of these were appropriately resolved. In addition, submitted responses on out-of-specification results in the finished product stability studies raised severe doubts on the performance of the bioassay (see also below).

A global discussion on the specifications and choice of tests was requested. The specifications (including deviations from the draft Ph. Eur. monograph 2286 Follitropin Concentrated Solution) were deemed sufficiently justified, with the remark that the applicant performs additional characterisation on deamidation. For the time being, the limits were deemed acceptable, given the limited number of batches.

Reference Standards

An in-house primary reference standard was qualified.

The applicant made a commitment to appropriately qualify and characterise each new reference standard to be released and provided an acceptable analytical characterisation program for the qualification of future in-house primary reference standards.

Container closure system

The container closure system of the active substance was sufficiently described.

Stability

A stability study of three commercial active substance batches was initiated. Results up to 24 months storage at less than -70°C showed no changes. The applicant proposed an extension of the study up to the 36 month time point. This was considered acceptable.

Accelerated and stress conditions were studied up to 6 months.

The claimed shelf life of 24 months was deemed sufficiently justified by the data provided.

Finished product

Formulation development

Formulation development was extensively described and discussed in the dossier, and a formulation development report was submitted as part of this description. The excipients are standard for biopharmaceutical preparations; the formulation is based on the reference product Gonal-f and another FSH-containing product (Puregon).

Benzylchloride was demonstrated to be a suitable preservative (no degradation of active substance), and that the combination of benzylchloride with benzalkonium is as effective as higher content of benzylchloride alone, while this combination is considered to have a better safety profile. These arguments are deemed acceptable from a quality viewpoint.

The control of excipients was sufficiently described and justified.

Manufacture

The batch size and batch formula were described.

An updated flow diagram was provided, unequivocally visualising the manufacturing process. Critical IPCs are defined, and upon request, a list of Critical Process Parameters was provided. These are sufficiently covered by the validation data and are deemed acceptable. The validation strategy is deemed acceptable.

The applicant was requested to justify its approach to base filling on activity (IU) instead of mass. Filling based on mass would normally be preferred, because it is more precise due to the high purity of the active substance. This issue was raised as a Major Objection. The applicant was requested to change to filling based on mass, with a fixed (target) protein content together with a label claim based either on mass or on a nominal activity claim in IU".

In response to the Day 180 issue, the applicant implemented the requested change from activity-based to mass-based filling. The applicant has chosen to implement a label claim in IU. Based on comparative studies with Gonal-f the applicant will indicate the concentration as being 600 IU/mL, which is equivalent to 44 µg/mL. An appropriate specification of nominal (target) protein content is set. The label claim is in line with the reference product Gonal-f label claim and the Ph.Eur, draft monograph Follitropin Concentrated Solution.

Once the final Ph.Eur. monograph will become available, the applicant will consider the testing of the product accordingly and amend if necessary.

In relation to this issue, in view of the 3R principles for animal testing and lack of precision of the bioassay, the applicant now performs the bioassay only at active substance release and key time points of stability studies.

The applicant was also requested to remove from the dossier one of the facilities responsible for the determination of biological activity.

Specifications

The final finished product specifications submitted by the applicant are considered acceptable.

Container closure system

The container closure system was sufficiently described.

Stability

The applicant claims a shelf life of two years, when stored at 2-8°C, with the additional option of storage at room temperature (not above 25°C) for up to three months. In addition, an in-use stability of 28 days at room temperature (not above 25°C) is claimed.

The stability protocol was sufficiently justified and stability-indicating parameters are appropriately identified.

In addition, supporting data from a limited number of batches is available.

The applicant claims an in-use period of 28 days at 25°C. This claim is acceptable.

Comparability with the reference medicinal product

Characterisation analyses for XM17 have been conducted in parallel with the reference medicinal product, Gonal-f, and have confirmed that structure, conformation, impurity profile and potency are comparable with those of follitropin alfa/Gonal-f. Results are summarised below.

Determination of molecular mass, of the integral protein and the individual subunits showed that electropherograms obtained for XM17 active substance are qualitatively comparable with those of Gonal-f; and spectra and mass calculations for representative XM17 active substance batches are comparable with those of Gonal-f batches analysed.

Peptide mapping demonstrated that molecular masses of peptide fragments were comparable between XM17 active substance and Gonal-f. In addition, sequence identity to the expected published sequence of follitropin alfa was confirmed further by N-terminal sequencing of XM17 active substance.

The secondary structure of follitropin alfa sourced from XM17 and Gonal-f was shown to be highly comparable.

The nature of the complex carbohydrate structure of follitropin alfa was analysed quantitatively on the integral protein and on the isolated oligoglycans. The analyses showed that XM17 and Gonal-f have similar isoform pattern and antennarity. Small differences were seen in sialylation patterns.

The potency of follitropin alfa was determined by a pharmacopoeial method, which measures the dose-dependent enlargement of ovaries in immature rats upon administration of rhFSH. Binding of rhFSH to its cognate receptor using a responsive cell line allows side-by-side analysis of XM17 and Gonal-f *in vitro*. The results showed that the biological activity of XM17 and Gonal-f were similar *in vitro* and comparable to the *in vivo* bioassay.

In comparative analysis of finished products, XM17 and Gonal-f underwent a similar magnitude of methionine oxidation. With regard to deamidation, comparative analysis showed no deamidation of either XM17 or Gonal-f.

The differences in Neu5Gc and small shift in sialylation compared to Gonal-f (see above) were adequately described and justified and are considered acceptable.

Overall, the data presented indicate that XM17 appears to be highly similar to Gonal-f.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Ovaleap is considered to be in line with the quality of other approved recombinant DNA products. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

Biosimilarity with the reference medicinal product Gonal-f has been sufficiently demonstrated. From a quality point of view, the observed differences and levels of these differences have been well documented and are acceptable.

The overall quality of Ovaleap is considered acceptable.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Structure of the active substance

XM17 drug substance (XM17) is a recombinant human follicle stimulating hormone (r-hFSH), expressed in genetically modified Chinese Hamster Ovary (CHO) cells.

Follicle stimulating hormone (FSH) is a heterodimeric glycoprotein hormone weighing 22,690 Da, the sum of two non-covalently bound subunits, alfa (10,205 Da) and beta (12,485 Da). The alfa chain (common to other heterodimeric glycoprotein hormones) has 92 amino acids with 10 cysteine residues resulting in five disulfide bridges. It has two N-glycosylation sites (Asn 52 and Asn 78) and contains three methionine residues. The beta chain, which is specific for r-hFSH,

consists of 111 amino acids with 12 cysteine residues resulting in six disulfide bridges. It also has two N-glycosylation sites (Asn 7 and Asn 24) and contains one methionine residue. r-hFSH in total has four N-glycosylation sites (two glycosylation sites for each subunit); there are no O-glycosylation sites.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

Determination of the biological activity of XM17 (drug product and drug substance) and Gonal-f in a cell-based receptor binding assay

The activity of batches of XM17 (drug product and drug substance) and Gonal-f was determined in a cell based receptor binding assay reliant on the response of a CHO cell line which constitutively expresses the human FSH receptor and which had been transfected with a cAMP responsive element. The activity of this responsive element regulates the transcription of a luciferase reporter gene and the resultant luciferase activity is determined photometrically. The potency of the different batches was determined in reference to batches of Gonal-f of known and defined potency.

In vivo studies

Determination of the activity of XM17 (drug product and drug substance) and Gonal-f in the rat ovary weight gain assay

The activities of batches of XM17 (drug substance and drug product) and Gonal-f were determined in the rat ovary weight gain assay (Steelman-Pohley assay) as described in the European Pharmacopoeia. The assay relies on the administration of three daily subcutaneous injections of reference and test FSH preparations, in combination with a fixed dose of chorionic gonadotrophin, to immature female rats. The animals are sacrificed 24 hours after the last administration and the ovaries excised and weighed. Fixed doses of reference and test FSH preparations were used and the potency of the test preparation relative to that of the reference agent was determined by parallel line assay based on the mean of the absolute weights of the combined ovaries for each treatment group. The assay was conducted with either the NIBSC standard 92/642 or the internal reference standard as reference material. Initial studies of XM17 drug substance were tested in comparison to the NIBSC standard. The in-house internal reference standard was established by testing in comparison to the NIBSC standard in a series of 7 individual assays and was subsequently used for testing of later batches of XM17 drug substance. XM17 drug product and Gonal-f were initially tested in comparison to the NIBSC standard with later tests using the internal reference standard. Across a series of 7 individual assays, the mean specific activity was determined. This method is routinely used to determine the relative potency of batches of XM17 drug substance and also for XM17 drug product.

In addition to the data of the internal reference standard, data from several batches of XM17 drug substance are included in this report, together with results for XM17 drug product and Gonal-f.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted with XM17 by the applicant. The pharmacological profile of hFSH is well known and it is considered unnecessary to investigate any secondary pharmacodynamic effects of XM17.

Safety pharmacology programme

Safety pharmacology studies with XM17 have investigated potential effects on three body systems – CNS, cardiovascular and respiratory.

Central nervous system (CNS)

Effects on the CNS were investigated through a modified Irwin behavioural screen conducted as an integral part of the single dose toxicity study. Groups of 5 male and 5 female rats received vehicle or XM17, 5000 IU/kg subcutaneously with a further 5 animals/sex being dosed intraperitoneally with caffeine, 30 mg/kg, acting as positive controls for the Irwin test. There was no observable neurobehavioural effect of XM17, whereas caffeine exerted the expected effects and thus confirmed the sensitivity of the test system.

Cardiovascular system (CV)

Effects on the CV system were investigated in telemetered conscious female Beagle dogs dosed subcutaneously with vehicle or 10, 50 or 100 IU/kg of XM17 according to an escalating design with a minimum washout period of 48 hours between control and low dose and a minimum of 7 days between low and mid doses and between mid and high doses. Treatment with XM17 had no effect on arterial blood pressure, heart rate or ECG. Analysis of circulating XM17 following the 100 IU/kg dose showed mean serum levels of 11.8, 14.3 and 11.3 ng/mL at 1, 16 and 24 hours after dosing, respectively: these values are comparable to those observed at the same dose level in the toxicity study, and considerably higher than the C_{max} of 9.184 IU/L (corresponding to approximately 0.6 ng/mL) observed in women after a single subcutaneous injection of 300 IU of XM17.

Respiratory system

The effect on respiratory parameters was monitored in female Wistar rats by whole body plethysmography: animals were dosed subcutaneously with vehicle or 10, 100 or 1000 IU/kg of XM17 with a further group acting as positive control (receiving 1 mg/kg of carbamylcholine chloride subcutaneously). XM17 did not induce any relevant changes in respiratory parameters (respiratory rate, peak inspiratory and expiratory flows, inspiration and expiration times, airway resistance index, tidal volume and minute volume). Under the same conditions, carbamylcholine chloride exerted the expected bronchoconstriction. Direct monitoring of serum levels of XM17 was not included in this study, but data from the first day of dosing in the 14-day toxicity study in female Wistar rats show the dose of 1000 IU/kg to give a C_{max} of 86.5 ng/mL.

Taken together, the safety pharmacology studies show XM17 to be devoid of effects on the central nervous, cardiovascular and respiratory systems at doses, and exposures, far in excess of those used or achieved clinically.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were conducted with XM17. Recombinant hFSH has been available clinically for a number of years and possible interactions based on its pharmacological activity are well recognised and reflected in the Summaries of Product Characteristics (SmPC) for the reference medicinal product, Gonal-f and for the other existing r-hFSH product Puregon (Merck-Serono, 1995; Organon, 1996). Thus, concomitant use of other products used to stimulate ovulation (for example hCG or clomiphene citrate) may potentiate the follicular response, whereas pituitary desensitisation through administration of a GnRH agonist or antagonist may increase the dose of XM17 needed to obtain an adequate ovarian response.

2.3.3. Pharmacokinetics

Non-clinical studies were performed to characterise the pharmacokinetics (PK) of XM17 in animals in comparison to the reference product, Gonal-f. Pharmacokinetics of Ovaleap and Gonal-f were compared in a rat study where both males and females were administered a subcutaneous dose of 10, 70 or 500 IU/kg/day for 7 days. The pharmacokinetic profile of both products as expressed by C_{max}, AUC, t_{1/2}, CL and V_z was similar.

Additional toxicokinetic data obtained in the 28-day repeated-dose toxicology study in rats generally supported comparability of both products, but measurements were too limited to base firm conclusions upon. Lower FSH levels at the end of the study in high dose animals treated with XM17 as compared to Gonal-f treated animals are possibly related to the higher anti-FSH antibody titers in the XM17-treated animals. Other toxicokinetic data obtained in 14-day repeated dose toxicology studies with XM17 in rats and dogs are not relevant for a comparability exercise.

Table 7: Descriptive statistics of primary and secondary pharmacokinetic parameters of XM17 and Gonal-f, pre-dose corrected

PK parameter [unit]	Statistics	XM17	Gonal-f®
AUC _{0-t} [IU*h/L]	n	36	36
	Mean (SD)	632.0 (167.1)	619.2 (191.1)
	Geom. mean	605.3	589.0
	Median	647.5	598.5
	Min – max	175-902	261 - 1131
C _{max} [IU/L]	n	36	36
	Mean (SD)	9.184 (2.421)	9.040 (2.487)
	Geom. mean	8.846	8.699
	Median	9.067	8.811
	Min – max	3.42 - 13.99	4.42 - 14.44
AUC _{0-168h} [IU*h/L]	n	36	36
	Mean (SD)	632.3 (167.0)	620.3 (189.8)
	Geom. mean	605.7	590.7
	Median	650.5	598.5
	Min – max	176 - 902	264 - 1131
AUC _{0-∞} [IU*h/L]	N _{calc}	15	15
	Mean (SD)	665.6 (179.4)	620.3 (208.6)
	Geom. mean	641.2	583.6
	Median	647.4	622.9
	Min – max	333 - 940	268 - 979
t _{max} [h]	N _{calc}	36	36
	Mean (SD)	19.78 (8.36)	19.72 (7.92)
	Geom. mean	NA	NA
	Median	16.00	16.00
	Min – max	10.0 - 48.0	10.0 - 36.0
t _{1/2} [h]	N _{calc}	15	15
	Mean (SD)	32.795 (11.124)	33.734 (10.235)
	Geom. mean	30.320	31.765
	Median	34.427	36.499
	Min – max	9.41 - 51.54	10.45 - 48.38
CL/f [mL/min]	N _{calc}	15	15
	Mean (SD)	8.130 (2.584)	9.203 (3.908)
	Geom. mean	7.798	8.568
	Median	7.723	8.027
	Min – max	5.32 - 15.02	5.11 - 18.66
Footnotes see next page			

Methods of analysis

Method of analysis for hFSH

Assays of serum levels of circulating hFSH in all studies were using a validated ELISA method developed for analysis of hFSH in rat, dog and human.

Method of analysis for ADA (anti-drug antibodies)

Anti-hFSH antibodies in rat and dog serum were also assayed by ELISA using a validated assay. The validation was extended to include the assay of samples from Gonal-f treated rats in the comparative 28-day repeat dose toxicity study.

Absorption

Comparative data on the pharmacokinetics of XM17 and Gonal-f are primarily available from the 7-day repeat dose study in rats which was conducted with this specific aim, but supplementary information is also available from the 28-day comparative toxicity study in rats.

The data from the 7-day comparative PK study in male and female rats show XM17 and Gonal-f to have very similar pharmacokinetic behaviour. Data from the 28-day comparative toxicity study in male and female rats also show comparative values for XM17 and Gonal-f.

Distribution

No specific distribution studies have been conducted with XM17. The data generated during the comparative 7-day pharmacokinetic study in male and female rats showed similar profiles for XM17 and Gonal-f, the reference product. The parameters determined included the volume of distribution which was similar for the two products. Given the absence of any indication of differences in pharmacokinetic behaviour between XM17 and Gonal-f, it is considered acceptable not to have conducted specific distribution studies with XM17.

Metabolism

No specific metabolism studies have been conducted with XM17. The metabolism of XM17 would be expected to follow that of endogenous proteins. The data generated during the comparative 7-day pharmacokinetic study in male and female rats showed similar profiles for XM17 and Gonal-f, the reference product. Given the absence of any indication of differences in pharmacokinetic behaviour between XM17 and Gonal-f and in view of the known degradation pathways of endogenous proteins, it is considered acceptable not to have conducted specific metabolism studies with XM17.

Excretion

No specific excretion studies have been conducted with XM17. The data generated during the comparative 7-day pharmacokinetic study in male and female rats showed similar profiles for XM17 and Gonal-f, the reference product. The parameters determined included clearance which was similar for the two products. Given the absence of any indication of differences in pharmacokinetic behaviour between XM17 and Gonal-f, it is considered acceptable not to have conducted specific clearance studies with XM17.

Pharmacokinetic drug interactions

No specific interaction studies have been conducted with XM17. The data generated during the comparative 7-day pharmacokinetic study in male and female rats showed similar profiles for XM17 and Gonal-f, the reference product. The only recognised interactions are pharmacodynamic rather than pharmacokinetic and this is appropriately reflected in the product SmPC. Given the

absence of any indication of differences in pharmacokinetic behaviour between XM17 and Gonal-f, and the recognised absence of pharmacokinetic interactions with Gonal-f, it is considered acceptable not to have conducted specific interaction studies with XM17.

2.3.4. Toxicology

Single dose toxicity

A single dose toxicity study was performed in rats using with 5000 IU/kg XM17. No effects were observed, including measurements of weights of spleen, thymus, ovaries and brain when animals were necropsied after 14 days.

Repeat-dose toxicity

The repeat-dose toxicity programme for XM17 consisted of three studies – two 2-week studies in female rats and dogs with XM17 alone and a 28-day study in male and female rats comparing the effects of XM17 with those of the reference product, Gonal-f. All studies included a recovery period for control and high-dose animals after the end of treatment. Sampling for toxicokinetics was included in all studies, with assay of serum samples for circulating FSH and anti-rhFSH antibodies by ELISA.

The most notable effects seen in rats and dogs repeat-dose toxicity studies were changes in the ovaries. In rats, ovary weights increased in a dose-related manner, starting at the lowest dose (10 IU/kg/day). Also, the ovaries were enlarged and the number of follicular cysts increased. In dogs, ovary weights were only significantly increased at 50 IU/kg/day while the number of multilocular follicular cysts increased in a dose-related manner starting from 50 IU/kg/day. Furthermore, in dogs, the uterus was enlarged from this dose and at doses above and the incidence of oestrous uterus showed an increase at all doses tested. These observations obviously reflect the pharmacological activity of rFSH in these animals.

In rats, body weights were slightly increased in females from 100 IU/kg/day and food consumption was transiently increased. Other effects seen in rats were slight changes in protein, albumin, glucose and haematological parameters, decreases in total bilirubin and increase in liver weight. Except for the decrease in bilirubin these effects were absent at the end of the recovery periods and are not considered to be of toxicological relevance.

In both rats and dogs, a dose-related increase in the incidence and titer of anti-rhFSH antibodies was observed.

Only the 4-week study in rats was designed in a way that may contribute to the comparability exercise, as in this study XM17 and Gonal-f were tested in a comparative way. Mostly, effects observed with XM17 and Gonal-f were qualitatively similar. Slight quantitative differences, including slight differences in incidence of cysts in the ovaries and corpora lutea hyperplasia were considered incidental.

Ovaries weights increased dose-dependently and comparably in rats treated with XM17 or Gonal-f. In the 4-week comparative repeated-dose toxicity study in rats a high incidence of local reactions at the injection site was observed, mainly chronic inflammation and haemorrhages.

Although these data are not fully consistent with the conclusion that local tolerance is good, it should be considered that an inflammatory response to a human recombinant protein in animals is not predictive for a response in humans and that clinically, local tolerance was acceptable and comparable.

Genotoxicity Carcinogenicity and Reproductive toxicity

Studies on genotoxicity and carcinogenicity have not been performed, which has been sufficiently justified by the Applicant. This is in accordance with both the ICH S6 guideline on the development of biotechnology-derived pharmaceuticals (Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals; CPMP/ICH/302/95) and the CHMP guideline on the development of biosimilar products (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005).

Studies on Reproductive Toxicity have not been performed, both for the well-known mechanism of action of FSH and in accordance with the CHMP guideline on the development of biosimilar products (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005).

Local tolerance

Subsequently, the local tolerance of XM17 in a concentration of 600 IU/ml was tested in comparison to 0.9% saline in 6 female New Zealand White rabbits after a single paravenous, subcutaneous and intramuscular administration of a volume of 0.5 ml (paravenous, resulting in 300 IU/animal) or 0.75 ml (subcutaneous and intramuscular, resulting in 450 IU/animal).

Paravenous, subcutaneous and intramuscular administration of the test item caused slightly increased erythema and edema formation within 72 h when compared to the administration of saline. No drug-related macroscopic and histological findings were observed.

Based on these results of this study it is concluded that a single administration of XM17 (600 IU/ml) in a dose of 450 IU/animal is well tolerated in female NZW rabbits after subcutaneous injection. Furthermore, it is concluded that all irritations seen after single paravenous and intramuscular administration of XM17 (600 IU/ml) are within a tolerable range.

Toxicokinetic data

Toxicokinetic data are available from a 28-day comparative toxicity study in the rat. Specific PK studies with XM17 alone have not been conducted but toxicokinetic data are available, on the first and last days of dosing, from 14-day repeat dose toxicity studies in the rat and dog.

Other toxicity studies

No other studies were performed.

2.3.5. Ecotoxicity/environmental risk assessment

XM17 is a recombinant glycoprotein without linkers or any other modifications and has the same structure and activity as endogenous FSH. FSH is a pituitary hormone that controls the reproductive system in both males and females.

Given the characteristics above, the performance of specific studies for Environmental Risk Assessment was not requested as proteins are biodegradable in the environment.

Therefore, XM17 is not expected to pose a risk to the environment.

2.3.6. Discussion on the non-clinical aspects

For a biosimilar recombinant FSH the most relevant property both in terms of efficacy and safety (in relation to the propensity to cause OHSS) is comparable biological activity. Receptor affinity studies showed comparable binding of Gonal-f and Ovaleap to the human FSH receptor. K_D values were 0.334 and 0.344 nM for Gonal-f and Ovaleap, respectively. In a cell-based assay employing human FSH-receptor expressing CHO cells, both products showed comparable biological activity. The Applicant provided the results from the Steelman-Pohley assay, a pharmacopoeial assay in rats covering both PD and PK aspects. However this assay is known to show high inter-animal variability and has therefore its limitations for a comparability exercise.

Safety pharmacology studies show XM17 to be devoid of effects on the central nervous, cardiovascular and respiratory systems.

A short-term study in rats showed comparable pharmacokinetic behaviour of both products. Additional comparative data obtained in the 28-day repeated dose toxicology study also supports the pharmacokinetic comparability, although high dose serum concentrations on day 14 and day 28 for males and on day 28 for females were higher for Gonal-f than for Ovaleap.

The most notable effects seen in rats and dogs repeat-dose toxicity studies were changes in the ovaries. These observations obviously reflect the pharmacological activity of rFSH in these animals.

Limited toxicokinetic data in a 28-day comparative toxicology study in rats suggest some differences in serum FSH levels at the end of this study. Lower FSH levels at the end of the study in some high dose or mid-dose animals treated with XM17 or high dose Gonal-f treated animals are possibly related to the higher anti-FSH antibody titers, which may be the cause for lower ovary weights at the end of treatment in these animals. However, overall the correlation between FSH levels anti-FSH titers and pharmacodynamic outcome was poor. Possibly, slight differences in quality attributes affected immunogenicity in rats. However, this finding does not reveal which differences are responsible for an apparent difference in immunogenic potential in rats. As XM17 and Gonal-f are recombinant human proteins, an immunogenic response in animals is expected and is not considered predictive of a human response. Therefore these observed differences in animals are not considered relevant for the evaluation of comparability of Ovaleap and Gonal-f in humans.

2.3.1. Conclusion on the non-clinical aspects

From a non-clinical point of view Ovaleap and Gonal-f are considered biosimilar.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

The clinical development program consists of 2 Phase I studies in healthy subjects and a Phase III study in infertile ovulatory women undergoing ART (Table 1).

Table 8 Clinical development programme for XM17						
Study No.	Phase	Subject/ Patient type	XM17	Comparator (Gonal-f)	Treatment duration	No. treated
XM17-01	I	Healthy	37.5, 75, 150, 300 IU	–	Single dose	40
XM17-02	I	Healthy	300 IU	300 IU	Single dose	36
XM17-05	III	Infertile ovulatory women undergoing ART	Fixed dose phase: 150 IU/day Dose adaptation phase: adjustment in steps / multiples of 37.5 IU (maximum 450 IU/day)	Fixed dose phase: 150 IU/day Dose adaptation phase: adjustment in steps / multiples of 37.5 IU (maximum 450 IU/day)	Fixed dose phase: 5 days Dose adaptation phase: up to 15 days	299
Follow- up Part B	III	Infertile ovulatory women undergoing ART, not pregnant in Main Study	Individual starting dose Dose adaptation: adjustment in steps / multiples of 37.5 IU (maximum 450 IU/day)		Up to 20 days per cycle for up to 2 treatment cycles	155 enrolled (77 in interim analysis)

The Phase III study was conducted in 5 countries: Belgium, Czech Republic, Germany, Hungary and Poland.

The Phase III study XM17-05 is the pivotal study in this submission.

- Follow-up Part A: Women who became pregnant in the main study were followed up until they gave birth.
- Follow-up Part B: Women who did not become pregnant in the main study could receive Ovaleap as the follicle stimulating drug for up to 2 additional cycles.

At the time of preparation of this marketing authorization application, there were no other ongoing clinical studies with Ovaleap.

2.4.2. Pharmacokinetics

Follicle stimulating hormone (FSH) is a heterodimeric glycoprotein hormone. Recombinant human follicle stimulating hormones (r-hFSH) have the same amino acid sequence as the natural human FSH but may differ in their glycosylation patterns. It has been shown that the pharmacokinetic (PK) characteristics of r-hFSH in humans are similar to those of urinary FSH.

The XM17 is being developed as a “*similar biological medicinal product*” according to Article 10 (4) and Annex 1, Part II, Chapter 4 of Directive 2001/83/EC as amended. The XM17 Drug Substance is developed to be similar to follitropin alfa (r-hFSH), the active substance used in Gonal-f. Therefore Gonal-f has been used as the reference medicinal product in analyses to support the claim of biosimilarity throughout development of XM17.

The XM17 Drug Substance (r-hFSH) is expressed from genetically modified Chinese Hamster Ovary (CHO) cells.

The XM17 is supplied as pre-filled cartridges at strength of 600 IU/mL, at three different presentations: 0.5 mL (300 IU), 0.75 mL (450 IU) and 1.5 mL (900 IU). The medicinal product is supplied as a solution for subcutaneous injection, which is administered using a re-usable CE-certified pen (not part of the medicinal product).

The dosage regimen of XM17 is dependent on the indication. In general the actual regimens are adapted depending on the response of individual patients:

In adult women

- Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate. A commonly used regimen commences at 75-150 IU of hFSH per day increased preferably by 37.5 or 75 IU at 7 or 14 day intervals until an adequate response is obtained. The maximum daily dose is usually not higher than 225 IU. If no adequate response is achieved after 4 weeks of treatment the cycle should be abandoned and another cycle with a different starting dose should be performed.
- Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies such as *in vitro* fertilization, gamete intra-fallopian transfer and zygote intra-fallopian transfer. The recommended regimen is 150-225 IU daily, commencing on day 2 or 3 of the cycle and continuing until

adequate follicular development is achieved, with the dose adjusted according to the response but usually not higher than 450 IU daily. In general adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days).

- XM17 in association with a luteinising hormone preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. The recommended regimen is 75-150 IU daily increasing as necessary by 37.5-75 IU increments at 7-14 day intervals. In each cycle the treatment can be extended up to 5 weeks.

In adult men

- XM17 is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin therapy. The recommended regimen is 150 IU three times a week for a minimum of 4 months; experience indicated that treatment for 18 months may be necessary.

The clinical development programme for XM17 consists of 2 studies comprising pharmacokinetics in young healthy female volunteers. One study was a First-in-Man Phase I study (XM17-01), the other was a phase I study comparing XM17 and Gonal-f (XM17-02), see table below.

Table 9 Studies including pharmacokinetics for XM17						
Study No.	Phase	Subject/ Patient type	XM17	Comparator (Gonal-f)	Treatment duration	No. treated
XM17-01	I	Healthy	37.5, 75, 150, 300 IU	–	Single dose	40
XM17-02	I	Healthy	300 IU	300 IU	Single dose	36

Absorption

Bioavailability

Absorption of XM17 was slow as indicated by t_{max} values ranging from 10 to 168 hours and a median t_{max} of 24 hours in the 3 higher dose groups (study XM17-01, 75 IU, 150 IU, and 300 IU). The higher median t_{max} value of 156 hours in the lowest dose group (37.5 IU reflects the secondary increase in serum concentrations after 36 hours post-dose.

Bioequivalence

In all clinical trials the final commercial formulation of XM17 was investigated, supplied in the Phase I trials in vials and in the Phase III trial in cartridges, which were inserted in a CE-marked pen for administration. The drug substance used in the first Phase I study (XM17-01) was manufactured on a pilot scale, whereas the XM17 Drug Substance used for both comparative studies was manufactured on a commercial scale (Merckle Biotec).

Study XM17-02 was a 2-way cross-over bioequivalence study with single s.c. doses of 300 IU of XM17 and Gonal-f in healthy female subjects with suppression of endogenous FSH production by a gonadotropin-releasing hormone (GnRH) agonist.

The pre-dose corrected mean concentration–time curves for FSH after administration of a single 300 IU dose of XM17 or Gonal-f to 36 healthy women were similar; mean values in terms of IU/L were almost identical.

Distribution

XM17 has shown the biosimilarity to Gonal-f, it is accepted that the plasma protein binding characteristics of the two products are comparable. Therefore, studies on plasma protein binding were not deemed necessary.

Elimination

XM17 has shown the biosimilarity to Gonal-f, therefore, additional studies to assess this issue were not deemed necessary.

Dose proportionality and time dependencies

Dose proportionality was assessed in study XM17-01 using single doses of 37.5 IU, 75 IU, 150 IU, and 300 IU of XM17 sc. The lowest dose of 37.5 IU was administered to 4 subjects; the 3 higher doses were administered to 12 subjects each. The mean serum concentration-time profiles of XM17 after single s.c. injections of the 3 higher doses of 75, 150, and 300 IU XM17 (12 subjects per dose group) showed dose-related peak values that occurred within 24 hours post-dose. This peak was followed by approximately mono-exponential decay up to 120 hours post-dose.

The mean concentration-time profile after single s.c. injections of 37.5 IU XM17 (4 subjects) also showed a primary peak within 24 hours post-dose, but from 36 hours post-dose onwards there was a secondary increase up to mean concentrations that were similar to those observed after 300 IU at 168 hours post-dose. Steady increases in XM17 concentrations after 36 hours post-dose were observed in 3 of the 4 subjects.

Geometric mean $t_{1/2}$ in the 3 higher dose groups ranged from approximately 54 to 90 hours (medians 63 to 77 hours) without a clear relationship to the XM17 dose. There were also no apparently dose-related differences in the subjects' geometric mean or median CL/f and V_z/f values.

Pharmacokinetics in target population

Specific studies to investigate pharmacokinetics in patients have not been performed. The PK studies XM17-01 and XM17-02 provide PK data in healthy female subjects. As the patients treated with XM17 are mainly healthy young women with fertility disorders only, the PK data generated in these two studies can also be regarded as relevant for the patients.

Special populations

Impaired hepatic/renal function

Not applicable.

Studies specifically designed to investigate the hepatic metabolism or potential drug interaction of XM17 have not been conducted nor have such standard studies been reported with the reference drug Gonal-f. As XM17 is biosimilar to Gonal-f the data available for Gonal-f will apply. Therefore drug-drug-interaction studies were not deemed necessary. This is in accordance with the recent draft guidance on similar biological medicinal products containing r hFSH (EMA/CHMP/BMWP/671292/2010).

Race/Weight

Not applicable.

Studies specifically designed to investigate the effects of intrinsic factors on the PK of XM17 have not been conducted. The XM17 showed bioequivalence to Gonal-f in the PK-study XM17-02.

Elderly/Children

The patients to be treated with XM17 will not be elderly or children, thus the influence of age is regarded not relevant.

Gender

As XM17 will mainly be used in women, the PK was investigated only in this group. The PK in men has been evaluated with Gonal-f. Single dose PK of Gonal-f was determined following subcutaneous administration of 225 IU Gonal-f to 12 healthy adult male volunteers. Steady state PK were also determined in 6 healthy adult male volunteers who were administered a single daily dose of 225 IU Gonal-f for 7 days. No significant difference in PK is expected in males versus females when Gonal-f is administered subcutaneously.

Pharmacokinetic interaction studies

Studies specifically designed to investigate the effects of extrinsic factors on the PK of XM17 have not been conducted. As XM17 is being developed as a similar biological medicinal product to Gonal-f, such studies were not necessary.

2.4.3. Pharmacodynamics

Primary and Secondary pharmacology

No separate pharmacodynamic study was conducted. The pharmacodynamic parameters were taken into account in one Phase III trial XM17-05 comparing Ovaleap with Gonal-f in patients undergoing controlled ovarian stimulation. The measured serum levels were: FSH, oestradiol, Luteinising Hormone (LH) and progesterone. In public literature, FSH administration has been reported to increase plasma concentrations of FSH, oestradiol and inhibin-B, but without

significant changes in the LH plasma concentrations⁴. Both oestradiol and inhibin-B are reported to correlate with the number of follicles seen on ovarian ultrasound^{5,6}.

In addition, other pharmacodynamic parameters taken into account were 'total r-hFSH dose', 'number of days of r-hFSH stimulation' and 'number and size of follicles' these are closely linked to the primary endpoint of the Phase III trial 'number of oocytes retrieved'.

In trial XM17-05 pituitary down-regulation was achieved with the gonadotropin-releasing hormone (GnRH) agonist Metrelef (buserelin acetate) nasal spray approved in Germany. The patient received a fixed subcutaneous dose of 150 IU of rFSH (either Gonal-f or Ovaleap) once daily for 5 days. The subcutaneous rFSH dose could be reduced or increased from Stimulation Day 6 on to achieve adequate follicular development. Following confirmation of adequate follicular development (≥ 3 follicles with 17 mm, oestradiol < 5500 pg/mL), hCG was to be administered for final follicular maturation and triggering of ovulation.

Based on LH and FSH levels, adequate down-regulation was achieved in both groups. The progesterone concentrations differed slightly on the day of hCG administration with a slightly higher concentration in the Ovaleap group (median 1.015 ng/mL versus 0.920 ng/mL).

Also, a small difference in oestradiol concentrations was noted at Stimulation Day 6, i.e. after the end of the fixed-dose treatment of five days. The concentration in the Ovaleap group was slightly higher (median 350.3 pg/mL for Gonal-f versus 479.6 pg/mL for Ovaleap). However, this difference was less apparent at the end of the treatment period on the day of hCG administration (median 2176.5 pg/mL for Gonal-f versus 2242.5 pg/mL for Ovaleap).

Phase III study (XM17-05)

Design

Women aged 18-37 years undergoing controlled ovarian stimulation (COS) were randomized to daily injections of Gonal-f (n=146) or Ovaleap (n=153). Pituitary down-regulation was achieved with the gonadotropin-releasing hormone (GnRH) agonist Metrelef (buserelin acetate) nasal spray, approved in Germany. The patient received a fixed subcutaneous dose of 150 IU of rFSH (either Gonal-f or Ovaleap) once daily for 5 days. The subcutaneous rFSH dose could be reduced or increased from Stimulation Day 6 on to achieve adequate follicular development. Following confirmation of adequate follicular development (≥ 3 follicles with 17 mm, oestradiol < 5500 pg/mL), hCG (Ovitrelle) was to be administered for final follicular maturation and triggering of ovulation.

The following serum concentrations were determined:

- FSH: at study enrolment, at start of r-FSH treatment (Stimulation Day 1);

⁴ Buckler HM, Healy DL, Burger HG. Purified FSH stimulates production of inhibin by the human ovary. *J Endocrinol* 1989; 122:279-85.

⁵ Buckler HM, Healy DL, Burger HG. Purified FSH stimulates production of inhibin by the human ovary. *J Endocrinol* 1989; 122:279-85.

⁶ Eldar-Geva T, Margalioth EJ, Ben-Chetrit A et al. Serum inhibin B levels measured early during FSH administration for IVF may be of value in predicting the number of oocytes to be retrieved in normal and low responders. *Hum Reprod* 2002; 17:2331-7.

- Oestradiol: at study enrolment, at start of r-FSH treatment (Stimulation Day 1), end of fixed dose Phase (Stimulation Day 6), on the day of hCG administration;
- LH: at start of r-FSH treatment;
- Progesterone: on the day of hCG administration;

Results

- **FSH:** Treatment with Metrelef resulted in adequate down-regulation in both groups. Between the enrolment visit and the start of the fixed-dose treatment, the median FSH concentration decreased from 6.9 to 4.6 IU/L in the Gonal-f group and from 6.9 to 4.8 IU/L in the XM17 group.
- **Oestradiol:** Between the enrolment visit and the start of the fixed-dose treatment with r-hFSH median oestradiol concentrations decreased in both groups as a result of down-regulation with the GnRH agonist Metrelef (from 47.7 to 27.1 pg/mL in the Gonal-f group and from 45.1 to 25.9 pg/mL in the XM17 group). A serum concentration of < 50 pg/mL was required for successful down-regulation. The baseline values at the start of r-hFSH treatment were comparable in both treatment groups.

At the end of treatment with the fixed r-hFSH dose on Stimulation Day 6, median concentrations had increased to 350.3 and 479.6 pg/mL, respectively. Concentrations increased further during the r-hFSH dose adaptation period, reaching 2176.5 pg/mL in the Gonal-f group and 2242.5 pg/mL in the XM17 group at the day of hCG administration. The change between baseline and end of study was slightly higher in the XM17 group than the Gonal-f group (2216.2 vs. 2008.7 pg/mL); this difference was not statistically significant.

- **LH:** Results at the start of r-FSH treatment confirmed adequate down-regulation (median concentration 3.0 IU/L in the Gonal-f group and 2.8 IU/L in the XM17 group).
- **Progesterone:** On the day of hCG administration, the progesterone concentration in the Gonal-f group was slightly lower than in the XM17 group: median 0.920 vs. 1.015 ng/mL, mean \pm SD 1.013 \pm 0.619 vs. 1.132 \pm 0.812 ng/mL.

2.4.4. Discussion on clinical pharmacology

Clinical pharmacokinetic (PK) information is available from the two single-centre, phase I, open-label clinical studies in 76 healthy female subjects (40 subjects in study XM17-01 and 36 subjects in XM17-02). The dose-proportionality of XM17 was investigated in Study XM17-01. In this study single ascending doses of XM17 (37.5 to 300 IU) were administered to healthy volunteers after suppression of endogenous FSH production by a gonadotropin-releasing hormone (GnRH) agonist.

The bioequivalence of XM17 was investigated in a cross-over study (Study XM17-02). In this study 300 IU of XM17 and Gonal-f were administered to healthy female subjects. Endogenous FSH production was suppressed again by a gonadotropin-releasing hormone (GnRH) agonist.

Study XM17-01 showed that absorption of XM17 is relatively slow. The median t_{max} was of 24 hours in the three higher dose groups. Unexpectedly, the mean concentration-time profile after single s. c. injections of 37.5 IU XM17 (4 subjects) also showed a primary peak within 24 hours post-dose, but from 36 hours post-dose onwards there was a secondary increase up to mean concentrations that were similar to those observed after 300 IU at 168 hours post-dose. Steady increases in XM17 concentrations after 36 hours post-dose were observed in 3 of the 4 subjects.

Study XM17-02 convincingly demonstrated that there is no statistically or clinically relevant difference between pre-dose corrected mean serum concentration-time profiles of FSH after single s. c. injections of 300 IU XM17 or Gonal-f.

No separate pharmacodynamic study was performed. The pharmacodynamic parameters were taken into account in the Phase III trial XM17-05 comparing Ovaleap with Gonal-f in patients undergoing controlled ovarian stimulation. Investigating the PD parameters as part of the phase III trial is in line with the 'Draft guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-FSH; EMA/CHMP/BMWP/671292/2010)'.

The measurement of serum levels of FSH, oestradiol, LH and Progesterone is considered adequate for supporting comparable pharmacodynamics properties of Ovaleap and Gonal-f. In the draft guideline EMA/CHMP/BMWP/671292/2010 also inhibin-B is indicated as one of the pharmacodynamics parameters that should be taken into account. Inhibin-B, as well as oestradiol, correlate with the number of follicles seen on ovarian ultrasound. As sufficient other pharmacodynamic parameters were measured (oestradiol levels, FSH levels, number and size of follicles), the lack of inhibin-B levels is not considered an issue.

Based on LH and FSH levels, adequate down-regulation was achieved in both groups.

Based on the oestradiol concentrations, Ovaleap is considered slightly more potent than Gonal-f, as shown in the initial fixed dose period of 6 days. However, the difference is considered small, and at the end of the treatment period on the day of hCG administration, this difference was less apparent. Further, there is large variation between the treated patients in oestradiol levels.

2.4.5. Conclusions on clinical pharmacology

The serum levels of FSH, oestradiol, LH and Progesterone are considered adequate for supporting comparable pharmacodynamic properties of Ovaleap and Gonal-f.

2.5. Clinical efficacy

Proof of clinical efficiency was based on one phase III study XM17-05 to support efficacy and safety.

2.5.1. Main study(ies)

Objectives

The primary objective was to demonstrate the equivalence of Ovaleap compared to Gonal-f with respect to the primary efficacy endpoint of the 'number of oocytes retrieved' in infertile but ovulatory women undergoing superovulation for ART.

Study participants

Inclusion criteria

- infertile female patients of any racial origin undergoing superovulation for ART;
- aged 18-37 years (inclusive) at the time of enrolment;
- BMI between 18-29 kg/m² inclusive;
- regular menstrual cycle length: 21-35 days and presumed to be ovulatory;

Exclusion criteria

- more than 2 previously completed consecutive unsuccessful IVF cycles (i.e. completed cycle = oocyte retrieval);
- primary ovarian failure or women known as poor responders;
- more than 3 miscarriages;
- history of a severe OHSS;
- malformations of sexual organs incompatible with pregnancy;
- ovarian enlargement or cysts of more than 2 cm;
- history of coagulation disorders;
- Patients fulfilling any of the following exclusion criteria at Visit 3 could not be randomised to study treatment:
 - Serum oestradiol \geq 50 pg/mL (approximately 200 pmol/L, local laboratory)
 - Ovarian cysts > 10 mm (verified by ultrasound)
 - Positive pregnancy test (β -hCG test)

Treatments

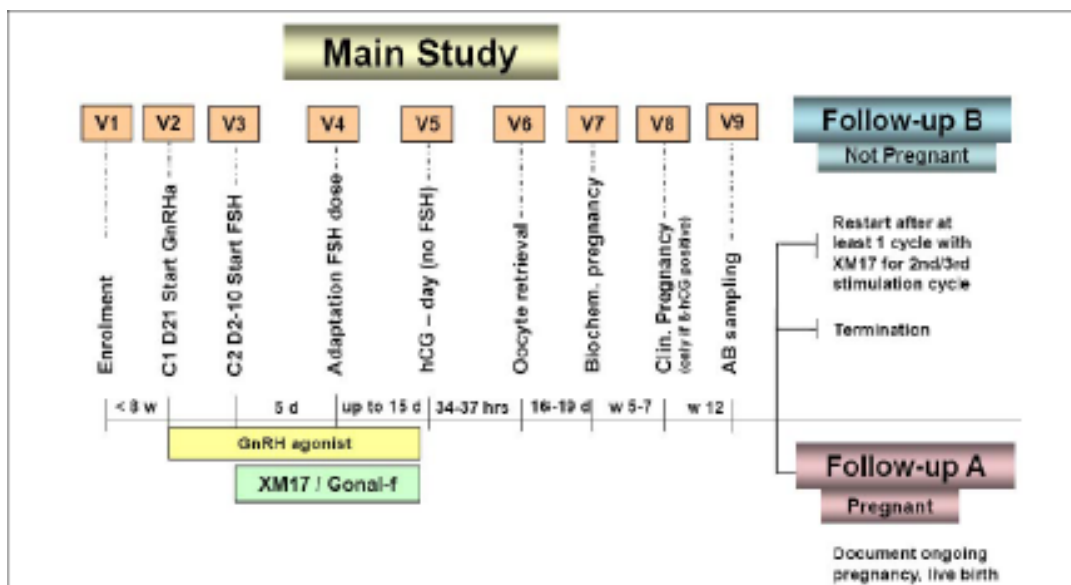
Patient eligibility was assessed at the enrolment visit. In eligible patients, pituitary down-regulation was to be started with the gonadotropin-releasing hormone (GnRH) agonist Metrelef (buserelin acetate) at about Day 21 of the patient cycle. The GnRH agonist Metrelef is marketed by Ferrring Arzneimittel GmbH in Germany and is intended for nasal use. Dosing had to be performed according to the package leaflet. The initial daily dose was 4 puffs (equal to 0.6 mg buserelin) distributed over the day. Due to inadequate suppression, doses of up to 8 puffs (equal to 1.2 mg buserelin) distributed over the day were allowed. The patient received a fixed subcutaneous dose of 150 IU of rFSH once daily for 5 days. The subcutaneous rFSH dose could be reduced or increased from Stimulation Day 6 on to achieve adequate follicular development. The investigator decided whether this was required based on serum oestradiol levels and ultrasound examinations. Adjustments were to be made no more than every 3 to 5 days in steps of 37.5 IU or multiples of 37.5 IU, but no more than 150 IU at each adjustment. Doses greater than 450 IU/day were not recommended. Due to a risk of OHSS the investigator could decide to withhold rFSH for a defined time period (coasting).

Following confirmation of adequate follicular development (≥ 3 follicles with 17 mm, oestradiol < 5500 pg/mL), hCG (Ovitrelle) was to be administered for final follicular maturation and triggering of ovulation (Visit 5). Luteal phase support was given at the discretion of the investigator and not standardised for all patients. Oocyte retrieval (Visit 6) was to take place 34 to 37 hours after administration of hCG. Biochemical pregnancy (β -hCG test) was to be evaluated at Visit 7 not earlier than 16 days (around 16 to 19 days) after oocyte retrieval and clinical pregnancy (gestational sac with heart activity) at Visit 8 approximately 5 to 7 weeks after oocyte retrieval. A blood sample for antibody testing was to be taken at Visit 9, 3 months after oocyte retrieval. An end of main study Visit for assessment of safety and tolerability was performed as the final visit for patients who terminated the study prematurely after start of XM17/Gonal-f treatment, had a negative pregnancy test at Visit 7, or attended Visit 8.

Rationale for the rFSH dose for the fixed dose phase (Stimulation Day 1 till 5):

The doses were selected based on the ones used for Gonal-F and were in line with common practice for randomised, controlled trials in ART (see figure 3 below).

Figure 3: Overall study schedule



Study endpoints

Primary efficacy endpoint

The primary endpoint is the “number of oocytes retrieved is in accordance with the draft guideline EMA/CHMP/BMWP/671292/2010. This endpoint is considered an adequate endpoint,

as it is strongly influenced by the effect of FSH on the ovaries, and at the same time represents an endpoint of clinical relevance.

Secondary efficacy endpoints

- Total r-hFSH dose (IU)
- Number of days of r-hFSH stimulation
- Number of patients needing dose adaptations of r-hFSH
- Number of oocytes retrieved in patients with no r-hFSH adaptation
- Number of follicles (≤ 10 mm, > 10 to 14 mm, > 14 to 17 mm, > 17 mm) on Stimulation Day 6 prior to dose adaptation
- 17- β oestradiol serum concentration on Stimulation Day 6 prior to dose adaptation
- Endometrial thickness (mm) on Stimulation Day 6 prior to dose adaptation
- Number of follicles > 14 mm on the day of hCG injection
- 17- β oestradiol serum concentration on the day of hCG injection
- Endometrial thickness (mm) on the day of hCG injection
- Cancellation rate prior to oocyte retrieval
- Oocyte maturity (only ICSI)
- Oocyte quality
- Fertilisation rate
- Clinical and ongoing pregnancy rate (per randomized patient, per oocyte retrieval, and per embryo transfer)
- Ectopic pregnancy rate
- Take-home baby rate
- Endocrinological parameters (FSH, LH, E₂, P)

Randomisation

It was done by central remote allocation using an Interactive Voice Response telephone System (IVRS). Randomization was stratified per centre, using blocks of two. The size of the randomisation blocks was not disclosed in the study protocol or to the study centres.

Blinding

A double-blind design was not technically feasible for this study. Ovaleap was provided in cartridges that had to be inserted into a special pen (medical device). Gonal-f was provided as a solution for injection in a pre-filled pen that already contained the cartridge with the medication. As the pen for Gonal-f was patent protected, the Applicant indicated that it was not possible to produce an identical pen for Ovaleap. Blinding of the patient was not possible, because the study medication was self-administered. To maintain the study blind for the investigator, co-investigator, and the embryologist, an appropriately medically qualified, "independent", third party drug administrator (e.g. physician or nurse) was appointed in each centre. The physician treating the patient and performing all assessments was kept blinded and was not involved in any aspects of the study medication. The investigator decided on any dose changes of r-hFSH based on oestradiol levels and ultrasound examinations, and informed the drug administrator to

perform these dose changes. The drug administrator communicated this information to the patient.

Statistical methods

The equivalence margin for the primary endpoint 'number of oocytes' retrieved was -3 and +3 oocytes and is adequately justified. The equivalence margin for Ovaleap [-3, +3] is tighter than has been used in the registered Elonva (modified r-hFSH with a longer half-life) equivalence trial comparing Elonva with r-hFSH (Puregon [-3, +5]). The sample size has a 90% power for rejecting the null hypothesis that Ovaleap is different to Gonal-f with an equivalence margin of -3, +3, which is appropriate.

The ZIP regression analysis model used for the analysis of the primary endpoint in the study specifically takes data with excess zeroes into account. This is important, as overstimulation as well as under stimulation can result in cycle cancellation and a number of zeroes oocytes retrieved. Additionally, four exploratory analyses were performed to check the robustness of the estimated treatment effect:

- 1) ZIP regression model used for main analysis but with interaction terms between treatment and country, between treatment and age.
- 2) Unadjusted ZIP regression model with only treatment as fixed effect.
- 3) Poisson regression model with treatment and country as fixed factors and age as a covariate only for patients with performed oocytes retrieval. This includes patients with performed retrieval but no oocytes retrieved.
- 4) ANCOVA with treatment and country as fixed effects and age as explanatory variable.

Sample size

'Number of oocytes retrieved' was the primary endpoint on which the comparison was based in order to establish *equivalence* versus Gonal-f. The sample size was determined to provide a power of at least 0.9 for rejection of the null hypothesis for the primary efficacy variable at a two-sided level of $\alpha = 0.05$ for the main analysis.

A sample size of 124 patients per group was necessary to have a 90% power for rejecting the null hypothesis that Ovaleap is different to Gonal-f (i.e. the difference in the expected mean number of oocytes is larger than $\Delta = 3$ oocytes) in favour of the alternative hypothesis that Ovaleap is equivalent to Gonal-f, assuming that the expected difference in the expected mean number of oocytes is ≤ 0.5 oocytes and the common SD is 6 oocytes.^{7,8,9}

⁷ Bergh C, Howles CM, Borg K, Hamberger L, Josefsson B, Nilsson L et al. Recombinant human follicle stimulating hormone (r-hFSH; Gonal f) versus highly purified urinary FSH (Metrodin HP): Results of a randomized comparative study in woman undergoing assisted reproductive techniques. *Hum Reprod* 1997; 12(10):2133-9.

⁸ Frydman R, Howles CM, Truong F. A double-blind, randomized study to compare recombinant human follicle stimulating hormone (FSH; Gonal-f) with highly purified urinary FSH (Metrodin HP) in woman undergoing assisted reproductive techniques including intracytoplasmic sperm injection. *Hum Reprod* 2000; 15(3):520-5.

⁹ Lass A, McVeigh E; UK Gonal-f FbM PMS Group. Routine use of r-hFSH follitropin alpha filled-by-mass for follicular development for IVF: a large multicenter observational study in the UK. *Reprod BioMed Online* 2004; 9(6):604-10.

Therefore, 140 patients per treatment group were to be randomised taking into account that about 10% of patients treated with r-hFSH would have major protocol violations.

Results

- **Study XM17-05**

The following table summarises the efficacy results from study XM17-05.

Table 10 Summary of efficacy for main trial XM17-05

Title: Efficacy, safety and tolerability of XM17 compared to Gonal-f in women undergoing assisted reproductive technologies		
Study identifier	XM17-05	
Design	Multi-national, multi-centre, randomized, controlled, assessor-blind, parallel group study including follow-up periods conducted in 5 countries: Belgium, Czech Republic, Germany, Hungary and Poland.	
	Date of first patient enrolled:	19 March 2010
	Date of last patient completed:	27 January 2011
Hypothesis	Equivalence, margin [-3, +3] for primary endpoint	
Treatments groups	Gonal-f	5 days fixed subcutaneous dose of 150 IU. From Day 6 on doses could be increased or decreased. Doses greater than 450 IU were not recommended. Stimulation continued until adequate follicular development (≥ 3 follicles with 17 mm, oestradiol < 5500 pg/mL) was reached, 146 subjects were randomized.
	Ovaleap	The treatment and duration were similar in the Ovaleap group, 153 subjects were randomized.
Endpoints and definitions	Primary endpoint	Number of oocytes retrieved

	Selection of secondary endpoints	<ul style="list-style-type: none"> - Total r-hFSH dose (IU) - Number of days of r-hFSH stimulation - Number of patients needing dose adaptations of r-hFSH - Ongoing pregnancy rate per randomized patient 	
<u>Results and Analysis</u>			
Analysis description	Primary Analysis		
Analysis population and time point description	According-to-protocol population (ATP): all patients of the full analysis set who did not have any major protocol violations.		
Descriptive statistics and estimate variability	Treatment group	Gonal-f	Ovaleap
	Number of subject	145	152
	Primary endpoint: number of oocytes retrieved -- mean	12.0	12.2
	SD	6.8	6.8
	Secondary endpoint: total dose of r-hFSH – mean	1614.3 IU	1535.8 IU
	SD	484.9	495.6
	Secondary endpoint: number of days of r-hFSH stimulation -- mean	9.7	9.3
	SD	1.6	1.8
	Secondary endpoint: number of patients needing dose adaptations of r-hFSH		
- increases	43.2%	35.9%	
- decreases	15.1%	15.0%	

	Secondary endpoint: Ongoing pregnancy rate per randomized patient	33.6% (49/146)	27.5% (42/153)
Effect estimate per comparison	Primary endpoint	GONAL-f	Ovaleap
		ZIP regression model	0.03
		95% confidence interval	-0.76, 0.82
Analysis description	Equivalence is established for the primary endpoint. The 95% confidence interval falls within the pre-specified equivalence margin [-3, +3].		

Participant flow

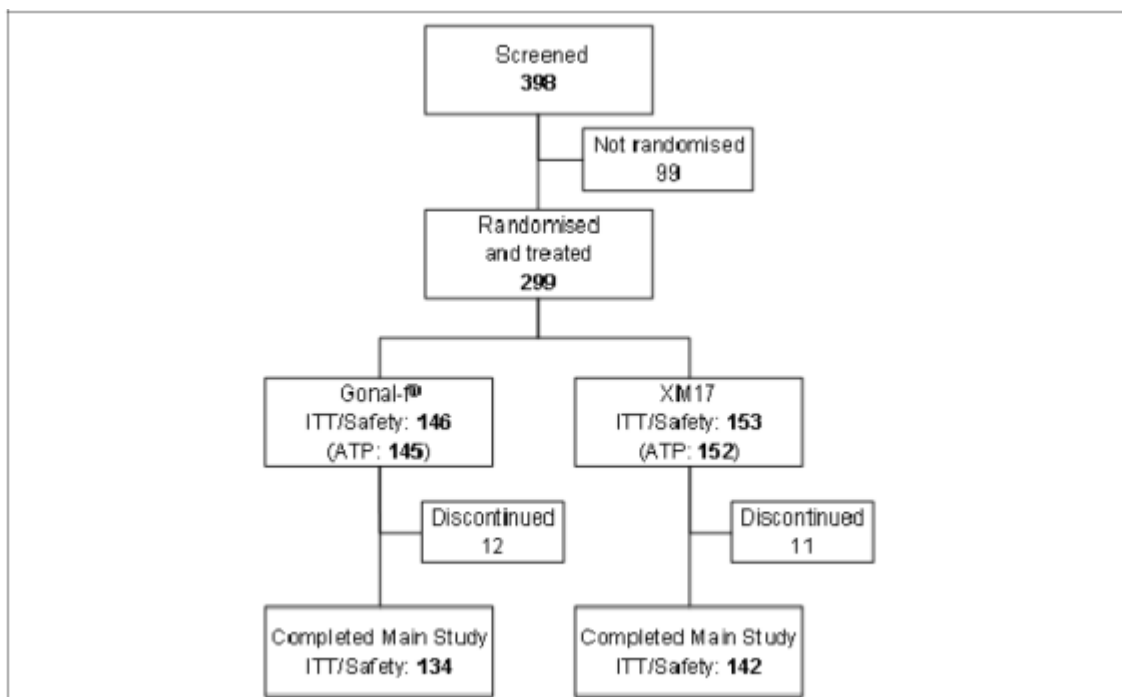
A total of 398 patients were enrolled in the study and screened at 22 centres in 5 countries. After screening 299 patients were randomized: Belgium (3 patients, 1%), Czech Republic (58 patients, 19%), Germany (62 patients, 21%), Hungary (77 patients, 26%) and Poland (99 patients, 33%).

Three analysis populations were identified:

- Full analysis set (intent-to-treat population, ITT): all randomised patients.
- Safety set (safety population, SP): all patients of the full analysis set who received at least one dose of Ovaleap or Gonal-f.
- Per protocol set (according-to-protocol population, ATP): all patients of the full analysis set who did not have any major protocol violations.

For the participant flow see Figure 4 below.

Figure 4 Flow diagram for Main Study



Recruitment

The dates of first and last subject observation were 19 March 2010 and 27 January 2011, respectively.

Conduct of the study

In the case of Follow-up Parts A and B, interim analyses were introduced by protocol amendment No. 1 for the provision of data on the follow-up of pregnant women and patients treated with several cycles of XM17 at the time of marketing authorisation application. These data were requested from the EMA in the Scientific Advice. These analyses are described in separate Statistical Analysis Plans and reports.

Major protocol violations

Occurred in 2 patients (1 in each treatment group) due to dose adaptation of study medication in the fixed dose period. Both patients received 225 IU instead of 150 IU of r-FSH on Stimulation Day 5.

Minor protocol violations

Occurred in 57 (19.1%) patients of the ITT population: 28 (19.2%) Gonal-f patients, 29 (19.0%) Ovaleap patients. The most frequent minor protocol violations were related to the additional exclusion criteria for inadequate down-regulation at Visit 3 (12 Gonal-f patients, 12 Ovaleap patients), inclusion criteria (10 vs. 7 patients) and hCG administration (7 vs. 9 patients).

Baseline data

The overall mean age, body weight and body mass index were 31.6 years, 63.5 kg, and 22.7 kg/m², respectively.

- The mean \pm SD age overall was 31.6 \pm 3.2 years and comparable between the treatment groups. The percentage of women older than 34 years was slightly higher in the Gonal-f group than in the XM17/Ovaleap group (24.0% vs. 16.3%) and the percentage aged between 30 to 34 years was lower (51.4% vs. 60.8%).
- Basal counts of antral follicles \geq 5 mm for the right and left ovaries were similar across the treatment groups.
- Mean total ovarian volume was slightly lower in the Gonal-f group than in the XM17 group (15.5 \pm 11.8 mL vs. 19.0 \pm 50.7 mL) but median values were similar (12.6 vs. 12.0 mL).
- Ethnic origin was Caucasian in all but 2 patients: 1 patient in the Gonal-f group was classified as Hispanic and 1 patient in the XM17 group as Asian.

Demographic characteristics of the ATP population were similar to those of the ITT population (see table 11).

Table 11 Demographic and ovary characteristics (ITT population)

Characteristic	Gonal-f [®] N=146	XM17 N=153	Total N=299
Mean (SD) age, years	31.7 (3.2)	31.6 (3.1)	31.6 (3.2)
Age, n (%)			
< 30 years	36 (24.7)	35 (22.9)	71 (23.7)
30 to 34 years	75 (51.4)	93 (60.8)	168 (56.2)
> 34 years	35 (24.0)	25 (16.3)	60 (20.1)
Mean (SD) weight, kg	63.1 (9.2)	63.8 (10.2)	63.5 (9.7)
Weight, n (%)			
\leq 60 kg	67 (45.9)	66 (43.1)	133 (44.5)
60 to 75 kg	61 (41.8)	62 (40.5)	123 (41.1)
> 75 kg	18 (12.3)	25 (16.3)	43 (14.4)
Mean (SD) BMI, kg/m ²	22.6 (2.9)	22.8 (2.9)	22.7 (2.9)
Smoker, n (%)	19 (13.0)	18 (11.8)	37 (12.4)
Alcohol consumption, n (%)	23 (15.8)	33 (21.6)	56 (18.7)
Mean number (SD) of basal antral follicles \geq 5 mm*	N=145	N=153	N=298
Right ovary	5.2 (4.3)	5.3 (3.4)	5.3 (3.9)
Left ovary	4.8 (4.3)	5.0 (3.2)	4.9 (3.8)
Mean (SD) total ovarian volume, mL	15.5 (11.8)	19.0 (50.7)	17.3 (37.2)
* N valid			
Note: Results for basal antral follicle count and ovarian volume are for the SP which is identical to the ITT population.			

Medical history of infertility

The mean overall duration of infertility before the study was 45.1 ± 27.6 months and 281 (94.0%) of the women had been infertile for over a year. The mean period between diagnosis of fertility and study entry was 23.7 ± 24.4 months. A higher percentage of women in the Gonal-f group than in the XM17 group reported previous pregnancies (34.9% vs. 29.4%) and previous miscarriages (24.0% vs. 14.4%). The proportion of live births was slightly higher in the XM17 group (17.6% vs. 13.7% in the Gonal-f group). The percentage of women that received previous treatment with ICSI + IVF was 41.1% in the Gonal-f group and 37.3% in the Ovaleap group.

Causal factors

The profile of causal factors for infertility was similar in the two treatment groups (see Table 12). Male factor was by far the most common cause (54.5% patients in the ITT population), followed by idiopathic causes (26.8%), tubal factor (18.7%), and endometriosis (6.7%). Other factors were reported as the cause in 16 (5.4%) patients which was unexplained in 12 of these patients; in the 4 remaining patients, the cause was specified as status post extrauterine (tubal) pregnancy (Gonal-f), myoma (Gonal-f), polycystic ovary syndrome (Gonal-f), and cervical factor (XM17).

Table 12 Causal factors for infertility (ITT population)

Cause	Gonal-f [®] N=146		XM17 N=153		Total N=299	
	n	%	n	%	n	%
Male factor	77	52.7	86	56.2	163	54.5
Idiopathic	41	28.1	39	25.5	80	26.8
Tubal factor	30	20.5	26	17.0	56	18.7
Endometriosis	10	6.8	10	6.5	20	6.7
Other factor	10	6.8	6	3.9	16	5.4

Note: "n" denotes number of patients with an occurrence. Multiple mentions per patient are possible.

Numbers analysed

Two patients with major protocol violations were excluded from the ATP population. Efficacy analyses were performed on both the ATP and ITT populations. Results for these two populations are almost identical, as they only differed by 2 patients (297 vs. 299 patients).

In total, 276 (92.3%) of the 299 randomised and treated patients completed the main study: 134 (91.8%) patients in the Gonal-f group and 142 (92.8%) patients in the XM17 group).

The most common primary reasons for discontinuation were no embryo transferred (1 Gonal-f patient vs. 5 XM17 patients), no oocytes fertilised (4 vs. 1 patient), and other reasons (3 vs. 1 patient). In the Gonal-f group, "other" primary reasons for discontinuation were as follows: 1 patient had only 1 follicle and was lost to follow-up, one patient did not undergo embryo transfer in order to prevent OHSS, and one patient did not meet the criteria for hCG administration

between Visits 4 and 5. In the XM17 group, one patient was withdrawn due to risk of OHSS. In 2 patients the primary reason for withdrawal was an AE (OHSS).

Outcomes and estimation

Primary efficacy analysis

For patients without oocyte retrieval a value of "0" was imputed (3 ATP patients, 4 ITT patients). The mean (SD) number of oocytes retrieved in the ATP group was 12.0 (6.8) for the Gonal-f group and 12.2 (6.8) for the XM17 group (Table 13). Values without imputation were almost identical to those with imputation: 12.1 (6.7) and 12.2 (6.8), respectively.

The estimated treatment difference was 0.03 oocytes in favour of XM17, while the 95% confidence interval was [-0.76; 0.82]. This indicates that the two treatment groups were equivalent based on the pre-defined equivalence range of (-3, +3) oocytes. Results for the ITT population were comparable.

The model showed that age and country had a statistically significant effect on the number of oocytes ($p < 0.001$). This was not the case for randomised study treatment ($p = 0.940$).

Table 13 **Number of oocytes retrieved (ATP population)**

Characteristic	Gonal-f [®] N=145	XM17 N=152	Total N=297
Number of oocytes (imputed)			
N valid	145	152	297
Mean (SD)	12.0 (6.8)	12.2 (6.8)	12.1 (6.8)
Median (range)	12 (0 to 44)	11 (0 to 36)	11 (0 to 44)
Number of oocytes (not imputed)			
N valid	143	151	294
Mean (SD)	12.1 (6.7)	12.2 (6.8)	12.2 (6.7)
Median (range)	12 (1 to 44)	11 (1 to 36)	11 (1 to 44)

Sensitivity analyses

Four exploratory analyses were performed to check the robustness of the estimated treatment effect found in the main analysis. See for details the paragraph statistical methods above. All four exploratory analyses satisfied the pre-specified limit of [-3 oocytes, +3 oocytes].

Secondary efficacy analysis

The mean (median) total dose of r-FSH was 1535.8 (1425) in the XM17 group and 1614.3 (1500) IU in the Gonal-f group. The mean (median) number of days of r-FSH stimulation was slightly lower in the XM17 group than in the Gonal-f group: 9.3 (9) days vs. 9.7 (10) days. The majority of patients received r-FSH stimulation for 8 to 11 days: 80.4% in the XM17 group and 82.9% in the Gonal-f group. The proportion of patients requiring dose adaptations was slightly lower in the XM17 group (51.0%) than the Gonal-f group (58.2%). This was due to a lower frequency of dose increases (35.9% vs. 43.2%).

A total of 136 patients completed the study without adaptation of the r-hFSH dose: 61 (42%) in the Gonal-f group and 75 (49%) in the XM17 group. The number of oocytes retrieved in patients with no r-hFSH adaptation was similar between the treatment groups, 12.5 and 11.9, respectively. The number of follicles (≤ 10 mm, > 10 to 14 mm, > 14 to 17 mm, > 17 mm) on Stimulation Day 6 (Visit 4) prior to dose adaptation and at the end of r-FSH treatment (Visit 5) was evaluated. At Visit 4, the frequency of patients with follicles > 14 mm was higher in the XM17 group than in the Gonal-f group (27% vs. 14%); frequencies at the end of treatment after dose adaptation were comparable (93% vs. 94%).

The serum oestradiol levels on Stimulation Day 6 prior to dose adaptation were very variable and the mean concentration was higher in the XM17 group than in the Gonal-f group (650.2 vs. 516.3 pg/mL). Endometrial thickness (mm) on Stimulation Day 6 prior to dose adaptation was comparable in both groups: 8.0 for Gonal-f and 8.2 for XM17. The number of follicles > 14 mm on the day of hCG injection was comparable in both treatment groups (10.5 in the Gonal-f group and 10.8 in the XM17 group) as well as serum oestradiol levels on the day of hCG injection (2598.5 pg/mL for Gonal-F and 2744.3 for XM17) and endometrial thickness (mm) on the day of hCG injection was similar in both treatment groups (10.9 mm).

The majority of the patients (77.9%) underwent ICSI procedures: 74.7% of patients in the Gonal-f group and 81.0% in the XM17 group. 14.0% of the patients underwent IVF procedures and 6.4% underwent both ICSI and IVF. The profiles of oocyte maturity (in subjects with ICSI only) in the two treatment groups were very similar. The highest count was observed for metaphase II oocytes which are preferably used for these fertilisation procedures: 8.4 ± 4.6 in the Gonal-f group and 8.4 ± 4.2 in the XM17 group. The overall clinical pregnancy rate for patients with embryo transfer is in line with results for Gonal-f shown in clinical trials using a GnRH agonist for down-regulation as reported in literature, varying from 23% to 39%).^{10,11,12,13,14}

Follow-up Part B of the main study XM17-05

The objective of Follow-up part B was to assess the non-immunogenicity and safety of Ovaleap. In Follow-up Part B, all patients received the test drug Ovaleap for stimulation (up to 2 ART

¹⁰ Frydman R, Howles CM, Truong F. A double-blind, randomized study to compare recombinant human follicle stimulating hormone (FSH; Gonal-f) with highly purified urinary FSH (Metrodin HP) in woman undergoing assisted reproductive techniques including intracytoplasmic sperm injection. *Hum Reprod* 2000; 15(3):520-5.

¹¹ Andersen AN, Devroey P, Arce JC. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor blind controlled trial. *Hum Reprod* 2006; 21(12):3217-27.

¹² European and Israeli Study Group on highly purified menotropin versus recombinant follicle-stimulating hormone. Efficacy and safety of highly purified menotropin versus recombinant follicle-stimulating hormone in in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized, comparative trial. *Fertil Steril* 2002; 78(3):520-8.

¹³ Schats R, De Sutter P, Bassli S, Kremer JAM, Tournaye H, Donnez J. Ovarian stimulation during assisted reproduction treatment: a comparison of recombinant and highly purified urinary human FSH. *Hum Reprod* 2000; 15(8):1691-7.

¹⁴ Westergaard LG, Erb K, Laursen SB, Rex S, Rasmussen P. Human menopausal gonadotropin versus recombinant follicle-stimulating hormone in normogonadotropic women downregulated with a gonadotropin-releasing hormone agonist who were undergoing in vitro fertilization and intracytoplasmic sperm injection: a prospective randomized study. *Fertil Steril* 2001; 76(3):543-9.

cycles), whereby the doses were chosen by the investigator. The drug for pituitary down-regulation, the hCG for ovulation induction, and any luteal support were selected by the investigator. The numbers of patients enrolled in Follow-up Part B are 155 women.

Interim analysis

The Applicant has submitted an interim analysis of Follow-up Part B (data cut-off 4 July 2011). This interim analysis includes 77 patients (38 treated with Gonal-f in the Main study, 39 treated with Ovaleap). All of the 77 patients were treated in cycle 2 and 20 of these patients were treated in cycle 3. The demographic characteristics for the patients in Follow-up Part B were comparable between the groups treated with Gonal-f and Ovaleap in the Main Study.

The total dose of r-hFSH in cycle 2 of Follow-up Part B was higher than in the Ovaleap group of the main study (interim results, mean 2004.1 vs. 1535.8 IU; final results, mean 1998.2 vs. 1535.8 IU). The justification for this finding might be the treatment regimens: in the main study, patients received a fixed daily dose of 150 IU r-hFSH for the first 5 days followed by dose adaptation, whereas in Follow-up Part B all doses of Ovaleap were selected by the investigator. Results for Follow-up Part B are in line with published values for the amount of Gonal-f needed for optimal follicular development in other clinical trials: 2775 IU (European and Israeli Study Group 2002), 2070 IU (Frydman 2000), 1695 IU (Schats 2000), and 2385 IU (Andersen 2006).

Pregnancy follow-up

Clinical pregnancies resulting from embryo transfers in the treatment cycle of the main study (from at least 5 to 7 weeks after oocyte retrieval) and documented by ultrasound were to be monitored until birth to measure the take-home baby rate and document complications during pregnancy, delivery, as well as the neonatal outcome including congenital malformations. In total, 99 patients gave birth to 111 live babies. Complications during pregnancy were reported in 7 patients from the Gonal-f group and 5 patients from the XM17 group: clinical abortion in 1 vs. 2 patients, missed abortion in 3 vs. 3 patients, and other complications in 3 vs. 1 patients. The other complications in the 3 Gonal-f patients were induced abortion due to chromosomal aberration, epilepsia paroxysm, and premature delivery (triplets). In the XM17 patient with clinical abortion Down’s syndrome was reported as a complication. A total of 10 patients therefore had abortions (5 in each treatment group).

Summary of main study(ies)

Study XM17-05

The following table summarises the efficacy results from study XM17-05.

Table 14 Summary of efficacy for main trial XM17-05

Title: Efficacy, safety and tolerability of XM17 compared to Gonal-f in women undergoing assisted reproductive technologies	
Study identifier	XM17-05

Design	Multi-national, multi-centre, randomized, controlled, assessor-blind, parallel group study including follow-up periods conducted in 5 countries: Belgium, Czech Republic, Germany, Hungary and Poland.	
	Date of first patient enrolled:	19 March 2010
	Date of last patient completed:	27 January 2011
Hypothesis	Equivalence, margin [-3, +3] for primary endpoint	
Treatments groups	Gonal-f	5 days fixed subcutaneous dose of 150 IU. From Day 6 on doses could be increased or decreased. Doses greater than 450 IU were not recommended. Stimulation continued until adequate follicular development (≥ 3 follicles with 17 mm, oestradiol < 5500 pg/mL) was reached, 146 subjects were randomized.
	Ovaleap	The treatment and duration were similar in the Ovaleap group, 153 subjects were randomized.
Endpoints and definitions	Primary endpoint	Number of oocytes retrieved
	Selection of secondary endpoints	<ul style="list-style-type: none"> - Total r-hFSH dose (IU) - Number of days of r-hFSH stimulation - Number of patients needing dose adaptations of r-hFSH - Ongoing pregnancy rate per randomized patient
<u>Results and Analysis</u>		
Analysis description	Primary Analysis	
Analysis population and time point description	According-to-protocol population (ATP): all patients of the full analysis set who did not have any major protocol violations.	

Descriptive statistics and estimate variability	Treatment group	Gonal-f	Ovaleap
	Number of subject	145	152
	Primary endpoint: number of oocytes retrieved -- mean	12.0	12.2
	SD	6.8	6.8
	Secondary endpoint: total dose of r-hFSH – mean	1614.3 IU	1535.8 IU
	SD	484.9	495.6
	Secondary endpoint: number of days of r-hFSH stimulation -- mean	9.7	9.3
	SD	1.6	1.8
	Secondary endpoint: number of patients needing dose adaptations of r-hFSH - increases - decreases	43.2% 15.1%	35.9% 15.0%
	Secondary endpoint: Ongoing pregnancy rate per randomized patient	33.6% (49/146)	27.5% (42/153)
Effect estimate per comparison	Primary endpoint	GONAL-f	Ovaleap
		ZIP regression model	0.03
		95% confidence interval	-0.76, 0.82

Analysis description	Equivalence is established for the primary endpoint. The 95% confidence interval falls within the pre-specified equivalence margin [-3, +3].
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Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analyses nor meta-analysis were performed.

Clinical studies in special populations

Analyses of safety in special groups were not performed.

2.5.2. Discussion on clinical efficacy

One pivotal Phase III study (XM17-05) was conducted in 299 patients to document the efficacy of Ovaleap compared to Gonal-f in the stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART), which is acceptable, as it is in accordance with the 'Draft guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-FSH, EMA/CHMP/BMWP/671292/2010)'. The design of the study was adequate. Gonal-f is appropriate as the reference product. The applied inclusion and exclusion criteria are adequate and in line with other ART studies.

A double-blind design was not technically feasible for this study, as Ovaleap is provided in cartridges that have to be inserted into a special pen (medical device), while Gonal-f is provided as a solution for injection in a pre-filled pen that already contains the cartridge with the medication. Although a double-blind design would have been preferred, in view of the hard primary efficacy endpoint 'number of oocytes retrieved' an assessor-blind design is considered acceptable.

The primary endpoint 'number of oocytes retrieved' is in accordance with the draft guideline EMA/CHMP/BMWP/671292/2010. This endpoint is an adequate endpoint, as it is strongly influenced by the effect of FSH on the ovaries, and at the same time represents an endpoint of clinical relevance.

Regarding the statistical methods, the equivalence margin for the primary end point 'number of oocytes retrieved' was -3 and +3 oocytes and is adequately justified. The sample size has a 90% power for rejecting the null hypothesis that Ovaleap is different to Gonal-f with an equivalence margin of -3, +3, which is appropriate. The ZIP regression analysis for the primary endpoint takes overstimulation as well as understimulation into account, as is recommended by the draft guideline EMA/CHMP/BMWP/671292/2010.

The fixed dose of 150 IU recFSH used for the first five Stimulation Days is the lowest advised starting dose as indicated in the SmPC of Gonal-f (i.e. 150 to 225 IU). Dose adjustment was made possible from Stimulation Day 6 onwards, which is in line with common practice in Europe. No clinically relevant differences were observed in the baseline characteristics.

The primary endpoint 'number of oocytes retrieved' was similar in both treatment groups: 12.2 in the Ovaleap group compared to 12.0 in the Gonal-f group. Equivalence was shown for the primary endpoint (0.03, 95% CI -0.76, +0.82), the 95% confidence intervals were well within the equivalence margin (-3, +3). The four exploratory analyses were in support of the main ZIP regression analysis.

The secondary endpoints (total r-hFSH dose; number of days of r-hFSH stimulation; number of patients needing dose adaptations of r-hFSH and number of follicles (≤ 10 mm, > 10 to 14 mm, > 14 to 17 mm, > 17 mm) on Stimulation Day 6 prior to dose adaptation) are directly linked to the pharmacodynamic action of FSH.

Small differences were noted in the mean total r-hFSH dose (1536 IU for Ovaleap vs. 1614 IU for Gonal-f), number of days of r-hFSH stimulation (9.3 days vs. 9.7 days, respectively) and number of patients needing dose increases (35.9% vs. 43.2%, respectively). A difference was also noted in the frequency of patients with follicles > 14 mm before dose adaptation was allowed, which was 27% in the Ovaleap group vs. 14% in the Gonal-f group. Though at the end of treatment the frequency of patients with follicles > 14 mm was similar (93% vs. 94%), as well as the oestradiol levels (2744.3 pg/mL for Ovaleap vs. 2598.5 pg/mL for Gonal-f).

All together, these data show a slightly higher potency of Ovaleap compared to Gonal-f though the noted differences in dose requirements are only considered small. The observed mean difference in total r-hFSH for a treatment period of about 9-10 days is 78 IU. Further, the average daily FSH dose was similar in both groups 165 IU/day for Ovaleap vs. 166 IU/day for Gonal-f.

The ongoing pregnancy rate per randomized patient (33.6% for Gonal-f and 27.5% for Ovaleap) was comparable and supportive of the primary endpoint. The overall clinical pregnancy rate for patients with embryo transfer is in line with results for Gonal-f shown in clinical trials using a GnRH agonist for down-regulation as reported in literature, varying from 23% to 39%. There were no clinically relevant differences in the pregnancy follow-up.

The take-home baby rate per embryo transfer was in line with the ongoing pregnancy rate per randomized patient (35.1% for Gonal-f and 29.1% for Ovaleap). The other secondary efficacy measures were also supportive of the primary endpoint. Therefore, the therapeutic equivalence for the primary efficacy endpoint 'number of oocytes retrieved' has been established for Ovaleap and the reference product Gonal-f.

2.5.3. Conclusions on the clinical efficacy

Therapeutic equivalence for the primary efficacy endpoint 'number of oocytes retrieved' has been established for Ovaleap and the reference product Gonal-f. Further, no major differences were identified in dose requirements between Ovaleap and Gonal-f. The demonstration of efficacy of Ovaleap for stimulation of multifollicular development in patients undergoing superovulation for ART allows extrapolation to other therapeutic indications approved for Gonal-f.

2.6. Clinical safety

The Applicant submitted three clinical studies to support safety (for details see table below):

Table 15 : Clinical development programme for XM17						
Study No.	Phase	Subject/ Patient type	XM17	Comparator (Gonal-f)	Treatment duration	No. treated
XM17-01	I	Healthy	37.5, 75, 150, 300 IU	–	Single dose	40
XM17-02	I	Healthy	300 IU	300 IU	Single dose	36
XM17-05 Main Study	III	Infertile ovulatory women under- going ART	Fixed dose phase: 150 IU/day Dose adaptation phase: adjustment in steps / multiples of 37.5 IU (maximum 450 IU/day)	Fixed dose phase: 150 IU/day Dose adaptation phase: adjustment in steps / multiples of 37.5 IU (maximum 450 IU/day)	Fixed dose phase: 5 days Dose adaptation phase: up to 15 days	299
Follow-up Part B	III	Infertile ovulatory women under- going ART, not pregnant in Main Study	Individual starting dose Dose adaptation: adjustment in steps / multiples of 37.5 IU (maximum 450 IU/day)	–	Up to 20 days per cycle for up to 2 treatment cycles	155 enrolled (77 in interim analysis)

Patient exposure

In total, 296 subjects received at least 1 dose of Ovaleap. A total of 76 healthy subjects were treated with a single dose in the Phase I trials (XM17-01 and XM17-02). In the Phase III trial XM17-05 (Main Study), 153 patients were randomised to Ovaleap. A further 67 patients who were randomised to Gonal-f were treated with open-label Ovaleap during Follow-up Part B. Within the active-controlled Phase III trial no clear differences were observed in the subjects' demographic and infertility characteristics between the treatment groups.

In study XM17-05, most of the XM17-treated patients (113, 51.4%) received XM17 as follicle stimulating drug for a single cycle; 73 (33.2%) patients received XM17 for a total of 2 cycles and 34 (15.4%) for 3 cycles.

Adverse events

Treatment-emergent adverse events

The applicant provided information on treatment emergent-adverse events (TEAEs), resolved TEAEs, and serious TEAEs in XM17-05. The overall frequencies were very low and comparable across treatment groups; 22 TEAEs occurred in 22 (15.1%) patients for the Gonal-f group and 28 TEAEs occurred in 25 (16.3%) patients in the XM17 group. The Applicant indicated that these low frequencies were expected in the study population of healthy women with a mean age of about 31 years.

Frequencies of TEAEs according to SOCs were all below 5% in both treatment groups. The most commonly affected SOCs were pregnancy, puerperium, and perinatal conditions (4.3%, 13 patients), reproductive system and breast disorders (4.3%, 13 patients), and gastrointestinal disorders (3.3%, 10 patients). Frequencies were similar between treatment groups except for gastrointestinal disorders that were more common in the XM17 group than in the Gonal-f group: 4.6% (7 patients) vs. 2.1% (3 patients) (see table below).

Table 16: Most frequent TEAEs reported by 2 or more patients in XM17-05 (Main Study, SP)

MedDRA preferred term	Gonal-f N=146		XM17 N=153		Total N=299	
	n	%	n	%	n	%
Ovarian hyperstimulation syndrome	4	2.7	7	4.6	11	3.7
Abdominal pain	1	0.7	5	3.3	6	2.0
Abortion missed	3	2.1	0	–	3	1.0
Ectopic pregnancy	1	0.7	2	1.3	3	1.0
Nasopharyngitis	2	1.4	1	0.7	3	1.0
Nausea	1	0.7	2	1.3	3	1.0
Antepartum haemorrhage	1	0.7	1	0.7	2	0.7
Headache	0	–	2	1.3	2	0.7

Note: "n" denotes number of patients with an occurrence. Multiple mentions per patient are possible.

OHSS was the most common event (11, 3.7% patients) and is a known undesirable effect of FSH treatment. It was more common in the XM17 group than in the Gonal-f group: 7 (4.6%) vs. 4 (2.7%). Abdominal pain was also more common in the XM17 group than in the Gonal-f group: 5 (3.3%) vs. 1 (0.7%) patients; none of the patients with the abdominal pain experienced OHSS.

Three ectopic pregnancies occurred in patients during the main study: 1 (0.7%) in the Gonal-f group and 2 (1.3%) in the XM17 group. Abortions were reported as TEAEs in 7 patients during the Main Study: 4 (2.7%) in the Gonal-f group and 3 (2.0%) in the XM17 group. There were no embolic or thrombotic events during the main study.

Treatment-emergent adverse drug reactions

Treatment-emergent adverse drug reactions (TEADRs) were reported in 16 (5.4%) patients, with a lower frequency in the Gonal-f group than in the XM17 group: 5 (3.4%) vs. 11 (7.2%) patients. There were fewer TEADRs of OHSS, abdominal pain, and nausea in the Gonal-f group than in the XM-17 group.

The overall incidence in subjects experiencing at least one AE was generally similar between the treatment groups, with 15.1% in Gonal-f group versus 16.3% in the Ovaleap group. These

frequencies are considered extremely low. In comparison, in the Phase III trials in which r-hFSH Puregon was compared to the modified r-hFSH Elonva the frequencies of subjects experiencing at least one AE were 54.7% and 62.4% for both Phase III trials (source: EPAR Elonva). One of the main reasons that could have resulted in this lower frequency is that the observation period was about 4-8 weeks shorter compared to the ENSURE/ENGAGE studies of Elonva. Further, differences in reporting adverse events were observed between countries. The most commonly affected SOCs were pregnancy, puerperium, and perinatal conditions, reproductive system and breast disorders, and gastrointestinal disorders.

Treatment-emergent adverse drug reactions (TEADRs) were reported in 16 (5.4%) patients, with a lower frequency in the Gonal-f group than in the XM17 group: 5 (3.4%) vs. 11 (7.2%) patients. There were fewer TEADRs of OHSS (4 vs. 7 patients), abdominal pain (1 vs. 4 patients), and nausea (0 vs. 1 patient) in the Gonal-f group than in the XM-17 group. The number of TEADRs is, however, considered very small.

Injection site reactions

Injection site reactions (bruising, burning, redness, skin irritation, swelling) were assessed as no reaction at all, mild, moderate, or severe. Frequencies were comparable between treatment groups and the majority of patients (> 80%) did not report any reactions. Overall frequencies of patients with mild reactions ranged from 1.0% to 3.4% for bruising, skin irritation, and swelling; 7.4% for burning; and 11.4% for redness. Moderate skin reactions comprised bruising in 1 patient (Gonal-f), burning in 2 patients (Gonal-f 1 patient, XM17 1 patient), and redness in 1 patient (XM17).

Serious adverse event/deaths/other significant events

No deaths were reported in the completed or ongoing studies.

Serious TEAEs were reported in 7 (4.8%) patients in the Gonal-f group and 9 (5.9%) patients in the Ovaleap group. The SAEs reported in both treatment groups were: OHSS (2 for Gonal-f and 3 for Ovaleap) and ectopic pregnancy (1 for Gonal-f and 2 for Ovaleap). There were no clinically relevant differences between both treatment groups. For a discussion on OHSS, see AEs of special interest below.

Discontinuation due to adverse events

In the pivotal phase III study XM17-05 only three patients (2 patients in Gonal-f group and 1 patient in Ovaleap group) were discontinued due to an adverse event. All these events were related to OHSS. There were no clinically relevant differences between the treatment groups.

AE of special interest – Ovarian Hyperstimulation Syndrome (OHSS)

OHSS represents one of the most serious complications in ART. The OHSS cases were classified in severity by the investigator (mild, moderate, severe). The number of cases was small, 4 cases (2.7%) in the Gonal-f group and 7 cases (4.6%) in the Ovaleap group, though appeared slightly higher in the Gonal-f group compared to the Ovaleap group. All of the events had resolved at the end of the study, except from one patient from whom it is unknown. The incidence reported in

the pivotal phase III study XM17-05 is in the same order as the incidence that is reported in the product information of Puregon (4%).

Of the reported OHSS cases the intensity was considered severe by the investigator in 1 patient in each treatment group, and moderate for 1 patient in the Gonal-f group and 3 patients in the Ovaleap group. In contrast, the discontinuation due to OHSS was higher (2 patients) in the Gonal-f group compared to the Ovaleap group (1 patient).

Table 17 OHSS intensity as assessed by the investigator

	Gonal-f	Ovaleap/XM17
TEAE	4 (2.7%)	7 (4.6%)
Mild	2	3
Moderate	1	3
Severe	1	1
OHSS leading to study discontinuation	2	1

The Applicant applied also other criteria, as defined by *Papanikolaou and Navot*.^{15,16}:

- Moderate: abdominal distension and discomfort; nausea with or without vomiting; ultrasound evidence of ascites; ovarian size of 8 to 12 cm.
- Severe: clinical ascites with or without hydrothorax, variable ovarian enlargement, haematocrit > 45%, white blood cell (WBC) count > 15000/ μ L, oliguria, creatinine 1.0-1.5 mg/dL, creatinine clearance \geq 50 mL/min, liver dysfunction, generalised oedema.
- Life-threatening: acute respiratory distress syndrome, tense ascites with or without hydrothorax, haematocrit > 55%, WBC count > 25000/ μ L, oliguria, creatinine > 1.6 mg/dL, creatinine clearance < 50 mL/min, renal failure, and thromboembolic phenomena. These AEs had to be documented as SAEs.

There is a broad spectrum of clinical manifestations by which the severity of OHSS is classified and graded (Zivi et al., 2010, Ovarian hyperstimulation syndrome: definition, incidence and classification, *Semin Reprod Med* 28:441-7).

Table 18 OHSS intensity according to the criteria of Papanikolaou and Navot

	Gonal-f	Ovaleap/XM17
TEAE	4 (2.7%)	7 (4.6%)
moderate	3	5
severe	0	2
life-threatening	0	0
not classified	1	0

There is a broad spectrum of clinical manifestations by which the severity of OHSS is classified and graded (Zivi et al., 2010, Ovarian hyperstimulation syndrome: definition, incidence and classification, *Semin Reprod Med* 28:441-7). The Applicant has also provided the additional

¹⁵ Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. *Fertil Steril* 1992; 58:249-61.

¹⁶ Papanikolaou EG, Pozzobon C, Kolibianakis EM, Camus M, Tournave H, Fatemi HM et al. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. *Fertil Steril* 2006; 85(1): 112-20.

retrospective classification according to the WHO Scientific Group (1973) criteria. However, since not all data was collected during the study for this classification, e.g. size of ovaries, the OHSS intensity according to the investigator and according to the criteria of Papanikolaou and Navot is considered more important.

It is agreed with the Applicant that the following parameters were comparable:

- the total dose of r-hFSH (median 1500 and 1425 for Gonal-f and Ovaleap, respectively);
- serum oestradiol levels on the day of hCG injection (2598.5 pg/mL for Gonal-f and 2744.3 pg/mL for Ovaleap);
- hCG dose (A full syringe was administered in 137 Gonal-f (93.8%) vs. 148 Ovaleap (96.7%) patients and half a syringe in 5 (3.4%) vs. 4 (2.6%) patients);
- body weight (63.1 in the Gonal-f group and 63.8 in the Ovaleap group);
- age (31.7 in the Gonal-f group and 31.6 in the Ovaleap group).

and cannot explain the difference that is observed in OHSS. The observed difference could therefore be a chance finding.

Immunological events

In the Quality section of the application file it is shown that the non-human sialic acid variety N-glycolyl neuraminic acid (Neu5Gc) was more present in Ovaleap compared to Gonal-f. This sialic acid cannot be synthesized by humans, though trace amounts are detected from consumption of animals in human diet. The sources are mainly red meats such as lamb, pork and beef. Studies have reported the presence of anti-Neu5Gc antibodies in all humans, up to 0.1–0.2% of circulating IgG. Ghaderi et al. (2010) speculated that circulating anti-Neu5Gc antibodies in humans can potentially fix complement and cause untoward reactions in some patients and/or affect half-life. The authors state that circulating anti-Neu5Gc antibodies could have relevant effects on clearance rate, and subsequently lead to lack of efficacy. Further, the authors indicate that pre-existing antibodies against a glycan on a glycoprotein can secondarily enhance antibody reactivity against the underlying protein backbone.

Validation of the antibody assay

In response to the various issues raised in the D120 LoQ on the validation of the antibody assay, the applicant has completely revised the ECL Bridging Immunogenicity Assay method used to determine anti-FSH antibodies (both in the screening and confirmatory assays) in human serum samples. The strategy to revise the assay and the (positive and negative) controls chosen can be agreed with.

Immunogenicity testing in clinical trials

The observed difference in Neu5Gc content between Ovaleap and Gonal-f was justified by the Applicant. The absolute quantity of Neu5Gc in Ovaleap is negligible compared to the dietary intake of this non-human sialic acid. Antibodies of IgA, IgG and IgM classes recognising Neu5Gc containing glycoproteins are present in humans, but are predominantly directed at Neu5Gc-R motifs not present in CHO cell produced glycoproteins. Anti-Neu5Gc antibodies of IgE class have not been identified.

Based on the provided clinical data by the Applicant for Ovaleap, it is reassuring that anti-Neu5Gc antibodies apparently are not affecting Ovaleap in such an extent that PK or efficacy are

significantly changed at a group level. However, these data do not reveal any potential effect at an individual level.

In response the Applicant provided the validation report of the new revised ADA assay and the re-analysis results of the Phase III study XM17-05 clinical samples. Pre-existing Neu5Gc antibodies were found in 18% of the patients. This percentage is lower than in the publication of Tangvoranuntakul et al. (2003, PNAS). in which the authors found that circulating anti-Neu5Gc antibodies are present in most normal humans. It appears that the assay by the Applicant is less sensitive than the ELISA assay deployed by these authors. However, the low level pre-existing antibodies apparently that are missed by applicant's assay and that are present in most of the population are unlikely to have an effect on Ovaleap's efficacy given the clinical equivalence between Ovaleap and Gonal-f.

Despite this apparent lower sensitivity for Neu5GC antibodies the method has sufficiently been validated and can be considered adequate. There is no evidence that a more sensitive assay would change the conclusion that antibodies against Neu5GC are of no clinical concern for Ovaleap.

Pre-existing antibodies

- Patients with pre-existing anti-Neu5Gc positive findings had a similar biochemical pregnancy rate (16 out of 27 patients, 59.3%) compared to the patients without pre-existing anti-Neu5Gc positive findings (155 out of 270 patients, 57.4%).
- Similarly, patients with pre-existing anti-Neu5Gc positive findings had a similar biochemical pregnancy rate (60.9%) compared to the patients without pre-existing anti-Neu5Gc positive findings (57.4%).
- When looking at the two treatment groups the biochemical pregnancy rates in the patients with pre-existing Neu5Gc and FSH-antibodies were 50.0% for Gonal-f and 63.2% for Ovaleap, whereas in the patients with only pre-existing Neu5Gc antibodies the biochemical pregnancy rate was 66.7% for Gonal-f and 33.3% for Ovaleap. The biochemical pregnancy rate in the Ovaleap group with only pre-existing Neu5Gc antibodies is lower (33.3%), however, only 6 patients were included in this subgroup, and this pregnancy rate could be lower due to chance. The pregnancy rate in the Ovaleap group with pre-existing Neu5Gc antibodies and Ovaleap antibodies was 63.2%, which is reassuring.

Based on these findings, it can be concluded that pre-existing Neu5Gc antibodies do not have an effect on the treatment with r-hFSH containing Neu5Gc.

Patients with post-dose positive findings

The biochemical pregnancy rate in the patients with at least one developed positive post-dose finding was 45.5% (10 out of 22 subjects), whereas it was 58.1% (161 out of 277 subjects) in patients without at least one developed positive post-dose finding. The biochemical pregnancy rate was only slightly lower (45.5%), and it has to be taken into account that the group was very small, i.e. 22 subjects. The immunological findings in both treatment groups are not of clinical concern.

In conclusion, the risk on an immune response is negligible. The immunogenicity of Ovaleap and Gonal-f can be considered similar.

Laboratory findings

No clinically relevant effects were observed between the treatment groups in the completed Phase III study on the clinical laboratory evaluation.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with Ovaleap. As Ovaleap is a biosimilar, it is acceptable that no formal drug interaction studies have been performed.

2.6.1. Discussion on clinical safety

The submission of three studies, from which one efficacy/safety study for the biosimilar Ovaleap is sufficient in support of clinical safety, provided that Ovaleap fulfils all the requirements for a biosimilar.

In total, 296 subjects received at least 1 dose of Ovaleap. The exposure is considered sufficient, provided that all requirements are fulfilled for a biosimilar. Within the active-controlled Phase III trial no clear differences were observed in the subjects' demographic and infertility characteristics between the treatment groups. The overall incidence in subjects experiencing at least one AE was generally similar between the treatment groups.

Treatment-emergent adverse drug reactions (TEADRs) were reported in a small number of subjects. There were fewer TEADRs in the Gonal-f group (5 subjects; 3.4%) compared to the Ovaleap group (11 subjects; 7.2%), although the number of TEADRs is considered small. There were no clinically relevant differences between both treatment groups in local tolerance, serious TEAEs, nor in discontinuations due to (S)AEs. The OHSS cases were classified in severity by the investigator (mild, moderate, severe). The number of cases were small, 4 cases (2.7%) in the Gonal-f group and 7 cases (4.6%) in the Ovaleap group, though appeared slightly higher in the Gonal-f group compared to the Ovaleap group. Of these cases the intensity was considered severe by the investigator in 1 patient in each treatment group, and moderate for 1 patient in the Gonal-f group and 3 patients in the Ovaleap group. In contrast, the discontinuation due to OHSS was higher (2 patients) in the Gonal-f group compared to the Ovaleap group (1 patient).

Immunogenicity

The higher content of Neu5Gc in Ovaleap and Gonal-f was justified by the Applicant. The absolute quantity of Neu5Gc in Ovaleap is negligible compared to the dietary intake of this non-human sialic acid. In response to the various issues raised in the D120 LoQ on the validation of the antibody assay, the applicant has completely revised the ADA assay used to determine anti-FSH antibodies in human serum samples. The re-analysis of the samples of the Phase III study XM17-05 with the revised ADA assay confirmed that the risk on an immune response is negligible and that the immunogenicity of Ovaleap and Gonal-f can be considered similar.

2.6.2. Conclusions on the clinical safety

Overall, the AE profile of Ovaleap is comparable with Gonal-f.

The incidence of OHSS was low in the Phase III trial. A slightly lower incidence was observed for the Gonal-f group (4 cases; 2.7%) versus the Ovaleap group (7 cases; 4.6%). The discontinuation rate due to OHSS was, however, in favour of the Ovaleap group (1 case) vs. Gonal-f group (2 cases). The following parameters were comparable and could not explain the slightly higher incidence in the Ovaleap group: the total dose of r-hFSH, serum oestradiol levels on the day of hCG injection, hCG dose, body weight and age. The observed difference could therefore be a chance finding.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance and risk minimisation activities at this time.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The following table provides an overall summary of the risk management plan.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
Ovarian hyperstimulation syndrome	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR. Additional pharmacovigilance activity: Post-authorisation safety study. Multi-national, multicentre, uncontrolled, prospective, non-interventional, observational cohort study: SOFIA: 'Safety of Ovaleap (Follitropin alfa) in Infertile women undergoing superovulation for Assisted reproductive technologies'.	OHSS is mentioned as undesirable effect in section 4.8 of the SmPC Warning in section 4.4 of the SmPC including a description of the symptomatology, possible complications and risk factors of OHSS. Mentioning that adherence to the recommended dose and regimen of administration and careful monitoring of therapy can minimise the risk, instructions in case OHSS occurs Mentioning of OHSS as possible effect of an overdose in section 4.9 of the SmPC Contraindication in section 4.3

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		<p>of the SmPC in case of ovarian enlargement</p> <p>Instruction in section 4.2 of the SmPC that treatment should be tailored to the patient's response and stopped in case of an excessive response and if so recommenced at a lower dose in the next cycle</p>
Multiple pregnancy	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR	Warning in section 4.4 of the SmPC that ovulation induction increases the incidence of multiple pregnancies, which increases the risk of adverse maternal and perinatal outcomes. Recommendation of careful monitoring of ovarian response to minimise the risk of multiple pregnancy. Information that in patients undergoing ART procedures the risk of multiple pregnancy is related mainly to the number of embryos replaced, their quality and the patient age.
Pregnancy loss	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR	Warning in section 4.4 of the SmPC that stimulation of follicular growth for ovulation induction or ART increases the incidence of pregnancy loss by miscarriage or abortion
Thrombotic events in women	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR	<p>Mentioning of thromboembolism as undesirable adverse effect in section 4.8 of the SmPC</p> <p>Warning in section 4.4 of the SmPC that treatment with gonadotropins may increase the risk for aggravation or occurrence of thromboembolic events in affected patients or patients at risk</p>
Hypersensitivity	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR.	<p>Contraindication in section 4.3 of the SmPC in case of hypersensitivity to the active substance follitropin alfa or FSH</p> <p>Mentioning of hypersensitivity reactions as undesirable effect in</p>

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		section 4.8 of the SmPC
Asthma aggravated/exacerbation	Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR	Mentioning of exacerbation or aggravation of asthma reactions as undesirable effect in section 4.8 of the SmPC
Gynaecomastia in males	Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR	Mentioning of gynaecomastia in men as undesirable effect in section 4.8 of the SmPC
Important potential risks		
Ectopic pregnancy	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR	Warning in section 4.4 of the SmPC that the prevalence of ectopic pregnancy was reported to be higher after ART and that a history of tubal disease is a risk factor for ectopic pregnancy
Reproductive system neoplasms in women	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR.	Warning in section 4.4 of the SmPC that in women who have undergone multiple treatment regimens for infertility treatment there have been reports of ovarian and other reproductive system neoplasms (benign and malignant), and that it is not yet established if treatment with gonadotropins increases this risk Contraindication in section 4.3 of the SmPC in case of ovarian, uterine or mammary carcinoma
Neonatal congenital malformations	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR	Warning in section 4.4 of the SmPC that the prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions, which is thought to be due to differences in parental characteristics and multiple pregnancies
Immunogenicity which may manifest as lack of effect	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR Review of all spontaneously	Section 4.2 of the SmPC: Patients that fail to respond to the treatment should undergo further evaluation.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	received ADR reports for the detection of cases that might be related to an immunogenicity reaction to follitropin alfa, and offering of antibody testing in such a case	
Porphyria	Routine pharmacovigilance incl. presentation of respective data in the corresponding chapter of the PSUR.	Warning in section 4.4 of the SmPC that patients with porphyria or family history of porphyria should be closely monitored during the treatment and that deterioration or a first appearance of this condition may require cessation.
Important missing information		
Women older than 40 years	Routine pharmacovigilance including presentation of respective data in the corresponding chapter of the PSUR	In the absence of specific safety signals relating to use in women older than 40 years the applicant does not propose any risk minimisation activities at this time.

The CHMP endorsed this advice without changes.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 2.2, the PRAC considers by consensus that the risk management system for follitropin alfa (OVALEAP) is acceptable.

The PRAC advises that the following should be conditions of the Marketing Authorisation:

Risk management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

The PRAC considers that no additional risk minimisation measures will be necessary for the safe and effective use of the medicinal product

Obligation to conduct post-authorisation measures

Not applicable

The CHMP endorsed this advice without changes.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Receptor affinity studies showed comparable binding of Gonal-f and Ovaleap to the human FSH receptor. In a cell-based assay employing human FSH-receptor expressing CHO cells, both products showed comparable biological activity.

One pivotal Phase III study (XM17-05) was conducted in 299 patients to document the efficacy of Ovaleap in the stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART). The study had an assessor-blind design. A double-blind design was not technically feasible for this study, as Ovaleap is provided in cartridges that have to be inserted into a special pen (medical device), while Gonal-f is provided as a solution for injection in a pre-filled pen that already contains the cartridge with the medication. Although a double-blind design would have been preferred, in view of the hard primary efficacy endpoint 'number of oocytes retrieved' an assessor-blind design is considered acceptable. Gonal-f is appropriate as the reference product.

The dose of 150 IU r-hFSH was fixed for the first five Stimulation Days. This is the lowest advised starting dose as indicated in the SPC of Gonal-f (i.e. 150 to 225 IU). The fixed recFSH dose for the first 5 days of stimulation is in accordance with the draft guideline EMA/CHMP/BMWP/671292/2010 and considered acceptable. Dose adjustment was made possible from Stimulation Day 6 onwards, which is in line with common practice in Europe.

The results for the primary endpoint 'number of oocytes retrieved' were 12.2 in the Ovaleap group compared to 12.0 in the Gonal-f group. Equivalence was shown by a ZIP regression model that takes specifically data with excess zeroes into account. The 95% confidence intervals for the difference between Ovaleap and Gonal-f were well within the pre-defined equivalence margin that is adequately justified. The four exploratory analyses were in support of the main analysis with the ZIP regression model.

The secondary endpoints that are considered the most relevant, as they are directly linked to the pharmacodynamics action of FSH, for this biosimilar application are:

- Total r-hFSH dose: 1536 IU (range 750 to 3600 IU) for Ovaleap vs. 1614 (range 900 to 3525 IU) for Gonal-f.
- Number of days of r-hFSH stimulation: 9.3 days for Ovaleap vs. 9.7 days for Gonal-f.
- Number of patients needing dose adaptations after the first fixed 5 days of stimulation: 51.0% for Ovaleap vs. 58.2% for Gonal-f. This was due to a lower frequency of dose increases: 35.9% for Ovaleap vs. 43.2% for Gonal-f. The frequency in dose decreases was identical: 15.0% for Ovaleap vs. 15.1% for Gonal-f.
- Number of follicles (≤ 10 mm, > 10 to 14 mm, > 14 to 17 mm, > 17 mm) on Stimulation Day 6 prior to dose adaptation. The frequency of patients with follicles > 14 mm before dose adaptation was allowed was 27% in the Ovaleap group vs. 14% in the Gonal-f group, though at the end of treatment the frequency of patients with follicles > 14 mm was similar (93% vs. 94%).
- Estradiol levels after the first fixed 5 days of stimulation were: 479.6 pg/mL for Ovaleap (range 37.0 – 3213.0) vs. 350.3 pg/mL for Gonal-f (range 32.3 – 2153.0). This difference was less apparent at the end of the treatment period on the day of hCG administration (2242.5 pg/mL for Ovaleap vs. 2176.5 pg/mL for Gonal-f).
- The ongoing pregnancy rate was 33.6% (49/146) for Gonal-f and 27.5% (42/153) for Ovaleap.

Regarding pharmacokinetics, study XM17-02 showed that the Ovaleap vs. Gonal-f ratios for the primary parameters C_{max} and AUC_{0-t} were within the 0.8-1.25 acceptance interval (0.958-1.080 and 0.931-1.134, respectively). Additionally, both products had sufficient similar clearance and t_{1/2} values. Provided that on chemical-pharmaceutical grounds the product is acceptable as biosimilar, it is sufficiently shown that the product is bioequivalent with the innovator product Gonal-f.

Uncertainty in the knowledge about the beneficial effects

The overall incidence in the Phase III study in subjects experiencing at least one AE was 15.1% in the Gonal-f group versus 16.3% in the Ovaleap group. The most commonly affected SOCs were pregnancy, puerperium, and perinatal conditions, reproductive system and breast disorders, and gastrointestinal disorders.

Treatment-emergent adverse drug reactions (TEADRs) were reported in 5 (3.4%) patients in the Gonal-f group compared to 11 (7.2%) patients in the Ovaleap group. There were fewer TEADRs of OHSS (4 vs 7 patients), abdominal pain (1 vs 4 patients), and nausea (0 vs 1 patient) in the Gonal-f group than in the Ovaleap group. Injection site reactions (bruising, burning, redness, skin irritation, swelling) were assessed as no reaction at all, mild, moderate, or severe. Frequencies were comparable between treatment groups and the majority of patients ($> 80\%$) did not report any reactions.

No deaths were reported. Serious TEAEs were reported in 7 (4.8%) patients in the Gonal-f group and 9 (5.9%) in the Ovaleap group. The SAEs reported in both treatment groups were: ovarian hyperstimulation syndrome (OHSS; 2 for Gonal-f vs. 3 for Ovaleap) and ectopic pregnancy (1 for Gonal-f vs. 2 for Ovaleap). Other serious TEAEs that were reported in one of the treatment

groups were: abortion (missed, early, incomplete, spontaneous complete), (lower) abdominal pain and antepartum haemorrhage.

The number of OHSS cases was low: 4 (2.7%) in the Gonal-f group and 7 cases (4.6%) in the Ovaleap group with discontinuation in 2 vs. 1 case, respectively. The lower frequency of OHSS in the Gonal-f group compared to the Ovaleap group (2.7% vs. 4.6%) was not statistically significant ($p = 0.542$). All cases had resolved (except for one patient from whom it is unknown). Three patients were discontinued due to an adverse event in the Phase III trial (2 Gonal-f, 1 Ovaleap). All these events were related to OHSS.

Risks

Unfavourable effects

The overall incidence in the Phase III study in subjects experiencing at least one AE was 15.1% in the Gonal-f group versus 16.3% in the Ovaleap group. The most commonly affected SOCs were pregnancy, puerperium, and perinatal conditions, reproductive system and breast disorders, and gastrointestinal disorders.

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Injection site reactions (bruising, burning, redness, skin irritation, swelling) were assessed as no reaction at all, mild, moderate, or severe. Frequencies were comparable between treatment groups and the majority of patients (> 80%) did not report any reactions.

No deaths were reported. Serious TEAEs were reported in 7 (4.8%) patients in the Gonal-f group and 9 (5.9%) in the Ovaleap group. The SAEs reported in both treatment groups were: ovarian hyperstimulation syndrome (OHSS; 2 for Gonal-f vs. 3 for Ovaleap) and ectopic pregnancy (1 for Gonal-f vs. 2 for Ovaleap). Other serious TEAEs that were reported in one of the treatment groups were: abortion (missed, early, incomplete, spontaneous complete), (lower) abdominal pain and antepartum haemorrhage.

The number of OHSS cases was low: 4 (2.7%) in the Gonal-f group and 7 cases (4.6%) in the Ovaleap group with discontinuation in 2 vs. 1 case, respectively. The lower frequency of OHSS in the Gonal-f group compared to the Ovaleap group (2.7% vs. 4.6%) was not statistically significant ($p = 0.542$). All cases had resolved (except for one patient from whom it is unknown).

Three patients were discontinued due to an adverse event in the Phase III trial (2 Gonal-f, 1 Ovaleap). All these events were related to OHSS.

Uncertainty in the knowledge about the unfavourable effects

As Ovaleap was developed as a biosimilar the safety data is limited. In the Phase III study about 150 patients were treated for the ART indication. The overall incidence in subjects experiencing at least one AE was comparable, but is considered relatively low with 15.1% in Gonal-f group versus 16.3% in the Ovaleap group. In comparison, in the Phase III trials in which r-hFSH Puregon was compared to the modified r-hFSH Elonva the frequencies of subjects experiencing at least one AE were 54.7% and 62.4% for both Phase III trials (source: EPAR Elonva). One of the main reasons that could have resulted in this lower frequency is that the observation period was about 4-8 weeks shorter compared to the ENSURE/ENGAGE studies of Elonva. Further, differences in reporting adverse events were observed between countries in the Ovaleap Phase III trial.

The non-human sialic acid variety N-glycolyl neuraminic acid (Neu5Gc) is more present in Ovaleap compared to Gonal-f. This Neu5Gc cannot be synthesized by humans, though trace amounts are detected from consumption of animals in human diet. The observed difference in Neu5Gc content between Ovaleap and Gonal-f was justified by the Applicant. The absolute quantity of Neu5Gc in Ovaleap is negligible compared to the dietary intake of this non-human sialic acid. Antibodies of IgA, IgG and IgM classes recognising Neu5Gc containing glycoproteins are present in humans, but are predominantly directed at Neu5Gc-R motifs not present in CHO cell produced glycoproteins. Anti-Neu5Gc antibodies of IgE class have not been identified.

In response to questions of the CHMP, the applicant has completely revised the ECL Bridging Immunogenicity Assay method used to determine anti-FSH antibodies in human serum samples. The strategy to revise the assay and the (positive and negative) controls have been chosen and the CHMP agreed with it.

Based on the provided clinical data by the Applicant for Ovaleap, it is reassuring that anti-Neu5Gc antibodies apparently are not affecting Ovaleap in such an extent that PK or efficacy are significantly changed at a group level. However, these data do not reveal any potential effect at an individual level. To rule out the presence of antibodies in all patients, the validation report of the new revised ADA assay and the re-analysis results of the Phase III study XM17-05 clinical samples should be presented to the agency pre-license. In response, the Applicant provided the validation report of the new revised ADA assay and the re-analysis results of the Phase III study XM17-05 clinical samples. The re-analysis of the samples of the Phase III study XM17-05 with the revised ADA assay confirmed that the risk on an immune response is negligible and that the immunogenicity of Ovaleap and Gonal-f can be considered similar.

Benefit-risk balance

Importance of favourable and unfavourable effects

Neu5GC content

A difference is observed in the non-human sialic acid Neu5Gc in the Quality part of the dossier. In contrast to Gonal-f, Ovaleap contains a higher amount of total sialic acid. FSH synthesised in the human body does not contain Neu5Gc due to the absence of a specific sialotransferase in

humans. The Applicant has provided an adequate discussion and justification for this difference in Neu5GC content from a quality, pre-clinical and clinical perspective.

The re-analysis of the samples of the Phase III study XM17-05 with the revised ADA assay confirmed that the risk on an immune response is negligible and that the immunogenicity of Ovaleap and Gonal-f can be considered similar.

Efficacy

In the one pivotal Phase III trial, Ovaleap was shown to be equivalent for the primary endpoint 'number of oocytes retrieved'. Several secondary endpoints were taken into account that investigated dose adjustments and possible differences between the dosages of Ovaleap and the reference product Gonal-f. The clinical data of the Phase III trial including the results after the fixed dose period at Day 6 are in accordance with the concept of biosimilarity. The observed dose differences in the pivotal Phase III study are only small. The total Ovaleap dose was only 4.8% lower than the total Gonal-f dose. This difference is not clinically relevant, and consequently the data of the pivotal Phase III study can be extrapolated to all other indications, including the indication 'hypogonadotropic hypogonadism'.

The major objection on the potentially increased immunogenicity risk as a consequence of the presence of a higher content of non-human sialic acid Neu5Gc is resolved. Ovaleap is considered a biosimilar of Gonal-f based on the provided quality, non-clinical and clinical data.

Benefit-risk balance

Discussion on the benefit-risk balance

The issue on the potentially increased immunogenicity risk as a consequence of the presence of a higher content of non-human sialic acid Neu5Gc is resolved. Ovaleap is considered a biosimilar of Gonal-f based on the provided quality, non-clinical and clinical data.

The re-analysis of the samples of the Phase III study XM17-05 with the revised ADA assay confirmed that the risk on an immune response is negligible and that the immunogenicity of Ovaleap and Gonal-f can be considered similar.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ovaleap in the following indications:

In adult women

- *Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomifene citrate.*
- *Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra fallopian transfer.*

- *Ovaleap in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/l.*

In adult men

- *Ovaleap is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.*

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal. When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.