European Medicines Agency
Evaluation of Medicines for Human Use

London, 19 November 2009
Doc.Ref.: EMA/CHMP/802299/2009

CHMP ASSESSMENT REPORT

FOR

Elonva

International Nonproprietary Name: corifollitropin alfa

Procedure No. EMEA/H/C/1106

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant N.V. Organon submitted on 04 December 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Elonva, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The applicant applied for the following indication:
"Controlled Ovarian Stimulation (COS) for the development of multiple follicles and pregnancy in women participating in an Assisted Reproductive Technology (ART) program."

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMEA Decision P/131/2008 for the following condition:

- Hypogonadotrophic hypogonadism.

on the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 27 January 2006. 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.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Patrick Salmon**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 04 December 2008.
- The procedure started on 24 December 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2009.
- During the meeting on 20-23 April 2009, 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 23 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 September 2009.

- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to all CHMP members on 17 September 2009.
- The final GCP integrated inspection report of the inspection carried out at one investigator site in South Korea (06-10/04/09), one investigator site in Taiwan (13-17/04/09) and at the sponsor site in the Netherlands (11-14/05/09) was issued on 22 September.
- During the CHMP meeting on 21-24 September 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 15 October 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 November 2009.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to all CHMP members on 13 November 2009.
- During the meeting on 16-19 November 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Elonva on 19 November 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 November 2009.

2. SCIENTIFIC DISCUSSION

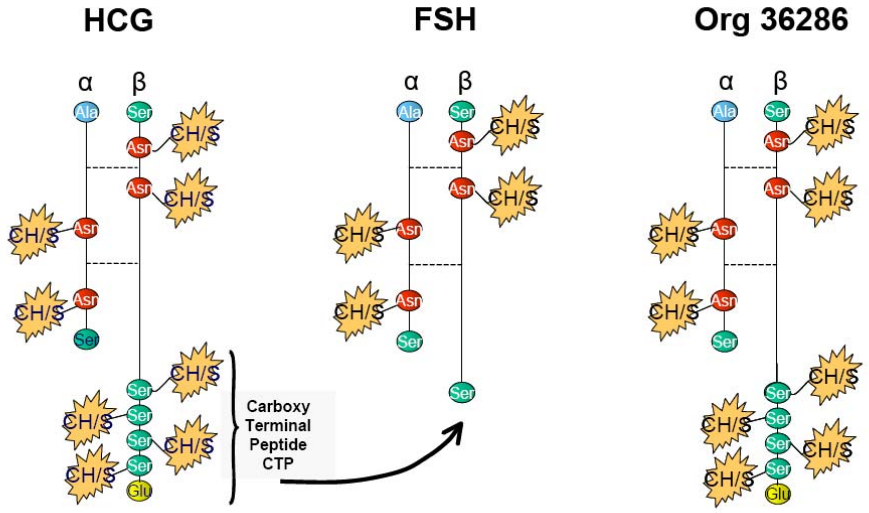
2.1. Introduction

This is an application for a biotech medicinal product containing corifollitropin alfa in the frame of the centralised procedure submitted in accordance with Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004 and with Article 8(3) of Directive 2001/83/EC, as amended (i.e. a complete and independent application with administrative, quality, pre-clinical and clinical data).

The medicinal product Elonva contains the active substance corifollitropin alfa (also called Org 36268), a new glycoprotein, which belongs to the pharmaceutical class of the gonadotropins. corifollitropin alfa is a new glycoprotein produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology, using chemically defined cell culture medium without the addition of antibiotics, human or animal derived proteins (protein-free) or any other components of human or animal origin.

By adding the carboxy-terminal peptide of the β-subunit of hCG to the β-chain of human FSH (Figure 1), the elimination half-life of Elonva was almost 2-fold increased compared to recFSH (33 hours, range 27-41 hours).

Figure 1: Schematic representation of the design of Elonva (adapted from Thesis of Beckers N.G.M., Follicular and Luteal Phase Aspects of Ovarian Stimulation for In Vitro Fertilization, 2006, Erasmus University, Rotterdam, The Netherlands).



FSH is available on the European market in combination with LH (hMG = human menopausal gonadotropin) and in purified forms derived from human menopausal urine or as recombinant peptide produced by cultured cells.[1,2]
The currently approved recombinant follicle stimulating hormones (FSH) in Europe are Puregon (follitropin beta) and Gonal-F (follitropin alfa), which have additional indications besides the indication "*Controlled Ovarian Stimulation in medically assisted reproduction programs*". Please refer to the EPAR for these products for more detailed information.

Corifollitropin alfa is proposed for ART programs only.

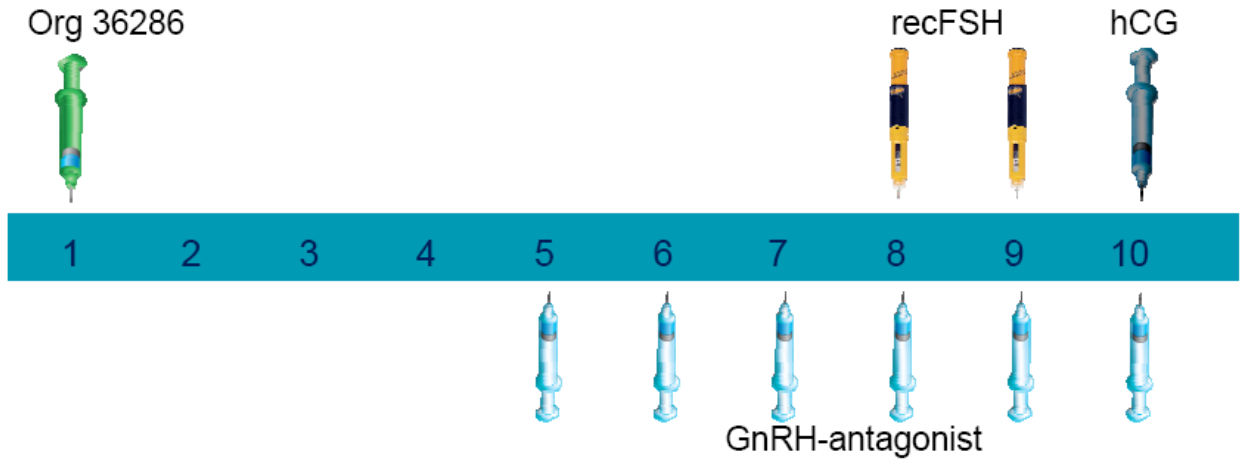
[1] Nugent D, Vandekerckhove P, Hughes E, et al. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev 2000;(4):CD000410.
[2] Bayram N, van Wely M, van Der Veen F. Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev 2001 ;(2):CD002121.

Due to its prolonged duration of FSH activity, a single subcutaneous injection of the recommended dose of corifollitropin alfa may replace the first seven injections of any daily (rec)FSH preparation in a COS treatment cycle.

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. FSH is essential for normal female gamete growth and maturation, and normal gonadal steroid production.
In the first protocols used in assisted reproduction techniques (ART; standard "long" protocol), a GnRH agonist was used to suppress the hypothalamic-pituitary ovarian axis for controlled ovarian stimulation and additionally to prevent a premature LH surge. When desensibilisation has been achieved, controlled 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.
Another option for ovarian stimulation in ART is the use of a GnRH antagonist. In contrast to the long-acting agonists that first stimulate and later inhibit pituitary gonadotropin secretion by desensitizing gonadotrophs to GnRH via receptor down-regulation, the antagonists block the GnRH receptor in a dose-dependent competitive fashion and have no flare effect; gonadotropin suppression is almost immediate.

Corifollitropin alfa is recommended for use in a GnRH-antagonist protocol. As stimulation starts in the early follicular phase of the natural cycle, the duration of stimulation is shorter and less FSH is used as compared to the standard ART protocol with a GnRH agonist. A schematic presentation of the dosing schedule is given in Figure 2:

Figure 2. Corifollitropin alfa /GnRH antagonist treatment regimen, as used in the pivotal Phase III studies 38819 and 107012



Note: The duration of FSH treatment and the day of hCG administration were dependent on the follicular response as assessed by ultrasonography.

The proposed therapeutic indication of corifollitropin alfa was *"Controlled Ovarian Stimulation (COS) for the development of multiple follicles and pregnancy in women participating in an Assisted Reproductive Technology (ART) program."*

The approved indication is:
"Controlled Ovarian Stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program"

Treatment with corifollitropin alfa should be initiated under the supervision of a physician experienced in the treatment of fertility problems.
Corifollitropin alfa is supplied in pre-filled syringes as a solution for injection (0.5 ml), either containing 100 µg or 150 µg of corifollitropin alfa. In women with a body weight ≤ 60 kilograms a single dose of 100 micrograms should be administered. In women with a body weight > 60 kilograms a single dose of 150 micrograms should be administered. The recommended doses of corifollitropin

alfa have only been established in a treatment regimen with a GnRH antagonist. For further information on the stimulation scheme please refer to section 4.2 of the SPC.

Paediatric aspects

With respect to the granted indication (COS) a *waiver* in all subsets of the paediatric population was granted on the grounds that clinical studies in COS cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the paediatric population.

Nevertheless for the indication "Treatment of hypogonadotrophic hypogonadism" studies within a paediatric subset will be performed.

2.2. Quality aspects

Introduction

The drug substance corifollitropin alfa is a glycoprotein consisting of two non-covalently linked subunits: an alfa subunit and a beta subunit corresponding to that of human FSH extended with a C-terminal peptide (CTP) corresponding to the beta subunit of hCG.

Corifollitropin alfa is derived from a Chinese Hamster Ovary cell line (CHO-K1) and a two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed by the applicant.

Corifollitropin alfa is produced using a chemically-defined cell culture medium without the addition of antibiotics, proteins or any other components of human or animal origin.
The fermentation process consists of pre-culture and culture steps followed by cell free clarification. Two production scales are proposed.

Purification from the cell culture harvest is performed in an 11-step process comprising a series of chromatography steps, ultrafiltration/diafiltration steps, steps to inactivate and remove potential viral contaminants and a microfiltration step.

The drug product manufacturing process includes thawing of the drug substance, formulation with the excipients and mixing, sterile filtration and fill-finish.

Elonva is presented as a solution for subcutaneous injection in a pre-filled syringe for single use. Two dosage forms have been developed: 100 µg and 150 µg.

Drug Substance

Nomenclature

INN Name:	corifollitropin alfa
Compendial Name:	not applicable
USAN/JAN:	corifollitropin alfa
Laboratory Code Name:	Org 36286
CAS Registry Number:	195962-23-3
Other Names:	Follicle-stimulating hormone (human alfa-subunit reduced) complex with follicle-stimulating hormone (human beta-subunit reduced) fusion protein with 118-145 chorionic gonadotropin (human beta subunit)

Description of the drug substance

The drug substance corifollitropin alfa is a glycoprotein consisting of two non-covalently linked subunits: an alfa subunit of 92 amino acids which is common to different glycoprotein hormones (FSH, LH, TSH, hCG) and a beta subunit corresponding to that of human FSH (111 amino acids) extended with CTP of the beta subunit of hCG (28 amino acids).
The alfa and beta subunits each contain two N-linked glycosylation sites and disulphide bonds (five and six, respectively). The CTP part contains six O-linked glycosylation sites.
The apparent molecular mass of corifollitropin alfa is 47 kDa.

- Manufacture

All manufacturing steps, Quality Control testing and release of the drug substance are performed at N.V. Organon, Oss, The Netherlands. This site is EU-GMP compliant and a valid manufacturing authorisation was provided.

Development genetics

The cell line producing corifollitropin alfa was generated by transfection of Chinese Hamster Ovary cells (CHO-K1) with an expression plasmid comprising DNA sequences which encode the alfa chain and the extended beta subunit, yielding CHO.FSH.CTP13 after cloning and sub-cloning steps.
The CHO.FSH.CTP13 cell line was gradually adapted to grow in protein-free and animal component free culture medium. The adapted clone CHO.FSH.CTP13.PF.5 ("Research" cell line) was thus generated and used for the preparation of a MCB and WCB.

Cell bank system

A two-tiered cell banking system of MCB and WCB has been developed and maintained in accordance to cGMP and ICH guidelines.

Seed cells corresponding to the high-producing clone CHO.FSH.CTP13.PF.5 were thawed, resuspended and cultured in a protein-free and animal component free culture medium, leading to the establishment of the MCB and WCB. Procedures followed for the preparation of MCB and WCB were appropriately described. An extensive range of tests has been performed for their characterisation, in accordance with ICH guidelines, including identity, viability, genetic stability and viral safety.

Fermentation process

Pre-culture is initiated from a single WCB vial and subsequent expansion in a culturing container, seed bioreactor and production bioreactor, successively. A production bioreactor is then inoculated. Following the production phase, the bioreactor is harvested using cross-flow filtration or dead end filtration in order to remove cells from the cell culture supernatant. The resulting cell culture filtrate is then further purified.

Purification process

Purification of the cell free culture supernatant is performed by chromatographic, concentration/diafiltration and virus removal/inactivation steps.

Manufacturing process development and process validation

Throughout development, changes have been introduced in the drug substance manufacturing process, including the protein free cell line, formulation and manufacturing scale.

A comprehensive process manufacturing history was provided, showing the different changes introduced, and the corresponding batches involved, as well as the use of these batches.

An extensive comparability exercise was conducted between the non protein-free process and the commercial protein-free process.
Comparability studies were also conducted to support the scale-up of the fermentation process.

The corifollitropin alfa manufacturing process was validated using data from both process scales with respect to consistency, robustness performance and quality attributes. It was demonstrated that the process consistently maintains process parameters within specified ranges and meets acceptance criteria for performance indicators. Overall, process validation was considered satisfactory.

Characterisation

A) Elucidation of structure and other characteristics:

The elucidation of the structure of corifollitropin alfa was mainly based on complete amino acid sequence analysis, peptide mapping and analysis of the post-translational modifications (glycosylation and disulfide bridges).
The amino acid sequence matches exactly the prediction based on the DNA nucleotide sequence and was further confirmed by the results for the amino acid composition and the N-terminal sequence. N-terminal heterogeneity was shown comparable to that of recombinant FSH (follitropin beta).

The N-linked glycan structures were determined to be bi-, tri- and tetra-antennary oligosaccharides with sialic heterogeneity, as expected for the FSH part. The O-linked glycan structures were determined to be mono- and bi-antennary oligosaccharides with sialic heterogeneity, as expected for the hCG part.

Five disulfide bridges in the alfa subunit and three of the beta subunit were determined, whereas three other disulfide bridges were inferred from the crystal structures of hCG and FSH. No other post-translational modifications are present.

Conformational analysis of corifollitropin alfa confirmed structural resemblance to gonadotropins.

B) Impurities:

Potential process-related impurities include cell substrate derived impurities (host cell proteins, host cell DNA), microbiological contaminants, column leachables, residual solvents and additives (antifoaming agent).

Potential product-related substances and impurities include deamidation products, oxidation products free subunits, oligomers (aggregation of two or more heterodimers), N-terminal residue loss.

- Specification

The drug substance release specifications, which include tests for identity, purity and impurities, potency, quantity and general attributes, are acceptable and well justified.

- Stability

The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance with current ICH 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 the proposed shelf life and the proposed storage conditions for the drug substance.

Drug Product

- Pharmaceutical Development

Elonva is presented as a solution for subcutaneous injection in a pre-filled syringe (type I hydrolytic glass) for single use. Each syringe contains 100 µg or 150 µg of corifollitropin alfa formulated with sodium citrate, sucrose, polysorbate 20, methionine, sodium hydroxide, hydrochloric acid and water for injections. These excipients are commonly used in formulating protein pharmaceuticals.
The syringe is assembled into an automatic safety system to prevent needle stick injuries after use and is packed together with a sterile injection needle. Each pre-filled syringe contains 0.5 ml solution for injection.

Throughout drug product development changes have been introduced, including a new formulation and primary container. The new formulation, corresponding to the commercial formulation, was used for Phase I, the Phase II dose finding study and all Phase III studies.

- Adventitious Agents

No human-/animal-derived raw materials were used in the preparation of the MCB or WCB and in the manufacture of the drug substance and drug product. Only cells prior to the Research cell line were cultivated with foetal calf serum (FCS) sourced from USA, Canada and Australia. Data were provided to support the use of FCS. MCB, WCB and host cell lines were tested for bovine viruses and no contamination was detected. Safety concerning TSE is considered sufficiently assured.
Control of potential contamination by other non-viral adventitious agents (mycoplasma, bioburden, endotoxins) was considered adequate.

Extensive virus screening was conducted. The MCB, WCB, post-production cells and bulk harvest were found to be free from infectious adventitious viral contamination. However, as expected for CHO cells, the transmission electron microscopy investigation showed minimal evidence of virus-like particles.
The purification process of corifollitropin alfa includes several steps for inactivation/removal of viruses. Viral safety has been sufficiently demonstrated. To further confirm the robustness of the process, the applicant will undertake post-approval studies.

- Manufacture of the product

The drug product is manufactured at Vetter Pharma-Fertigung, GmbH & Co. KG, Ravensburg, Germany. Assembly with the safety device and secondary packaging of the drug product is carried out at Organon (Ireland) Ltd., Swords, Ireland. Quality control testing and batch release are performed at Organon (Ireland) Ltd., Swords, Ireland or NV Organon, Oss, The Netherlands.

The frozen purified drug substance is thawed, formulated with the different excipients, sterile filtered and aseptically filled into sterile glass syringes which are then closed with a plunger and a tip cap.

Process validation was performed and provided a documented, thorough understanding of the ability of the manufacturing process to consistently and reliably meet predetermined product specifications and quality attributes.

- Product specifications

Appropriate specifications have been developed. The drug product specifications contain tests for identity, impurities, potency, quantity and general attributes.

- Stability of the Product

Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of drug product. On the basis of the

data provided, the approvable shelf life for the drug product is 24 months at 2-8°C, or 23 months at 2-8°C followed by 1 month at room temperature (below 25°C).

Discussion on chemical, pharmaceutical and biological aspects

The source, history and generation of the cell substrate, including generation and characterisation of the MCB and WCB have been well described and documented.

The upstream and downstream processes have been adequately described. In-process controls (IPCs) are in place and are generally considered adequate.

Process validation for the drug substance is considered satisfactory. Issues raised during the evaluation procedure on the validation and control strategy were adequately addressed by the applicant.

Impurities have been adequately described and their clinical relevance elucidated and documented by the applicant. The results are considered acceptable.

The Major Objections raised during the assessment regarding the characterisation of the drug substance and validation of an analytical method used to control the drug substance and drug product were satisfactorily addressed by the applicant.

Most of the issues identified during the evaluation procedure on the control of the drug substance and setting of the specifications also applied to the drug product. All the concerns were considered resolved.
The applicant has revised the drug substance and drug product specifications; the acceptance criteria of some tests have been tightened and are acceptable.

Viral safety and the safety concerning other adventitious agents including TSE has been adequately assured. To further confirm the robustness of the process, the applicant will undertake post-approval studies.

The drug product manufacturing process is straightforward and has been sufficiently described. IPCs are in place and are generally considered well chosen and adequate.

Based on the stability data provided, the proposed shelf life for the drug substance and the proposed shelf life of 24 months (2-8°C) (or 23 months at 2-8°C followed by 1 month at room temperature) for the drug product were considered acceptable.

Except for a number of points, which will be addressed as part of the post-approval follow-up measures, the overall Quality of Elonva is considered acceptable.

2.3. Non-clinical aspects

Introduction

All pivotal toxicology studies and safety pharmacology studies, including toxicokinetics and immunogenicity monitoring, have been performed according to Good Laboratory Practice (GLP).
The applicant sought Scientific Advice on the non-clinical development program of toxicology, safety pharmacology and pharmacokinetic studies.

Pharmacology

- Primary pharmacodynamics

Corifollitropin alfa is a new biological entity. It is a gonadotropin designed as a Sustained Follicle Stimulant with a prolonged half-life time, but similar pharmacological features as compared to Follicle

Stimulating Hormone (FSH). The carboxy-terminal peptide (CTP) of the β-subunit of human chorionic gonadotropin (hCG) was fused to the carboxy-terminus of the β-chain of human FSH, resulting in corifollitropin alfa (Org 36286).

The *in vitro* characterisation of the pharmacodynamics of Org 36286 showed a comparable affinity to the FSH receptor, a lower signal transduction, but still comparable activity in a mouse follicle culture, when compared with rec-hFSH.

The specific bioactivity for inducing ovarian weight augmentation in immature rats following six subcutaneous FSH injections (Steelman-Pohley assay) was approximately 2-fold higher for Org 36286 than for rec-hFSH. The Steelman-Pohley assay shows that similar ovarian weights were achieved at lower doses of Org 36286 than of Rec-hFSH. However, the Org 36286 curve seems not to have reached a maximum in the assay. It is therefore not possible to estimate the consequences of this difference between Org 36286 and Rec-hFSH for clinical practice. In the ovarian weight augmentation test following single dose FSH administration, ED_{50} was approximately 1.5 times higher for rec-hFSH than for Org 36286. In this test, a plateau was reached for ovarian weight, at a higher level after Org 36286 administration than after rec-hFSH administration. In 2 superovulation assays in immature rats, Org 36286 induced at equal doses higher ovarian weights than rec-hFSH (up to approximately 4 times higher specific bioactivity). The maximal increase in oocytes/rat caused by Org 36286 was either approximately 4 times higher or at the same level, but was reached at a 4 times lower dose compared to rec-hFSH.

In vitro activity was somewhat lower for Org 36286 compared to rec-hFSH, whereas *in vivo* activity was higher. This is likely associated with the difference in pharmacokinetics between Org 36286 and rec-hFSH, causing hormone levels to be higher for a longer time after administration of Org 36286.

Early non-clinical studies were performed with non-protein-free Org 36286 (i.e. produced in medium containing foetal calf serum). Later on FCS was removed from the culture medium used for the production of Org 36286. This “protein-free” drug substance used in later studies and used for the production of corifollitropin alfa is designated Org 36286pf. Pharmacological activity of Org 36286pf and non-protein-free Org 36286 (Org 36286) was comparable in the *in vitro* receptor binding and bioactivity assays and in the Steelman-Pohley assay. In the superovulation assay in which the test substance is administered with shorter intervals, uterine and ovarian weight augmentation was similar for Org 36286pf and Org 36286. The number of ova was similar or only slightly higher for Org 36286pf up to the dose at which the maximum level was reached.

- Secondary pharmacodynamics

To monitor possible side effects of Org 36286 the compound was evaluated in an *in vitro* receptor binding screening system (Novascreen®, Hanover, Maryland, USA). This system comprised validated receptor, enzyme, ion channel, transporter, and cell-based screening assays.
No significant *in vitro* binding was observed to a range of receptors and ion channels. Org 36286 showed no relevant binding affinity to the LH receptor or activation of the LH receptor or TSH receptor.

- Safety pharmacology programme

Cardiovascular safety was investigated in the hERG channel assay and in an *in vivo* dog study. In the hERG channel assay, Org 36286 did not cause inhibition of the potassium tail current (I_{Kr}) in stably hERG-transfected human embryonic kidney cells, at concentrations up to approximately 1000 times the human C_{max}. In the cardiovascular safety pharmacology assay in dogs, no treatment-related effects were observed at exposures which were more than 200 times the human exposure, based on AUC and C_{max}. No other safety pharmacology studies were performed. This is acceptable, since the pharmacological action of Org 36286 is that of FSH, which is in principle well-known.

- Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions were performed. This is acceptable, as the pharmacological action and potential interactions of Org 36286 and the interplay of FSH with other effectors on the HPG-axis are well-known.

Pharmacokinetics

In general, following sc administration in animals, Org 36286 showed linear kinetics and a relatively slow absorption and elimination phase. The volume of distribution is low in animals and man, i.e. close to the physiological volume of blood plus that of extracellular water. The absolute bioavailability of Org 36286 after subcutaneous dosing in a representative clinical formulation is estimated to be > 85% in the dog, approximately 40% in the rat, and approximately 58% in humans. Due to the CTP addition, Org 36286 shows a significantly longer plasma elimination half-life as compared to that of rec-hFSH in women (ratio of 1.6-1.7). A comparable ratio was found in the rat and the dog. The comparison in animals was based on historical data with rec-FSH.
In rats, after relatively slow absorption from the sc injection site, Org 36286 is taken up into the blood and distributed mainly to the ovary and the kidney. The urinary route is the major excretion pathway of Org 36286 confirming the central role of the kidney in clearing relatively small peptides and gonadotropins, including FSH and hCG. In addition, the identified α- and β-subunits, including the CTP-part of Org 36286, as well as intact Org 36286 in urine show that the clearance resembles that of FSH and partly of hCG (which shows more extensive catabolism). In analogy with FSH and hCG/LH, this catabolism is likely to occur in the kidney after glomerular filtration and proximal tubular resorption. No catabolism in rat plasma occurred. No binding of Org 36286 to melanin or uptake in the brain was found.
Pharmacokinetic comparability studies of Org 36286 non-pf versus pf in rats were poorly performed. Comparison in dogs was based on data from different studies, mostly using the i.m. route of administration instead of the sc route. Although on the average pf and non-pf, or 100L scale manufacture and 500L scale manufacture batches showed similar pharmacokinetic behaviour in animals, significant differences between individual batches were observed in rats, with typical differences in C_{max} or AUC of 20-25%. A difference in glycosylation/sialation patterns is a likely cause for the observed pharmacokinetic differences. Comparison with the pharmacokinetic behaviour of the same batches in humans showed that batch-to-batch variability in pharmacokinetic behaviour in humans is more limited (approximately 10% C.V.) This variation is limited when compared with interindividual variation and has relatively little effect on the pharmacodynamic outcome; therefore the observed pharmacokinetic batch-to-batch variability in rats is of limited clinical relevance. Nevertheless, to minimise the risk of OHSS in humans, batch-tot-batch variability in glycosylation/sialation patterns, which potentially can affect pharmacokinetic behaviour, should be kept to a minimum.

Toxicology

Org 36286 (non-pf material) was tested in general toxicology, genetic toxicology, reproduction toxicology, and local tolerance studies using the mouse, rat, rabbit and dog, to support the safety of the clinical indication infertility/Controlled Ovarian Stimulation (COS).

- Single dose toxicity

Acute single dose toxicity studies using iv and sc routes in rat did not show any drug-related toxic effect. In the acute single dose study in mice (103 µg/kg sc) two animals died 12 days after treatment showing on examination hepatocellular necrosis. This finding was thought to be coincidental as it has been observed previously in historical controls of this species/strain; however, a treatment-related effect can not be ruled out. In subsequent repeated dose toxicity studies in rats and dogs no mortality has been observed.

- Repeat dose toxicity

Repeated dose toxicology studies with administration periods of 13 weeks up to 39 weeks in rats and dogs showed primarily the expected exaggerated pharmacological effects on the reproduction organs. Other effects seen in female rats were increase of thyroid and adrenal gland weight, and in female dogs atrophic changes in the adrenal cortex, thrombocytopenia and other haematological changes. These effects are considered to be the result of secondary hormonal responses by sex steroids and are consistent with those observed for rec-hFSH (follitropin beta, Puregon®/ Follistim®). The adverse effects on off-target organs were observed with systemic exposures below the anticipated clinical exposure in humans. However, the adverse effects were seen in repeated dose studies, whereas in humans corifollitropin alfa will be given as a single dose. Therefore the adverse effects seen in animals are considered to have little relevance for the clinical use of corifollitropin alfa in humans.

- Genotoxicity

Org 36286 did not show genotoxic potential in routine genotoxicity tests.

- Carcinogenicity

Carcinogenicity has not been investigated. This is accepted in view of the single dose posology. Extended stimulation (13 weeks) of gonadal tissue by corifollitropin for 13 weeks in female dogs led to a luteoma in one animal. Other, occasionally observed incidences of proliferative lesions (at 2.87 and 8.2 $\mu g.kg^{-1}.2\ days^{-1}$) are well-known estrogen-related cases in the dog (eg. urothelial hyperplasia; ovarian mesothelial hyperplasia; mesothelial hyperplasia of the uterus), that were also found incidentally for rec-hFSH (Puregon®) in the dog toxicity study (at ~2.5 and ~5 $\mu g.kg^{-1}.day^{-1}$).

- Reproduction Toxicity

The conducted rat and rabbit reproduction toxicology studies were tailor-made to mimic the period of Org 36286 exposure relative to conception and pregnancy, however they may still be considered a worst case approach. Dosing of Org 36286 resulted in the expected stimulation of the ovaries and induced an increased incidence of super-ovulation as well as pre- and post-implantation loss in rats and rabbits. The biological ceiling value of implantation and growth as observed in the animal species causing embryonic loss is not representative for the human situation of COS (prior to IVF), where one or a limited number of fertilized ova are eventually transferred to the uterus.
In rats, at super-ovulatory doses, Org 36286 did not cause teratogenicity when dosed prior to mating, during mating, and early pregnancy. In addition, dosing (at doses producing approximately twice the systemic exposure in humans) during early pregnancy in rabbits was also not indicative for a teratogenic potential. When dosed prior to mating (at relatively low doses) in the rabbit, teratogenicity was observed associated with super-ovulation only. For Humegon® (an established urinary gonadotrophin product on the market for COS), a similar teratogenic effect was found predominantly, but not exclusively, in relation to a super-ovulatory response in a comparative study. Therefore, this abnormal embryo-foetal development associated with a super-ovulatory response is considered to be irrespective of the super-ovulation inducing gonadotrophic agent.

- Toxicokinetic data

<u>Rat 13 weeks subcutaneous toxicity study</u>
In the rat 13 weeks subcutaneous toxicity study, serum levels tended to increase proportional to the increasing dose. Serum levels in the low dose group increased upon repeated dosing whereas in the mid and high dose groups serum levels were comparable for both single and multiple dosing. There seems to be no difference in kinetic behaviour between male and female rats. The elimination half-life was between 12 and 14 h.

Table 1 Mean toxicokinetic parameters of Org 36286 in rats (13-wk)

	Treatment group					
	1.64 µg·kg^{-1}		8.2 µg·kg^{-1}		41 µg·kg^{-1}	
	Kinetic value	Exposure multiple (animal/human)[#]	Kinetic value	Exposure multiple (animal/human)[#]	Kinetic value	Exposure multiple (animal/human)[#]
Single dose	n=20		n=20		n=20	
C_{max} (ng·mL^{-1})	4.32	**1.0**	16.6	3.8	115	26
AUC_{0-48} (ng*h·mL^{-1})	63.8	**0.1**	535		3399	
$AUC_{0-\infty}$ (ng*h·mL^{-1})	-		617	0.9	3794	5.7
$t_{½}$ (h)	-		13.7		12.0	
t_{max} (h)	8.0		8.0		22.0	
Multiple dose (12 weeks)	n=16		n=11		n=3	
C_{max} (ng·mL^{-1})	6.23	**1.4**	22.8	5.2	116	27
AUC_{0-48} (ng*h·mL^{-1})	154	**0.2**	596	0.9	3432	5.1
t_{max} (h)	10.0		10.0		6.0	

[#] For calculation of exposure multiples human C_{max} (4.35 ng×mL^{-1}) en $AUC_{0-\infty}$ (668 ng*h×mL^{-1}) values are based on empirical estimates in a population PK analysis of data from Trial 38819 (report INT00056976). In bold: values at NOAEL
Animal AUC values are based on composite sampling of 4-8 rats per time-point (10 time-points in total). Following multiple dose administration, animals with antibodies against Org 36286 (> 5% after day 65) were excluded for kinetic evaluation; n represents the number of rats without antibody formation against Org 36286. $t_{½}$ could only be reliably determined at 8.2 and 41 µg.kg-1 after single dose. There was no gender difference in exposure, thus male and female kinetic data were evaluated collectively. - : not calculated.

All dosing groups contained animals with percentages of anti-Org 36286 antibodies (Ab) exceeding 25%. In males 10, 50 and 90% of the animals in the 1.6, 8.2 and 41 µg.kg^{-1} groups exhibited > 25% of Ab-titers. In females 20, 40 and 85% of the animals in the 1.6, 8.2 and 41 µg.kg^{-1} groups exhibited Ab-titers of >25%. The first detection of antibodies against Org 36286 was observed from day 37 in 4/20 animals dosed at 1.6 µg.kg^{-1}, and from day 9 in 8/20 rats dosed at 8.2 µg.kg^{-1} and 35/40 rats treated at 41 µg.kg^{-1}, and after increase to maximum levels in the assay sustained over the duration of the study. In 10 female and 10 male animals of the recovery group dosed at 41 µg.kg^{-1}, anti-Org 36286 antibody formation was also tested ca. 1 and 3 weeks after the last Org 36286 injection. Most rats still exhibited Ab-titers of >25%, except for 5 male rats that had < 4% titers after ample 3 weeks of recovery.
Due to induction of Ab-formation over time, the mean serum Org 36268 exposure (24 h measurements) of the 41 µg.kg^{-1} group declines over time. However, individual non-Ab responders have high serum Org 36286 levels. This good inverse correlation between individual Org 36286 exposure and Ab-formation also exists in the 1.6 and 8.2 µg.kg^{-1} treatment groups.
Representative rat samples with low or high anti-Org 36286 binding or from control rats were analyzed for their neutralizing capacity in an in vitro bioactivity assay. From these positive samples the ones with >25% anti-Org 36286 antibodies were able to neutralize Org 36286. However, samples with ≤ 25% anti-Org 36286 antibodies were not able to neutralize Org 36286. In addition, rat serum samples with neutralizing capacity had serum Org 36286 concentrations below LOQ.

Dog 13 weeks subcutaneous toxicity

After single and multiple subcutaneous administration for approximately 11 weeks of either 1.025, 2.87 or 8.2 µg•kg^{-1} Org 36286 to male and female dogs, steady state levels were reached after two weeks of dosing. After a single dose, dose proportionality was found in males whereas in females serum levels increased super-proportionally to the increasing dose. Multiple dosing showed a tendency towards proportional increase in serum levels with increasing dose for males and females.
Serum levels from the high dose group after a single dose were higher in females than in males. On the contrary, multiple dosing tended to higher serum levels in males than in females. Org 36286 reached a plateau level around 10 h after dosing with almost no decline from 10 to 48 h. The elimination half-life was estimated to be around 76 h.

Antibody formation
None of the male dogs dosed at 1.0, 2.8 and 8.2 µg Org 36286 per kg exhibited anti-Org 36286 antibodies exceeding 25%. In addition, only one male dog treated at 1.0 $\mu g.kg^{-1}$ showed a limited response (< 25% Ab-titer) at the end of the study (> day 75) without affecting Org 36286 levels.
In female dogs the anti-Org 36286 antibody incidence and titers were not dose-related: 2/3, 0/3 and 2/5 dogs of the 1.0, 2.8 and 8.2 µg Org 36286 per kg group, respectively, exhibited Ab-titers above 25%. In addition, one female dosed at 8.2 $\mu g.kg^{-1}$ showed a limited (< 25% titers) and transient Ab-response. Exposure to Org 36268 only declined significantly when anti-Org 36286 Ab-titers exceeded 25%, and reversed when anti-Org 36286 Ab-titers declined over time.

- Local tolerance

A single dose local tolerance study in rats and observations from repeated dose toxicity studies in rats and dogs did not indicate any issue relevant for the clinical use of corifollitropin alfa.

- Other toxicity studies

There is no toxicological issue regarding impurities. With respect to the immunogenic potential no safety signal has been identified in clinical studies thus far. However, immunogenicity will need to be closely monitored, as it is clear from animal studies that antibodies against Org 36286, once formed can be cross-reactive to endogenous FSH and have neutralising capacity.

Ecotoxicity/environmental risk assessment

An environmental risk assessment has not been performed, since corifollitropin alfa is a non-chemically modified glycoprotein. Proteins are exempted from the scope of the ERA guideline for obvious reasons. Proteins are ready biodegradable and non-persistent in the environment. Once they are released in the environment they will be quickly broken down. Also for pharmacological activity the structure of proteins needs to be strictly conserved; this can only be achieved under specific storage conditions, which will be different from the variable conditions in the environment. Moreover, proteins will due to their nature (especially size) not be absorbed by organisms in the environment through skin contact. Yet, should corifollitropin be entering through the oral route, it will be digested by enteric enzymatic activity, and therefore will lose its pharmacological endocrine activity. Therefore it is not expected that corifollitropin alfa when released in the environment will have a biological endocrine effect on the organisms living in the environment.

Discussion on the non-clinical aspect

As expected, (neutralizing) antibodies against Org 36286 have been observed in animal toxicity studies. The formation of antibodies in animals was not predictive for the human situation where no antibody formation was noted in over 2000 patients treated with Org 36286. In animals without or with low or transient antibody formation, clear exposure multiples of serum Org 36286 levels existed between animals and man. Paradoxical findings in rats such as absence of corpora lutea and developing follicles (associated with an increase in interstitial cell mass and leading to an almost atrophic appearance of ovaria) were associated with hypertrophy of pituitary gland cells. These findings can be related to exposure dynamics due to interfering immunogenicity. There was a nearly 1:1 correlation between the presence of antibodies against Org 36286 and the absence of Org 36286, because it was bound to the circulating antibodies against Org 36286. The hypertrophic response in rat pituitary is likely the result of reduced endogenous FSH/estradiol levels due to cross-reactivity of anti-Org 36286 antibodies to endogenous FSH.

2.4. Clinical aspects

Introduction

The rationale for developing Elonva is to replace the first 7 injections of any daily FSH preparation in a COS treatment cycle with a single subcutaneous injection of the recommended dose of corifollitropin alfa, and thus improve patient's convenience. Although fewer injections can be regarded as favourable the benefits of the Elonva regimen as such could not be measured in the pivotal Phase III studies, as the studies had a double-blind, double-dummy design, and consequently the benefits of the corifollitropin alfa regimen as such could not be measured.

Dose-finding was based on 1 Phase II trial (38826) and subsequent PK-PD modelling (study report INT00073698). Benefit-risk assessment was based on two pivotal Phase III clinical studies: one study investigates women with a body weight $\geq$ 60 and $\leq$ 90 kg (38819), whereas the other study included women with a body weight $\leq$ 60 kg (107012). All these studies made use of a GnRH antagonist for pituitary down-regulation.

Scientific Advice was sought from the FDA and the EMEA, but from the Member States. Based on this scientific advice several adjustments were made to the clinical development:

Further to the **EMEA** Scientific Advice, a lower dose (100 µg) for women weighing 60 kg or less was developed, and the study protocol allowed flexibility in gonadotropin dosing as of Day 6 of stimulation. The number of oocytes was included as a co-primary efficacy endpoint, with predefined equivalence margins (in addition to the primary efficacy parameter pregnancy rate as required by the FDA). The number of patients in the repeated exposure trial (38825) was increased.
The EMEA also indicated that s*ince the expected advantage of corifollitropin alfa over Puregon is merely convenience of dosing, the evidence of comparable efficacy and safety will need to be exceptionally compelling.*

Further to the FDA Scientific Advice, the applicant changed the design of the pivotal Phase III trials (38819, 107012) to double-blind, double dummy. For trial 38819, the ongoing pregnancy rate was adopted as the primary efficacy parameter endpoint and a predefined limit of -8% was set for the lower bound of the two-sided 95% confidence interval.

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Nevertheless, the CHMP has requested a routine GCP inspection of the clinical Phase III study 107012: A phase III, randomized, double-blind, active-controlled, equivalence clinical trial to investigate the efficacy and safety of a single injection of 100 µg Org 36286 (corifollitropin alfa) to induce multifollicular development for controlled ovarian stimulation (COS) using daily recombinant FSH (recFSH) as a reference.

Two investigator sites and the site of the sponsor were inspected. At these two investigator sites 80 patients of the total of 396 randomized patients (20%) had been randomized. No critical but several major findings were revealed by the inspection; the clinically relevant findings pertained to:
1) possible underreporting of OHSS : The overall incidence of OHSS might have been underreported in trial 107012, due to the fact that women in case of a risk for OHSS were allowed to be withdrawn from the study and because of the more strict definition of mild OHSS. In some studies in public literature incidences for mild OHSS have been observed of 20-23%[3], while in trial 107012 the overall

[3] Golan A, Ron-El R, Herman A et al. Ovarian hyperstimulation syndrom: an update review. Obstet Gynecol Surv 1989:44:430-440.

incidence of OHSS was 6.7% in the corifollitropin alfa group and 4.7% in the recFSH (Puregon) group.
2) possible underreporting of Ectopic Pregnancy : 'ectopic pregnancy' might have been underreported, and might have been classified as 'missed abortion' instead.
3) lack of clarity with regard to the assay to detect anti-corifollitropin alfa antibodies (Please refer to the discussion under section Clinical Safety).

All points were satisfactorily addressed by the applicant.

The inspectors` observation regarding OHSS is not a reason for major concern for the following reasons:

- In the SmPC of Puregon it is stated that in clinical trials of Puregon the incidence of OHSS was approximately 4%, which is in line with the 4.7% found in trial 107012.
- There were only 7 subjects, who were discontinued due to 'risk for OHSS' or 'too high ovarian response'. The fact that women were allowed to be withdrawn from the study due to 'risk for OHSS' did therefore not result in a lower total incidence of OHSS.
- The definition of mild OHSS was slightly modified compared to the WHO criteria (1973). This modification was submitted to the IEC/IRB (and/or Regulatory Authorities) for review and a favourable opinion was obtained. This change is also considered acceptable by the CHMP. The same criteria were applied in all Phase III studies.
- Another factor that might have resulted in the lower overall incidence of OHSS was that a specific patient population was included. All subjects who had a risk of developing OHSS were excluded, such as 1) subjects with a history of ovarian hyper-response or OHSS; 2) subjects with a history of/or current polycystic ovary syndrome (PCOS); and 3) subjects with more than 20 basal antral follicles <11 mm (both ovaries combined) as measured on USS in the early follicular phase (menstrual cycle day 2-5).

The exact percentage of OHSS has been stated at the beginning of SPC section 4.8 (See also the discussion under Clinical safety).

Furthermore in view of the specific symptoms of ectopic pregnancy, it is not likely to be missed or to be misdiagnosed as missed abortion. There were only 2 cases of missed abortion, both in the corifollitropin alfa group. In the worst case scenario these 2 cases should have been classified as 'ectopic pregnancy', which would have resulted in an incidence of ectopic pregnancy of 4.1% in the corifollitropin alfa group. This is still comparable with the incidence of 3.3% in the rec-FSH group, and therefore the CHMP agreed that there is no reason for a product-specific concern.

The Inspectors observed no shortcomings that would have had a structural impact on the overall validity and/or credibility of the data submitted for this specific application. The CHMP concluded that the data is acceptable for the evaluation in the process of this MAA. Remedial actions by the sites and by the sponsor, to safeguard a GCP-compliant conduct of future clinical trials have been taken, as detailed in the follow up response of the sponsor to the final GCP inspection report. The implementation of any corrective actions will be followed up according to the relevant procedures as part of the GCP inspection programme; this follow-up is not the subject of this MAA as it is not product specific.

Pharmacokinetics

In ten clinical trials pharmacokinetic (PK) data with corifollitropin alfa were obtained (see Table 2). In accordance with the anticipated single dose regimen for COS, only single dose regimens of corifollitropin alfa were evaluated. Single dose levels ranged between 7.5 µg and 240 µg Org 36286. Concentrations of corifollitropin alfa in human serum were determined using a solid phase enzyme-immunoassay (EIA). The performed assays are validated and sufficient to measure corifollitropin alfa well.

Table 2 Overview of Clinical studies involving pharmacokinetics of corifollitropin alfa

Study Ref. No.	Short Title	Dose, route and formulation corifollitropin alfa	Subjects
38801	Phase I trial in hypogonadotropic hypogonadal male subjects	15 µg, SC, non-pf	13 healthy male
38802	Phase I trial in healthy female volunteers	15-120 µg, SC, non-pf	24 healthy female
38823	Bioequivalence trial of pf versus non-pf formulation	120 µg, SC, non-pf and pf	16 healthy female
38803	Absolute bioavailability trial	100 µg, SC and IV, pf	16 healthy female
38805	Phase II feasibility trial to induce monofollicular ovulation	7.5-60 µg, SC, non-pf	55 patients
38807	Phase II feasibility trial to induce multifollicular growth	120-240 µg, SC, non-pf	80 patients
38826	Phase II dose-finding trial to induce multifollicular growth	60-180 µg, SC, pf	315 patients
107012	Phase III equivalence trial of 100 µg corifollitropin alfa to induce multifollicular growth in subjects with body weight ≤ 60 kg	100 µg, SC, pf	268 patients
38819	Phase III non-inferiority trial of 150 µg corifollitropin alfa to induce multifollicular growth in subjects with body weight > 60kg	150 µg, SC, pf	755 patients
38833	Phase II feasibility trial to induce multifollicular growth in a long GnRH agonist protocol	100-150 µg, SC, pf	50 patients

Formulation:
Corifollitropin alfa was developed as a solution for subcutaneous injection. During early clinical development, Phase I and early Phase II trials were performed with drug substance produced under non-protein free (non-pf) conditions. Later the production of drug substance was switched to protein-free (pf) conditions (proposed market formulation). Small differences in pharmacokinetic profile are detected for the pf and non-pf formulation. While no difference in absorption is detected, half-life is longer (15%) and clearance smaller for the pf formulation leading to an increased AUC of approximately 20%. These differences are not considered to have any clinical complications especially as the pf formulation was used in the pivotal Phase II (38826) and Phase III trials (38819; 107012; 38825).

Pharmacokinetic data analysis:
Statistical methods used are adequate. Several population models were developed. The pivotal model is the pooled POP-PK (population pharmacokinetic) model which included the intent-to-treat population and included most subjects. Sparse pharmacokinetic sampling was performed for study 38833 in order to evaluate pharmacokinetics with population pharmacokinetic analysis.

- Absorption

Following subcutaneous administration of corifollitropin alfa, absorption was slow with maximal concentrations being reached at 36 h (ranging 25-48 hours) after injection. The absolute bioavailability of the pf formulation after subcutaneous (SC) injection was assessed in Study 38803 and was estimated to be 58%.

- Distribution

As determined in trial 38803, the central volume of distribution (V_c) was 4.15 L and the steady state volume of distribution (V_{ss}) was 9.4 L. No *in vitro* studies were performed using human biomaterial to study the pharmacology of corifollitropin alfa.

- Elimination

In healthy volunteers, corifollitropin alfa was eliminated from the body with a half-life of approximately 70 hours (ranging from 60-110 hours). The apparent clearance (CL/f) was 0.25 L/h (ranging from 0.18-0.31 L/h) after SC administration and the actual clearance was 0.13 L/h after IV administration of corifollitropin alfa. Similarly to other gonadotropins / hormonal glycoproteins, the excretion of corifollitropin alfa is thought to occur mainly via the kidney after glomerular filtration and proximal tubular resorption. No human ADME studies were performed; however pre-clinical studies confirmed the metabolic fate of corifollitropin alfa to be similar to hCG and FSH.
Corifollitropin alfa is expected not to be a substrate of cytochrome P450 enzymes. The applicant supported this with a rat ADME study. Though in animal studies no breakdown fragments in plasma were found, it can not be excluded that no corifollitropin alfa breakdown fragments are present in human plasma. Additional identification of breakdown fragments in humans is believed to be redundant since the Org 36286 ADME properties follow the usual physiological metabolic routes, distribution and elimination of gonadotrophins and the (anticipated) fate of the novel entity (CTP-part) has been demonstrated.

- Dose proportionality and time dependencies

The pharmacokinetics of corifollitropin alfa are well described by non-compartmental pharmacokinetics and population pharmacokinetic evaluation. Pharmacokinetics are comparable between patients and pituitary suppressed volunteers of reproductive age indicating that the endocrine status of subjects does not affect the pharmacokinetics of corifollitropin alfa. The pharmacokinetic properties of corifollitropin alfa were observed to be independent of the administered dose over a wide range (7.5 – 240 µg).

- Special populations

In subjects with renal insufficiency the excretion of corifollitropin alfa might be impaired, as corifollitropin alfa is mainly excreted via the kidney. The pharmacokinetics of corifollitropin alfa have not been determined in renally impaired subjects. Therefore, the applicant proposes that the use of corifollitropin alfa in patients with renal insufficiency is not recommended, as is expressed in the SPC. Corifollitropin alfa is not recommended for patients with all gradations of renal impairment. Information has been added in section 4.2 of the SPC regarding renally impaired patients in section 4.2. The influence of (mild) renal impairment on the exposure of corifollitropin alfa is unknown but might be quite high, however it is agreed that as Org 36286 has a long elimination half-life of 70 hours and this might even be prolonged in patients with renal impairment, as Org 36286 is mainly renally excreted.

Hepatic metabolism contributes to a minor extent to corifollitropin alfa metabolism. The pharmacokinetic profile of corifollitropin alfa is therefore unlikely to be affected by hepatic impairment. However, as no data is available in hepatic impaired patients caution is warranted. It is stated in section 5.2 of the SPC that no data are available in hepatically impaired patients. Information has also been added in section 4.2 of the SPC regarding hepatically impaired patients in section 4.2.

In a pooled population pharmacokinetic analysis of corifollitropin alfa in patients, body weight and race were identified as determinants for drug exposure. The pharmacokinetics of corifollitropin alfa were not related to age though it should be noted that the age range in the population studied is narrow, i.e. 19 to 39 years.

Exposure to corifollitropin alfa was similar for subjects with body weight ≤ 60 kg after treatment with 100 µg (Study 107012) and subjects with body weight > 60 kg after treatment with 150 µg (Study 38819).
The applicant provided an overview of differences in pharmacokinetics for women with body weight up to 100 kg. The applicant sufficiently supported the chosen difference in dosing between patients weighing >60 kg and <60 kg. It is agreed that no additional dosing advice is necessary for patients with body weight over 80 kg, as over 60 kg the differences in pharmacokinetics are relatively smaller and therefore the impact of bodyweight is less relevant.

It was shown that at similar body-weight, Asian subjects had approximately 30% lower exposure to corifollitropin alfa. The applicant discussed this observed difference sufficiently but could not identify the reason. The lower exposure in Asian subjects is not fully understood, but may be related to lower bioavailability due to differences in body composition. However, the number and size of follicles induced by 100 µg corifollitropin alfa was comparable between Asian and non-Asian subjects. Also other clinical parameters seem to be comparable.

Corifollitropin alfa is only to be used by adult female subjects of fertile age for treatment of COS. Hence, the compound has not been evaluated in paediatric or geriatric patient populations.

- Pharmacokinetic interaction studies

No in vitro studies were performed using human biomaterial to study the pharmacology of corifollitropin alfa and no drug-drug interaction studies with corifollitropin alfa have been performed in vivo. No plasma protein binding studies have been conducted with corifollitropin alfa, because no plasma protein carriers exist for FSH or gonadotropins. Additionally, corifollitropin alfa is not a substrate of cytochrome P450 enzymes and does not bind to plasma proteins; no interactions with other medicinal products are anticipated. The excretion of corifollitropin alfa is thought to occur mainly via the kidney through glomerular filtration followed by proximal tubular resorption. The applicant sufficiently addressed the possibility of drug-drug interactions on the level of renal excretion. Based on the currently available knowledge such interactions are not expected.

- Pharmacokinetics using human biomaterials

No plasma protein binding studies have been conducted with corifollitropin alfa, because no plasma protein carriers exist for FSH or gonadotropins. The applicant provided a literature study on this subject.

Pharmacodynamics

Three Phase I trials were performed, one trial in hypogonadotropic hypogonadal male volunteers (38801) and two trials in pituitary-suppressed healthy female volunteers (38802 and 38823). In addition, single dose administration of corifollitropin alfa was studied in two Phase II (38807 and 38826) and two Phase III trials (107012, 38819) in patients undergoing Controlled Ovarian Stimulation (COS).

- Mechanism of action

Corifollitropin alfa is designed as a sustained follicle stimulant with the same pharmacodynamic profile as (rec)FSH, but with a markedly prolonged duration of FSH activity. Due to its ability to initiate and sustain multiple follicular growth for an entire week, a single subcutaneous injection of the recommended dose of corifollitropin alfa may replace the first seven injections of any daily (rec)FSH preparation in a COS treatment cycle. The long duration of FSH activity was achieved by adding the carboxy-terminal peptide of the β-subunit of human chorionic gonadotropin (hCG) to the β-chain of human FSH.

Serum levels of the hormones inhibin-B, estradiol (E_2), luteinising hormone (LH) and progesterone (P) were measured to monitor the PD effect of corifollitropin alfa. In addition, FSH immunoreactivity

levels were measured by a fluoro-immunoassay, which is not specific to corifollitropin alfa. The total FSH immunoreactivity of corifollitropin alfa, endogenous FSH and recombinant FSH was determined by this assay. Transvaginal ultrasound scans (USS) were performed to monitor follicular development. Inhibin-B is synthesized by granulosa cells in response to FSH and can therefore serve as a prognostic indicator in women undergoing COS. In addition, inhibin-B and estradiol have shown to be correlated with the number of follicles. The pharmacodynamic parameters measured in the PD studies are acceptable.

- Primary and Secondary pharmacology

Phase I pharmacology studies in healthy volunteers
Studies 38801 and 38802 were conducted with the formulation produced under non-protein free (non-pf) conditions, which is not the formulation-to-be-marketed. From 2002 onwards a switch was made to drug substance that was produced in a protein free (pf) medium. In the bioequivalence trial 38823, a dose of 120 μg of either formulation (pf versus non-pf) was compared.

Serum inhibin-B concentrations
- Study 38801 in hypogonadotropic hypogonadal male subjects demonstrated that a single dose of 15 μg non-pf corifollitropin alfa causes a mean increase in inhibin-B concentrations of 1.4-fold after 144h compared to baseline.
- Study 38802 investigated the effect of different doses of non-pf corifollitropin alfa (15 μg, 40 μg, 60 μg and 120 μg) in pituitary-suppressed female volunteers. In contrast to study 38801, in the 15 μg group more than half of all females had inhibin-B levels below LLOQ on all assessments. Increasing the corifollitropin alfa dose resulted in higher maximum inhibin-B levels. Even more, with increasing dose of corifollitropin alfa the maximum inhibin-B peak was reached later: Day 3, Day 4 and Day 6 for the 30, 60 and 120 μg groups, respectively.
- In the bioequivalence study 38823, the inhibin-B concentrations were higher after treatment with the pf-formulation (772 pg/mL) compared to the non-pf formulation (659.5 pg/mL), and the maximum inhibin-B peak appeared later for the pf- versus non-pf formulation (Day 7 vs. Day 6).

Serum estradiol and testosterone concentrations
- No relevant changes were observed in serum testosterone or estradiol concentrations in hypogonadotropic hypogonadal males.
- In addition, serum estradiol levels were close to the Lower Limit of Quantification in pituitary-suppressed females, because estradiol synthesis was largely impaired due to profound LH suppression by an oral contraceptive.

Follicular development
- Transvaginal ultrasound scans to monitor follicular development in female volunteers showed a dose-dependent increase in the number and the size of the follicles as shown by the "maximum number of follicles ≥5 mm": in the lowest dose groups (10 and 30 μg non-pf), only 1.1 and 1.7 follicles met this criterion, while in the 60 and 120 μg non-pf group a mean number of 17.3 and 26.7 follicles had this diameter.
- In accordance with the higher inhibin-B concentrations for the pf formulation, the maximum number of follicles was higher after treatment with the 120 μg pf formulation compared to the 120 μg non-pf formulation: 26.4 and 29.9, respectively.

Delay in response
The results indicate that administration of corifollitropin alfa results in the following consecutive PD responses, which start with an increase in inhibin-B, followed by an increase in follicle growth. This delay in response is dose-dependent.
For instance, for the 120 μg dose: the corifollitropin alfa pf-peak was observed after 36 hours, versus 6 days later for inhibin-B (144h), and the mean value on which the maximum number of follicles was observed was 9.4 days (226h). For the 60 μg dose: the corifollitropin alfa pf-peak was observed after

36 hours, versus 4 days later for inhibin-B (96h), and the mean value on which the maximum number of follicles was observed was 6.9 days (166h).
Such a delay has also been observed in literature by Porchet et al.[4] for 1-week daily administration of 150 IU rFSH (Gonal-F®) in pituitary-suppressed female volunteers. The inhibin-B peak was observed after 168h, whereas the total follicular volume (> 10 mm) peaked at 264h.

Clinical pharmacology data in Phase II and III pharmacology trials in patients
Phase II study 38807 was performed with the non-pf formulation, whereas the other studies (38826, 107012 and 38819) used the pf formulation. Therefore, the most important Phase II trial is 38826.

Serum inhibin-B and estradiol (E_2) concentrations
- Serum inhibin-B and E_2 levels increased with increasing exposure to corifollitropin alfa. In Phase III clinical trials, in line with the higher FSH immunoreactivity levels in the early follicular phase, serum inhibin-B and E_2 levels were higher on Stimulation Day 5 after treatment with corifollitropin alfa as compared to daily recFSH. On Day 8 and on the Day of hCG these hormone levels were comparable between the treatment groups in both Phase III trials.

Serum LH and progesterone concentrations
- Median serum LH and progesterone levels were observed to be low during stimulation with the corifollitropin alfa/ganirelix regimen, which is indicative for an adequate suppression of endogenous gonadotropins throughout ovarian stimulation.
- In the Phase III trials, a difference was observed in incidence of premature LH surge before the start of the GnRH antagonist on stimulation day 5 between subjects stimulated with corifollitropin alfa and recFSH; in trial 107012 5.2% vs. 3.9%, respectively, and in trial 38819 7.0% vs. 0.8%, respectively. Despite this difference, the percentage of subjects with embryo transfer was comparable between all treatment groups. Also for women with a premature LH rise with a concomitant P rise, the percentage of subjects with embryo transfer was comparable between all treatment groups. In addition, pregnancy rates did not seem to be compromised. Therefore, the clinical impact of the slightly higher incidence can be considered negligible.

Follicular development
- A relationship was demonstrated between the dose of corifollitropin alfa and the number and size of recruited follicles (60 µg, 120 µg and 180 µg). The number of follicles with diameter ≥11 mm was 11.4, 13.5, 16.4 and 10.6 for the 60 µg, 120 µg, 180 µg and 150 IU rFSH dose groups, respectively.
- In the Phase III trials, the number of follicles with diameter ≥17 mm induced by 100 µg corifollitropin alfa in subjects with a body weight ≤ 60 kg (107012) and 150 µg corifollitropin alfa in subjects with body weight > 60 kg (38819) were similar in each trial: 5.3 and 5.1 for 100 µg corifollitropin alfa and 150 IU recFSH, respectively, and 5.7 and 5.6 for 150 µg corifollitropin alfa and 200 IU, respectively.
- However, in the corifollitropin alfa groups slightly more medium-sized follicles were observed, indicating that the corifollitropin alfa regimen is recruiting a larger cohort of follicles than daily recFSH. The number of follicles with diameter ≥11 mm was 14.9 and 12.9 for 100 µg corifollitropin alfa and 150 IU recFSH, respectively, and 16.0 and 13.9 for 150 µg corifollitropin alfa and 200 IU, respectively. This is in accordance with higher levels of FSH immunoreactivity during the first days of stimulation after treatment with corifollitropin alfa as compared to daily recFSH.

Duration of treatment
- The duration of stimulation to reach the criterion for administration of hCG was the same in all groups (9 days).

[4] Porchet HC, le Cotonnec J-Y, Loumaye E. Clinical pharmacology of recombinant follicle-stimulating hormone. III. Pharmacokinetic-pharmacodynamic modelling after repeated subcutaneous administration. Fertil Steril 1994;61:687-695.

Pharmacodynamic interactions

Pharmacodynamic interactions with other medicinal products or substances were not studied, which is acceptable.

Clinical efficacy

One Phase II (38826) dose-selection study and two pivotal Phase III studies (107012, 38819) were submitted to document the efficacy of corifollitropin alfa in the indication "Controlled Ovarian Stimulation (COS)" (Table 3). The Phase II study was an open-label, active-controlled (150 IU recFSH Puregon), randomized, dose-finding trial. Based on the outcome of this trial and subsequent PK/PD modelling, the recommended doses of 100 µg in women ≤ 60 kg and 150 µg in women >60 kg were chosen for the Phase III clinical program. One Phase III study (107012) assessed equivalence of 100 µg corifollitropin alfa compared to 150 IU rFSH in women with a body weight ≤ 60 kg, whereas the other Phase III study assessed non-inferiority of 150 µg corifollitropin alfa compared to 200 IU rFSH in women with a body weight >60 and ≤ 90 kg (38819). In addition, a Phase III (38825), open-label, uncontrolled clinical trial evaluating multiple COS attempts, is still ongoing to assess the non-immunogenicity and safety.

Table 3: Tabular listing of the efficacy and safety studies

Study ID	No. of study centres / locations	Design	Study Posology	Subjs by arm enrolled/compl.	Mean age; Race	Diagnosis Incl. criteria	Primary Endpoint
38826	17 sites in Europe (BE, DE, DK, FI, UK, NL, NO, SE)	Open-label, active-controlled, randomized dose-finding trial **(Phase II)**	60, 120 and 180 µg pf corifollitropin alfa (Elonva) or 150 IU rFSH (Puregon)	325 randomized 315 ITT 60 µg: 77 120 µg: 77 180 µg:79 Puregon: 82	32.1 years, Caucasian (95%), Black (2.2%), Asian (1.6%), Other (1.0%)	Females of couples with an indication for COH and IVF or ICSI; ≥18 and ≤ 39 years of age; BMI ≥ 18 and ≤ 29 kg/m2; normal menstrual cycle length: 24-35 days.	The number of oocytes (=cumulus-oocyte-complexes) retrieved.
38819	20 sites in Europe (BE, CZ, DK, FI, FR, NL, NO, ES, SE, UK, US), 13 sites in the US, 1 site in CA,	Double-blind, active-controlled, randomized, non-inferiority trial **(Phase III)**	150 µg pf corifollitropin alfa (Elonva) or 200 IU rFSH (Puregon)	1509 randomized 150 µg: 757 Puregon: 752 1367 embryo transfer 150 µg: 672 Puregon: 704	31.5 years, Caucasian (86%), Black (4.1%), Asian (2.8%)	Females of couples with an indication for COS and IVF or ICSI; ≥ 18 and ≤ 36 years of age; **body weight > 60 and ≤ 90 kg** and BMI ≥ 18 and ≤ 32 kg/m2; normal menstrual cycle length: 24-35 days.	Ongoing pregnancy rate assessed at least 10 weeks after ET. Co-primary endpoint: number of oocytes retrieved.
107012	14 sites in Europe (AT, CZ, DK, FR, PL, ES, SE), 2 sites in Asia (Korea, Taiwan)	Double-blind, active-controlled, randomized, equivalence trial **(Phase III)**	100 µg pf corifollitropin alfa (Elonva) or 150 IU rFSH (Puregon)	396 randomized 100 µg: 268 Puregon: 128 367 embryo transfer 100 µg: 246 Puregon: 121	31.0 years, Caucasian (55%), Asian (44%), Black (0.3%)	Females of couples with an indication for COS and IVF or ICSI; ≥ 18 and ≤ 36 years of age; **body weight ≤ 60 kg** and BMI ≥ 18 and ≤ 32 kg/m2; normal menstrual cycle length: 24-35 days.	The number of oocytes (=cumulus-oocyte-complexes) retrieved.

- Dose response studies

Dose selection

Phase II dose-finding trial (38826)
The study (n=325) was designed to investigate the dose-response relationship of a single injection of corifollitropin alfa (60, 120 and 180 µg pf corifollitropin alfa) in women aged 20-39 years undergoing COS. A fixed reference dose of daily 150 IU recFSH (Puregon®) treatment was included as reference.
The primary efficacy endpoint, i.e. mean number of oocytes retrieved, increased significantly with the corifollitropin alfa dose (Table 6).
The lower number of oocytes retrieved in the recFSH group are most likely the result of the protocolized regimen, which did not allow increase of the 150 IU dose, and subsequently led to suboptimal reference treatment. The primary endpoint for this study is appropriate, as it has been used before to assess safety and efficacy of gonadotropins for COS (EPAR Puregon). The EMEA proposed to add this endpoint as a co-primary endpoint in the Phase III 38819 trial in their Scientific Advice Meeting. Ongoing pregnancy rates were assessed as secondary outcome. The resulting pregnancy rates were relatively low, and ranged between 13.6% and 15.6% per started cycle.

PK/PD modelling (INT00073698)
Based on the outcome of the dose-finding trial and subsequent PK/PD modelling, it was concluded that the recommended dose for the Phase III clinical program of corifollitropin alfa was 100 µg for subjects with body weight ≤ 60 kg and 150 µg for subjects with body weight >60 kg. Four outcome parameters were included in the modelling framework: 1) inhibin-B response, 2) the initial follicular response, 3) number of oocytes retrieved, and 4) number of fertilized 2-pronuclei (2PN) oocytes retrieved. Body weight was identified as a determinant to exposure to corifollitropin alfa. It was anticipated that the 100 µg and 150 µg would result in 12.1 and 13.2 oocytes retrieved.
The data suggest that a dose of 125 µg instead of 150 µg could also have been chosen in subjects with body weight >60 kg (both rFSH started on Day 8). The predicted mean number of oocytes retrieved and mean number of fertilized 2PN oocytes were only slightly lower with 125 µg compared to 150 µg. In addition, 125 µg would also have resulted in <10% of inhibin-gaps (≥1.5 days). However, the applicant indicated that the clinical outcome was anticipated to be optimal for a slightly higher dose of 150 µg, and therefore decided to use 150 µg in the Phase III trial in women with a body weight >60 kg (38819).

Phase II pilot trial using a long protocol of GnRH agonist
The results on oocytes retrieved obtained in this uncontrolled study that used a GnRH agonist for pituitary down-regulation, indicated a higher number of oocytes retrieved (15.4 and 17.8 for the 100 µg and 150 µg, respectively) than noted in both Phase III studies 13.3 and 13.7 for the 100 µg and 150 µg, respectively, that used a GnRH antagonist protocol to down-regulate the pituitary. As a result, the applicant has included the wording "in combination with a GnRH antagonist" in the indication (section 4.1), as recommended by the CHMP.

These findings are in line with the systematic review and meta-analysis by Kolibianakis et al., which showed that significantly more oocytes were retrieved with the GnRH agonist protocol compared with the GnRH antagonist protocol (weighted mean difference 1.19 more oocytes, 95% CI: 0.56, 1.82). Other factors that could have contributed to this higher number of oocytes are the fixed dose of recFSH from stimulation day 8 onwards, the fact that all patients received recFSH on the day of hCG, and that all patients received 10,000 hCG.

- Main studies

The two pivotal Phase III studies are:
  - Study 38819: Double-blind, active-controlled, randomized, equivalence trial of 150 µg corifollitropin alfa (single injection) or 200 IU recFSH (daily) to induce multifollicular growth in subjects > 60kg

- Study 107012: Double-blind, active-controlled, randomized, non-inferiority trial of 100 µg pf corifollitropin alfa (single injection) or 150 IU recFSH (daily) to induce multifollicular growth in subjects ≤ 60 kg

METHODS

Study Participants
Both main Phase III studies were designed as randomized, double-blind double-dummy, active-controlled, multicentre trials, involving IVF centres in North America (38819), Europe (38819 and 107012) and Asia (107012).
The numbers of patients randomized and completed in each study and disposition of patients (by IVF stage) is presented for both studies in table 4 and Table 5.

Table 4: Disposition of IVF patients by IVF stage in Trial 38819

	Trial 38819 150 µg corifollitropin alfa	**Trial 38819 200 IU recFSH**
Randomized	757 (100.0%)	752 (100.0%)
Treated with Elonva or recFSH	756 (99.9%)	750 (99.7%)
Treated with ganirelix	754 (99.6%)	749 (99.6%)
Treated with hCG	733 (96.8%)	741 (98.5%)
Oocyte retrieval	732 (96.7%)	742 (98.7%)
Sperm/oocyte incubation	727 (96.0%)	737 (98.0%)
Embryo transfer	672 (88.8%)	704 (93.6%)

Table 5: Disposition of IVF patients by IVF stage in Trial 107012

	100 µg corifollitropin alfa	150 IU recFSH
Randomized	268 (100.0%)	128 (100.0%)
Treated with Elonva or recFSH	268 (100.0%)	128 (100.0%)
Treated with ganirelix	268 (100.0%)	128 (100.0%)
Treated with recFSH from day 8 onwards	268 (100.0%)	127 (99.2%)
Treated with hCG	266 (99.3%)	127 (99.2%)
Oocyte retrieval	266 (99.3%)	127 (99.2%)
Sperm/oocyte incubation	264 (98.5%)	124 (96.9%)
Embryo transfer	246 (91.8%)	121 (94.5%)
Total discontinued	22 (8.2%)	7 (5.5%)

Except for the difference in body weight, similar inclusion and exclusion criteria were applied in both studies.

Inclusion criteria:
- Females of couples with an indication for COS and IVF or ICSI;
- ≥ 18 and ≤ 36 years of age at the time of signing informed consent;
- body weight > 60 and ≤ 90 kg and BMI ≥ 18 and ≤ 32 kg/m2 (Study 38819)
- body weight ≤ 60 kg and BMI ≥ 18 and ≤ 32 kg/m2 (Study 107012)
- normal menstrual cycle length: 24-35 days;
- availability of ejaculatory sperm (use of donated and/or cryopreserved sperm was allowed).

Exclusion criteria:
- history of non-or low ovarian response to FSH/hMG treatment;
- more than three unsuccessful IVF cycles since the last established ongoing pregnancy;
- history of ovarian hyper-response or OHSS (see Page 7 for definitions);
- history of/or current PCOS;

- more than 20 basal antral follicles <11 mm (both ovaries combined) as measured on USS in the early follicular phase (menstrual cycle day 2−5).

The applied inclusion and exclusion criteria are adequate. Patients with a history of hyperresponse or OHSS, PCOS or an antral follicle count > 20 were excluded for safety reasons, and this was reflected in the proposed SPC. In addition, patients were excluded with a history of non- or low ovarian response to FSH/hMG treatment or with more than three unsuccessful IVF cycles since the last established ongoing pregnancy.

Treatments

Study 38819: On day 2 or 3 of the menstrual cycle, a single SC injection of 150 µg (0.5 mL) (placebo-) Elonva was administered (Stimulation Day 1). Daily SC injections with (placebo-) recFSH (equivalent to 200 IU fixed dose) were started on Stimulation Day 1 and continued up to and including Stimulation Day 7. The dose of (placebo-) recFSH could be reduced from Stimulation Day 6 onwards. From Stimulation Day 8 onwards treatment was continued with a daily SC dose of recFSH up to and including the Day of hCG. As soon as three follicles ≥ 17 mm were observed by USS, hCG (10,000 IU/USP Units) was administered the same day or the day thereafter to induce final oocyte maturation. The maximum duration of stimulation was 19 days.

Study 107012: On day 2 or 3 of the menstrual cycle, a single SC injection of 100 µg (0.5 mL) (placebo-) Elonva was administered (Stimulation Day 1). Daily SC injections with (placebo-) recFSH (equivalent of 150 IU fixed dose) were started on Stimulation Day 1 and continued up to and including Stimulation Day 7. The dose of (placebo-) recFSH (maximally 200 IU) could be adjusted from Stimulation Day 6 onwards (e.g. in case of an inappropriate observed follicular response). From Stimulation Day 8 onwards treatment was continued with a daily SC dose of recFSH (maximally 200 IU) up to and including the Day of hCG. The maximum total duration of stimulation was 19 days.

The selection of the comparator recFSH (Puregon) is acceptable, as it is a frequently used recFSH preparation in COS. Puregon is approved for the COS-indication by the centralised procedure (EU/1/96/008).

Dose of the comparator (Puregon®)
In both 38819 and 107012, the dose of recFSH was set at maximum 200 IU. In the SPC of Puregon it is indicated *"that a starting dose is recommended for at least the first four days. Thereafter, the dose may be adjusted individually. In clinical studies it was shown that maintenance dosages ranging from 75-375 IU for six to twelve days are sufficient."*

Maximum dose of 200 IU recFSH
The lack of uptitration above 200 IU of the recFSH dose is acceptable for the following reasons:
- Discontinuation due to "insufficient ovarian response" and "no/too few/bad quality oocytes retrieved" was very low.
- Patients were relatively young (≤ 36 years) with serum FSH and LH levels indicating sufficient ovarian reserve.
- Patients with a "History of non-or low ovarian response to FSH/hMG treatment" were excluded.
- The dosing regimen was similar for both treatment groups from Stimulation Day 8 onwards in both trials. For both treatment groups the maximum dose of 200 IU was applied.
- The total duration of stimulation was similar for both treatment groups in both trials.

Even more, there are no concerns for suboptimal treatment as the ongoing pregnancy rate in the recFSH group was high, 38.1% in trial 38819 and 34.4% in trial 107012 (see 'Results' section). This pregnancy rate is higher than was expected, as clinical routine pregnancy rates per ART cycle are in Europe (~24%) and in the USA (34.3%).

Dose adjustment from Stimulation Day 6

To avoid that FSH dose reductions were performed on top of the start of the GnRH antagonist ganirelix at stimulation day 5, recFSH dose adjustments were only allowed one day later (i.e. from day

6 onwards). Dose adjustment of rec FSH is within the current SPC and it is also in line with the recommendations given in the review by Arce et al. 2005 regarding methodological and clinical issues in the design of efficacy trials in ART: "A fixed starting dose for at least 5-7 days should be proposed for all efficacy trials".[5]

Justification of starting dose in trial 38819

Justifications provided by the applicant for the starting dose of 200 IU recFSH in trial 38819 can be accepted:

- A starting dose of 200 IU Puregon is consistent with the labelling both in Europe and the USA.
- The withdrawal due to a too high ovarian response was low, and the chosen dose is therefore not too high. Four subjects discontinued in the 200 IU recFSH group, because of 'risk of OHSS' (2 subjects), 'too high ovarian response' (1 subject) and 'due to (S)AE' (1 subject). The AE in this subject was OHSS.
- Discontinuation due to insufficient ovarian response was low, and the chosen dose is therefore not too low. In study 38819, 2 subjects for 200 IU Puregon and 8 subjects for 150 µg corifollitropin alfa.
- The median total duration of stimulation was 9 days for both treatment groups and only 2 days were required to complete ovarian stimulation from Day 8 onwards.
- Dose adjustment was possible for the Puregon comparator dose from Stimulation Day 6 onwards.
- The dosing regimen was similar for **both** treatment groups from Stimulation Day 8 onwards.

Objectives

The objective of study 38819 was to investigate the efficacy and safety of a single injection of 150 µg corifollitropin alfa in women weighing >60 kg and ≤90 kg to induce multifollicular development for COS, using daily recFSH as a reference.

The objective of study 107012 was to investigate the efficacy and safety of a single injection of 100 µg corifollitropin alfa in women weighing 60 kg or less undergoing COS for IVF/ICSI, using daily recFSH as a reference.

Endpoints

In trial 38819, the primary endpoint was 'ongoing pregnancy rate assessed at least 10 weeks after embryo transfer' and the co-primary endpoint was 'number of oocytes retrieved'. The primary endpoint was requested by the FDA in their Scientific Advice-meeting, whereas the co-primary endpoint 'number of oocytes retrieved' was asked for by the EMEA in their Scientific Advice-meeting. The primary and co-primary endpoint are both considered acceptable.
In study 107012, the primary endpoint is 'number of oocytes retrieved'. Preferably, ongoing pregnancy rate would also have been included as primary endpoint, as it is a better estimate of treatment success (delivery of a healthy baby). However, to adequately establish non-inferiority in ongoing pregnancy rates the sample size needed to be at least 3-4 fold higher compared to a trial powered on oocytes. Therefore, the applicant decided to establish non-inferiority in ongoing pregnancy rates as primary endpoint only for the highest 150 µg dose in trial 38819 and not also in the study evaluating a subgroup of the population with a body weight ≤ 60 kg. This is acceptable to the CHMP, as the EMEA in their Scientific Advice meeting asked specifically for 'number of oocytes retrieved' to be included as primary efficacy endpoint. In the latter trial, however, 'ongoing pregnancy rate' was included, but only as a secondary endpoint.

Sample size

In study 38819 the ongoing pregnancy rate was the primary endpoint on which the comparison was based in order to establish *non-inferiority* versus recFSH. For the difference between the ongoing

[5] Arce J-C, Nyboe Andersen A, Collins J. Resolving methodological and clinical issues in the design of efficacy trials in assisted reproductive technologies: a mini-review. Hum Reprod 2005:20:1757-1771.

pregnancy rates of the corifollitropin alfa group and the recFSH treatment group a predefined limit of -8% was set for the lower bound of the two-sided 95% confidence interval. This margin was considered a meaningful difference between the treatment groups in view of the variation in routine clinical pregnancy rates between centres and the difference of around 10% between clinical routine pregnancy rates per ART cycle in Europe (~24%)[6] and the USA (34.3%)[7]. This variation in pregnancy rates is mainly due to differences in the number of embryos transferred. In view of the fact that this global trial was to include many European centres that were to opt to perform single embryo transfer in a large proportion of their patients the resulting ongoing pregnancy rate was expected to be in the range of 20-30%. A sample size of at least 1380 subjects was then the minimum required to demonstrate non-inferiority using an 8% margin, assuming the ongoing pregnancy rate could not exceed 30%. This margin was associated with an observed maximum difference in ongoing pregnancy rates of less than 4% between the treatment groups. Based on these data, 700 subjects per group, in total 1400 subjects were to be randomized.

In study 107012 the number of oocytes retrieved was the primary endpoint on which the comparison was based in order to establish equivalence, using the pre-specified equivalence margins of -3 and +5 oocytes. Anticipating an SD of about 7.5-8 and assuming no actual treatment difference and a randomization ratio of 2:1 (twice as many subjects on corifollitropin alfa as on recFSH), a total sample size of 330 was required to show equivalence with a power of 90% using the equivalence margins of -3 and +5 oocytes. A total of 330 subjects were to be randomized in a 2:1 ratio (220 subjects in the investigational group, 110 subjects in the reference group).

Randomization

Randomization was done by central remote allocation using an Interactive Voice Response telephone System (IVRS). Randomization was done per centre and was stratified for age (< 32 and ≥ 32 years); randomization in study 107012 was also stratified for planned fertilization procedure (IVF or ICSI).

Blinding (masking)

All medication delivered by the study sponsor was blinded and coded by protocol number, the amount of medication, the expiry date, the storage conditions, the packaging number and, if applicable, the name of the investigator. Since both the investigational products and placebos used during this trial were indistinguishable (all transparent liquids), no additional measures were needed to ensure medication blinding.

Statistical methods

Analysis of the (co-)primary endpoints was performed on a 'per attempt' and on a 'per stage' basis both for the ITT and PP groups. The 'per attempt' basis is considered most relevant. According to the 'Points to consider on switching between superiority and non-inferiority' (CPMP/EWP/482/99), in a non-inferiority trial the ITT and PP analysis set have equal importance. For showing equivalence the PP analysis is more important, as the results of the ITT analysis set may be biased towards demonstrating equivalence. However, both data sets should lead to the same conclusions.
The treatment groups were compared in trial 38819 with a generalized linear model for the ongoing pregnancy rate including factors treatment group, age at randomization and region (Europe vs. North-America). In addition, treatment groups were compared in trial 38819 with ANOVA for the number of oocytes including factors treatment group, age at randomization and centre. In trial 107012, also the planned fertilization procedure (IVF vs. ICSI) was taken into account as a variable following the recommendation from the FDA after review of protocol 38819, and as 107012 was a much smaller trial than trial 38819 and could therefore be more vulnerable to imbalance. The planned fertilization procedure is primarily based on sperm characteristics of the patient's partner and previous IVF results.

[6] The European IVF monitoring programme (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2001. Results generated from European Registers by ESHRE. Hum Reprod 2005; 20 (5): 1158-76.
[7] 2002 Assisted Reproductive Technology Success Rates. National Summary and Fertility Clinic Reports. Accessed at: http://www.cdc.gov/reproductivehealth/art02/index.htm

The subjects who had embryo(s) transferred or cryo-preserved before Day 3 were excluded from the assessment of embryo quality, since at Day 3 all embryos were to be assessed according to the Phase III protocols.
The chosen non-inferiority margin of 8% between the ongoing pregnancy rates of corifollitropin alfa versus recFSH is considered rather wide. However, in light of the differences between the clinical routine pregnancy rates per ART cycle in Europe (24%) and the USA (34%), and the fact that the observed maximum difference in ongoing pregnancy will not exceed 4%, this 8% margin is acceptable.

The equivalence margin for the number of oocytes retrieved was -3 and +5 oocytes. The rationale provided by the applicant is as follows: "If the corifollitropin alfa regimen resulted in 3 or more oocytes less than the reference treatment, such difference was considered as clinically relevant because 3 oocytes usually result in one good quality embryo for transfer or freezing. Anticipating to induce an average of 12-13 oocytes with the applied recFSH doses in the two reference groups, an excess of more than 5 oocytes would be undesirable as subjects with more than 18 oocytes are known to have an increased risk of OHSS[8,9]. Hence, an upper margin of +5 oocytes is applied for the difference in the number of oocytes retrieved between the corifollitropin alfa and recFSH treatment groups." The CHMP considers the rationale for the equivalence margin of -3 and +5 oocytes acceptable.

RESULTS

Participant flow

In both trials the discontinuation in the corifollitropin alfa group was higher compared to the recFSH group: 11.1% and 6.1% for 150 μg corifollitropin alfa and 200 IU recFSH, respectively, and 8.2% and 5.5% for 100 μg corifollitropin alfa and 150 IU recFSH, respectively. In 38819, the differences were highest in categories: (1) Due to (S)AE, (2) Risk of OHSS, (3) Too high ovarian response. The data imply that 150 μg corifollitropin alfa might evoke a too high ovarian response, and consequently a higher risk on OHSS and (S)AE than seen with 200 IU recFSH.

Baseline data

Baseline demographics were comparable within each trial. No clinically relevant differences were observed in the baseline characteristics within each trial, such as type of infertility (male factor, unexplained infertility, tubal factor) and previous IVF cycle. The groups were not matched for severity of male factor infertility and stage of endometriosis. However, the exclusion criterion "Less than two ovaries or any other ovarian abnormality (including endometrioma > 10 mm; visible on USS)" and the inclusion criterion "availability of ejaculatory sperm" were used. As no differences in fertilization were observed in trials 107012 (67.6% vs. 67.7%) and 38819 (66.0% vs. 67.6%), there is no reason for concern. The overall mean age was 31 years. A large percentage in study 107012 were Asian patients (44%).

Numbers analysed / Outcomes and estimation

(Co-)Primary efficacy results
Major efficacy data of the intent-to-treat and per-protocol population are summarized in Table 6 In 38819, non-inferiority for the primary endpoint, i.e. ongoing pregnancy rate, was adequately established. For the co-primary endpoint 'number of oocytes retrieved' equivalence has been shown. Also, in 107012, equivalence has been shown for number of oocytes retrieved, i.e. the primary endpoint. For both populations similar results were obtained.

[8] Papanikolaou EG, Pozzobon C, Kolibianakis EM, et al. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil Steril. 2006;85:112-120.
[9] Verwoerd GR, Mathews T and Brinsden PR. Optimal follicle and oocyte numbers for cryopreservation of all embryos in IVF cycles at risk of OHSS. RBM online. 2008;17, 312-317.

Table 6: Overview of trials used to support efficacy and the outcome of the predefined efficacy analyses

			Number of oocytes retrieved		**Ongoing pregnancy rate**	
Trial (Phase)	Trial design (Number of subjects enrolled)	Treatment	Mean (SD)	Estimated difference[a] [95% CI]	%	Estimated difference[a] [95% CI]
38826 (II)	Open-label Dose-finding trial (N=325)	60 µg Elonva	5.2 (5.5)	Dose-response established **primary endpoint**	15.4%	
		120 µg Elonva	10.3 (6.3)		15.6%	
		180 µg Elonva	12.5 (8.0)		13.9%	
		150 IU recFSH	7.7 (6.3)		13.6%	
38819 (III)	Double-blind Non-inferiority trial ITT population (N=1509)	150 µg Elonva	13.7 (8.2)	+1.2 [0.5;1.9] Equivalence established **co-primary endpoint**	38.9%	+0.9% [-3.9; 5.7] Non-inferiority established **primary endpoint**
		200 IU recFSH	12.5 (6.7)		38.1%	
	PP population (N=1472)	150 µg Elonva	13.7 (8.2)	+1.2 [0.5;2.0] Equivalence established **co-primary endpoint**	39.4%	+1.1% [-3.8; 6.0] Non-inferiority established **primary endpoint**
		200 IU recFSH	12.6 (6.8)		38.5%	
107012 (III)	Double-blind Equivalence trial ITT population (N=396)	100 µg Elonva	13.3 (7.3)	+2.5 [1.2;3.9] Equivalence established **primary endpoint**	25.4%	-9.2% [-18.9; 0.5%] **secondary endpoint**
		150 IU recFSH	10.6 (5.9)		34.4%	
	PP population (N=396)	100 µg Elonva	13.3 (7.3)	+2.5 [1.2;3.9] Equivalence established **primary endpoint**	25.4%	-9.2% [-18.9; 0.5%] **secondary endpoint**
		150 IU recFSH	10.6 (5.9)		34.4%	
38825 (III)	Open-label Non-controlled safety trial (N=681)	Cycle 1: 150 µg Elonva	11.9 (7.2)		31.1%[b]	

[a] Estimated difference Elonva – recFSH; [b]Biochemical pregnancy rate presented as trial is ongoing

Key secondary efficacy results

In trial 107012, evaluating efficacy in women with body weight ≤ 60 kg, the percentage of ongoing pregnancy rates was not in favour of 100 µg corifollitropin alfa. The difference of 9% and the lower margin of -19% are considered substantial. The applicant discussed differences in patient history and baseline characteristics, stimulation characteristics and fertilization procedures and embryo transfer between the two treatment groups. None of these factors could explain the observed difference in pregnancy rates. Thus, the observed difference is most likely a chance finding. Reassuring is the larger 38819 trial, with similar variables as 107012, which revealed a similar pregnancy rate for corifollitropin alfa and Puregon.

Pregnancy follow-up

The full study reports (38821 and 107014) of the pregnancy and neonatal outcome data from the two pivotal clinical trials were submitted. The take-home baby rates reflect the ongoing pregnancy rates: 35.6% in the 150 µg group compared to 34.4% in the 200 IU recFSH group, and 23.5% in the 100 µg group compared to 34.4% in the 150 IU recFSH group.

- Clinical studies in special populations

The impact of a number of factors on the primary efficacy outcome parameters (number of oocytes retrieved and ongoing pregnancy rate) was reviewed. Results from the Phase III trials revealed that the number of oocytes retrieved declined with increasing age, with increasing baseline FSH level and with decreasing basal antral follicle count at the start of stimulation in both treatment groups.

Further analyses of the ongoing pregnancy rates observed in subgroups of the Phase III trials showed that subjects without a previous IVF treatment cycle and subjects with double embryo transfer had higher success rates compared to those with a previous cycle or single embryo transfer. These factors may explain partly the higher overall ongoing pregnancy rates in North America as compared to those in Europe. However, for neither of these factors statistically significant differences were observed in ongoing pregnancy rate between the treatment groups.

- Supportive studies

Study 38825 is an ongoing Phase III, open-label, uncontrolled clinical trial to assess the non-immunogenicity and safety of corifollitropin alfa in patients undergoing repeated COS cycles, performed in Europe, Australia and Latin America. Subjects are treated with 150 μg corifollitropin alfa for up to three treatment cycles.
The recommended daily dose to continue treatment is 150 IU, which is similar to trial 38819 that also included women above 60 kg body weight. No primary efficacy parameter is defined for this trial. Interim analyses of the efficacy parameters obtained from the first treatment cycle show a mean number 11.9 retrieved oocytes. The corresponding biochemical pregnancy rate of 31.1% is lower than the ongoing pregnancy rates observed in study 38819 (47.5%). This difference might be the result of a slightly higher mean age in study 38825 and a lower basal antral follicle count.

Clinical safety

The safety data presented summarized adverse events for all subjects who were included in the 4 Phase I trials, 4 Phase II trials, 2 active-controlled Phase III trials, and 2 pregnancy and neonatal follow-up trials. In addition, interim safety data from ongoing trials were included: 1 Phase II trial, 1 uncontrolled Phase III multicycle trial and 4 pregnancy and neonatal follow-up trials.

- Patient exposure

In the completed trials, 309 subjects and 779 subjects have been exposed to a dose of 100 μg (body weight of ≤ 60 kg) and 150 μg (>60 kg), respectively. Moreover, in the ongoing Phase III immunogenicity trial 681 subjects, 321 subjects and 105 subjects had received once, twice or three times a dose of 150 μg corifollitropin alfa. The safety data available are considered adequate for exposure to 100 μg and 150 μg corifollitropin alfa.
Within the active-controlled Phase III trials (107012 and 38819) no clear differences were observed in the subjects' demographic and infertility characteristics between the treatment groups. As a result of the difference in trial design, the body weight and BMI were different between the Phase III trials: 54.2 kg and 20.5 for the 107012 trial, and 68.6 kg and 24.8 for the 38819 trial, respectively. In addition, there were more subjects without a previous IVF cycle in trial 38819 (74.4%) compared to trial 107012 (56.9%). In 107012, women were Caucasian (55.2%) or Asian (44.6%), except for one black subject, thus reflecting the geographical location of the studies: Europe and Asia. In contrast, subjects in 38819 were primarily Caucasian (85.9%).
The most frequently reported cause of infertility was male factor (48.9%), followed by unexplained infertility (27.4%) and tubal factor (25.7%). Of note is that a subject can have more than one cause of infertility.

- Adverse events

The overall incidence in subjects experiencing at least one AE was generally similar within the two controlled Phase III studies, with 55.2% in the 100 µg group versus 53.3% in the 150 IU recFSH group and 63.7% in the 150 µg group versus 61.1% in the 200 IU recFSH group.
Most subjects in both corifollitropin alfa dose groups as well as in the two recFSH groups reported AEs in the following System organ Classes (SOCs): Reproductive system and breast disorders, Nervous system disorders and Gastrointestinal disorders. The most common AEs were pelvic pain, pelvic discomfort, headache and nausea. There were no clinically relevant differences for these frequently reported AEs between the treatment groups.

Events that were most frequently considered drug-related were Pelvic discomfort, OHSS, Headache, Pelvic Pain, Nausea and Fatigue. The incidences were very similar between the four treatment groups; 100 µg corifollitropin alfa, 150 IU recFSH, 150 µg corifollitropin alfa and 200 IU recFSH, except for a slightly higher incidence of OHSS. (See discussion below on OHSS).

- Serious adverse event/deaths/other significant events

The overall SAE incidence in the corifollitropin alfa groups was comparable to the reference groups within each Phase III trial (38819 and 107012).
The SAEs reported in more than one subject per treatment group were: OHSS, ectopic pregnancy, ovarian torsion, abortion missed, ruptured ectopic pregnancy and abortion spontaneous. No clinically relevant differences in overall SAEs were observed between the treatment groups, apart from a higher observed incidence of OHSS (2.1% corifollitropin alfa vs. 1.0% recFSH; see discussion below on OHSS).
No deaths were reported in any completed or ongoing studies.

Ovarian hyperstimulation syndrome (OHSS)

- Although the number of OHSS cases observed in the comparative Phase III studies is low, OHSS represents one of the most serious complications in Assisted Reproductive Technology. Two forms of OHSS have been described: early-onset and late-onset OHSS. Early-onset OHSS appears to be associated with an excessive ovarian response to gonadotropin stimulation, whereas late-onset OHSS occurs as a consequence of endogenously produced hCG from an implanting pregnancy.

-- *OHSS in comparative Phase III studies (107012 and 38819)* --

- Though the overall incidence of OHSS was comparable in the Phase III trial 38819, the overall incidence was 2% higher in the corifollitropin alfa-group compared to the Puregon-group in trial 107012 (6.7% vs. 4.7%).
- The incidence of early onset OHSS, which is associated with an excessive ovarian response, was higher after corifollitropin alfa treatment compared to Puregon-treatment in both Phase III trials, 107012 (3.0% vs. 1.6%, respectively) and 38819 (5.2% vs. 4.0%, respectively). The incidence of late-onset OHSS was comparable within both trials between the treatment groups.
- OHSS was reported more frequently as a SAE in the corifollitropin alfa groups compared to the Puregon groups in both Phase III trials, 107012 (2.6% vs. 0.0%, respectively) and 38819 (1.9% vs. 1.2%, respectively).
- OHSS that led to study discontinuation was higher in the corifollitropin alfa group compared to the Puregon group in trial 38819 (1.6% vs. 0.1%).

The data above indicate a slightly higher incidence of early-onset OHSS after corifollitropin alfa-treatment compared to Puregon-treatment. In addition, the OHSS observed appeared more severe, and more often led to discontinuation.

Additionally, there are several findings that point to a higher ovarian response:

- Dose adjustment of (placebo-)recFSH could be made from Stimulation Day 6 on in case of too high ovarian response. The results of both active-controlled Phase III studies show that the (placebo-)

recFSH dose was decreased in a higher percentage of subjects in the corifollitropin alfa treatment groups compared to the Puregon treatment groups for Stimulation Days 6, 7 and 8.

- When 150 μg corifollitropin alfa was used in a long protocol with a GnRH agonist, the average number of oocytes came close to 18 oocytes, thereby increasing the chances on developing OHSS. Although no OHSS was observed and it was a small study (only 25 subjects randomized to 150 μg), the applicant included a warning that corifollitropin alfa is not recommended in combination with a GnRH agonist (SPC Section 4.4).
- The corifollitropin alfa groups had more follicles ≥11 mm on the day of hCG administration compared to their respective Puregon reference groups: the mean number of follicles was 14.9 and 12.9 for subjects treated with 100 μg corifollitropin alfa and 150 IU recFSH, respectively, and 16.0 and 13.9 for subjects treated with 150 μg corifollitropin alfa and 200 IU recFSH, respectively.
  In public literature, a correlation has been shown between the number of follicles of diameter ≥11 mm on the day of hCG administration and the development of early-onset OHSS[10].

-- *OHSS in ongoing Phase III study (38825)* --
Data was provided regarding the ongoing uncontrolled Phase III study 38825. The treatment protocol of this study is more close to current medical practice. The mean age of the included women was 32.9 years, which is higher than for the women included in trial 107012 and 38819 in the corifollitropin alfa group, 30.9 and 31.5 years, respectively. Correspondingly, the Antral Follicle Count (AFC) was lower in the women in 38825, 10.9, compared to the women included in trial 107012 and 38819, 11.1 and 12.3, respectively. This study had a lower overall incidence of OHSS of 3.5% compared to trial 38819, 7.0%. These data are reassuring as the treatment protocol of 38825 resembled more current medical practice, and the age of the included women is more a reflection of the IVF population, which tends to get higher.

-- *Race and OHSS* --
Sub-group analysis of OHSS per race in trial 107012, indicated that the overall incidence of OHSS (6.7%) in the Asian population exposed to 100 μg corifollitropin alfa was higher than exposed to 150 IU recFSH (1.8%). However, the incidence of OHSS in Asian subjects is comparable (6.7%) with the incidence in Caucasian subjects (6.8%). Even more, the number of growing follicles is not different between Caucasian and Asian subjects. Therefore, a difference in risk is not expected. The low incidence of OHSS (1.8%) in Asian subjects treated with 150 IU recFSH might be due to chance, as it concerns a small number of patients (n=57).

-- *Body weight and OHSS* --
Sub-analyses of study 38819 were provided by the applicant of 1) body weight of the subjects related to 'ongoing pregnancy rate' and 2) body weight of the subjects related to 'number of oocytes retrieved', as theoretically it may be that women with a higher body weight have a lower 'ongoing pregnancy rate' and a lower 'number of oocytes retrieved'. However, 'Ongoing pregnancy rates' and 'number of oocytes retrieved' were comparable in all body weight categories.

A woman of 60 kg receives 100 μg corifollitropin alfa, whereas the dose of a woman of 61 kg is 1.5 times higher, i.e. 150 μg corifollitropin alfa. Theoretically, it may be that women with a body weight close to 60 kg have a higher risk on developing OHSS. However, the incidence of OHSS was similar between the different body weight categories. Further, there seems to be a considerable amount of variation between women in the ovarian response. The variability in AUC in Trials 107012 and 38819 was 25% (CV%) in non-Asian subjects, which implies that a 50% difference of AUC between two randomly selected subjects is not unusual. Other data in support of a similar risk are coming from studies 38807 and 38826. In conclusion, a woman weighing 60 kg is expected to have a similar risk of OHSS as compared to a woman weighing 61 kg.

The slightly higher incidence of OHSS with corifollitropin alfa treatment is considered acceptable, taking into account the results of the ongoing Phase III study (3.5% OHSS), the fact that all women had recovered by the end of the trials, and the fact that there is no relation between race and OHSS,

[10] Papanikolaou EG, Pozzobon C, Kolibianakis EM, et al. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil Steril 2006;85:112-120.

nor body weight and OHSS. In addition, the difference in absolute numbers was small between the corifollitropin alfa and Puregon treatment groups, and the incidence of OHSS was comparable to what has been reported in public literature. Appropriate measures, in line with the measures taken in the Phase III studies, have been taken in order to minimise the risk for OHSS:

1) All women with a history of Ovarian Hyperstimulation Syndrome are contra-indicated for use of corifollitropin alfa;
2) A previous COS cycle that resulted in more than 30 follicles ≥ 11 mm on ultrasound scan" has been added in the list of contraindications;
3) In line with the indication *"Controlled Ovarian Stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles and pregnancy in women participating in an Assisted Reproductive Technology (ART) program"* the SPC includes a warning that combined use with a GnRH-agonist is not recommended as the available data are insufficient to support efficacy and safety of corifollitropin alfa in a long GnRH agonist protocol.

It is acceptable that the condition of PCOS is mentioned only in section 4.4. With the inclusion of the contra-indications "A basal antral follicle count > 20" and "Ovarian cysts or enlarged ovaries", women with PCOS with polycystic ovaries, who are at risk, are excluded for corifollitropin alfa treatment.

Potential signs and symptoms of hypersensitivity

The AEs within the Standardized MedDRA Query (SMQ) Anaphylactic reactions, local tolerance scores, and vital sign values 30 minutes after corifollitropin alfa injection, do not suggest a specific safety concern related to a hypersensitivity reaction.

Immunogenicity was specifically assessed in the ongoing Phase III trial 38825 after repeated administration. Three patients are positive for anti-corifollitropin antibodies, but these antibodies are of low affinity and are not neutralizing. Therefore, these antibodies do not have a clinically relevant effect.

An extensive description of the assay strategy was submitted with further clarifications provided upon request from the CHMP, also following observations from the GCP inspection. In general, the assay strategy is appropriate and in line with current guidance. The assays are sufficiently validated and the analytical strategy (screening, re-screening, depletion) is suitable for the detection and characterisation of anti-corifollitropin antibodies.

Relevant results of antibody testing in ongoing clinical trials or post-marketing surveillance should be submitted as part of the PSURs.

Pregnancy follow-up

The CHMP, as a matter of principle requested the full study reports of the pregnancy and neonatal follow-up trials of the pivotal trials prior registration, as in ART eventually the goal is to deliver a healthy baby. In addition, neonatal outcome data were also present in previous centralised submissions of recFSH preparations (Gonal-F and Puregon).

Complete pregnancy and neonatal follow-up information (38821 and 107014) was provided for the two pivotal clinical Phase III trials. Data was collected on 342 (expectant) mothers and 440 foetuses after corifollitropin alfa treatment and on 312 (expectant) mothers and 381 foetuses after recFSH treatment.

- The most frequently reported AEs in the (expectant) mothers were in the SOC 'Pregnancy, Puerperium and perinatal conditions'; for approximately 66% in all treatment groups. Most frequently reported AEs in this SOC were 'Premature labour', 'Placenta praevia', 'Twin pregnancy', 'Premature rupture of membranes', 'Threatened Labour' and 'Arrested labour'. No relevant differences between the treatment groups were observed.
- No differences were revealed in the incidence of congenital malformations between the two treatment groups in the live born infants. When the congenital malformations were evaluated per System Organ Class, High Level Group Term and Preferred Term, the distribution was similar for

the two treatment groups. The largest difference was observed for 'Atrial septal defect and ventricular septal defect', which was in favour of corifollitropin alfa. The data do not suggest any safety concern for the offspring of corifollitropin alfa treated subjects.

The other full study reports (38817, 38827 and 38834) and the interim study report of the ongoing Phase III study (38829) are in support of these conclusions. The applicant will provide the full study reports of the ongoing pregnancy and neonatal follow-up trial 38829 (including pregnancy and neonatal outcome) and the FTET (Frozen thawed embryo transfer) trials 107015 and 38831, as soon as these studies are finished. The company has undertaken a post-approval commitment to provide the full study reports as soon as these are available.

- Laboratory findings

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

- Safety in special populations

Corifollitropin alfa is mainly eliminated by the kidney through glomerular filtration followed by proximal tubular resorption and subsequent metabolism. Therefore, in subjects with renal insufficiency the excretion of corifollitropin alfa might be impaired.
Hepatic metabolism contributes to a minor extent to corifollitropin alfa metabolism (see also Pharmacokinetics).

- Safety related to drug-drug interactions and other interactions

No interaction studies with Elonva and other medicines have been performed. Since corifollitropin alfa is not a substrate of cytochrome P450 enzymes, no metabolic interactions with other medicinal products are anticipated.

- Discontinuation due to adverse events

None of the subjects in trial 107012 discontinued due to (S)AEs. In trial 38819, 16 subjects (2.1%) in the 150 µg corifollitropin alfa group and 3 subjects (0.4%) in the 200 IU recFSH group discontinued due to (S)AEs.
Of the 16 subjects in the corifollitropin alfa group, 12 subjects were discontinued due to OHSS, of which in 4 subjects the OHSS was considered a SAE. In all 12 cases, the OHSS was considered drug-related. The following events were reported in the remaining 4 subjects: uterine polyp (two cases), ovulation disorder and cervix carcinoma. Except for one case of uterine polyp, these events were considered not drug related.
In the recFSH group, the subjects discontinued due to the following AEs: OHSS, uterine polyp and tachycardia. The OHSS and the uterine polyp were considered drug-related.
A difference is observed in OHSS in favour of the 200 IU recFSH treatment (see discussion above on OHSS).

- Post marketing experience

The product was not licensed in any country.

2.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table 7: Summary of the risk management plan (INT00126513 Version 4.0, November, 2009)

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risk		
OHSS	The use of a specific OHSS addendum to the AE reporting form. The regulatory authorities will be kept informed about the reported number of cases of OHSS and the consequences thereof via the periodic safety reports.	Inclusion of measures in SmPC: - Restricted Indication: Controlled Ovarian Stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program. - Contraindications • Ovarian cysts or enlarged ovaries. • A history of Ovarian Hyperstimulation Syndrome (OHSS). • A previous COS cycle that resulted in more than 30 follicles > 11 mm measured by ultrasound examination • A basal antral follicle count > 20. - Extensive Warnings and Precautions • Elonva has not been studied in patients with PCOS. In these women the use of Elonva is not recommended. • The ovarian response was shown to be higher after treatment with Elonva than after treatment with daily recFSH. Therefore, women with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with Elonva. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, careful monitoring for potential ovarian hyperresponse is recommended. • Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical event distinct from uncomplicated ovarian enlargement. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhoea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening. Clinical signs and symptoms of severe OHSS are large ovarian cysts (prone to rupture), acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnoea, oliguria, haematological abnormalities and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS. Signs and symptoms of OHSS are stimulated by administration of human Chorionic Gonadotropin (hCG) and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotropin stimulation. Usually, early OHSS resolves spontaneously with the onset of menses. Late OHSS occurs more than 10 days after hCG administration, as a consequence of (multiple) pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration. To minimise the risk of OHSS, ultrasonographic assessments of follicular development and/or determination of serum estradiol levels should be performed prior to treatment and at regular intervals during treatment. In ART there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter. When there are 30 or more follicles in total it is advised to withhold hCG administration. Depending on the ovarian response, the following measurements can be used to prevent OHSS: • withhold further stimulation with a gonadotropin for a maximum of 3 days (coasting); • delay triggering final oocyte maturation with hCG administration until estradiol levels stabilize or decrease; • administer a dose lower than 10,000 IU of hCG for triggering final oocyte maturation, e.g. 5,000 IU hCG or 250 micrograms rec-hCG (which is equivalent to

		approximately 6,500 IU); • cryopreserve all embryos for future transfer; • withhold hCG and cancel the treatment cycle. For luteal phase support, administration of hCG should be avoided. Adherence to the recommended Elonva dose and treatment regimen and careful monitoring of ovarian response is important to minimise the risk of OHSS.
Important potential risk		
Hypersensitivity	Completion of the clinical trial report of the repeated exposure immunogenicity trial (38825) (November 2009). In the planned human QTc trial and the planned additional Phase III trial (Pursue) anti-Org 36286 antibody measurements will be performed (both start 2010). No further action will be undertaken.	Since the available data do not suggest a specific safety concern in terms of a hypersensitivity reaction or anti-Org 36286 antibody formation, no warning is needed for the potential risk hypersensitivity.
Important pharmacological class effects		
Congenital malformations	Completion of pregnancy and neonatal follow-up trial 38829	The following warning has been included in the SmPC Section 4.4 (Special warnings and precautions for use): The incidence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and the higher incidence of multiple pregnancies.
Multiple pregnancy	None	The following warning has been included in the SmPC Section 4.4 (Special warnings and precautions for use): Multiple pregnancies and births have been reported for all gonadotropin treatments. The woman and her partner should be advised of the potential risks for the mother (pregnancy and delivery complications) and the neonate (low birth weight) before starting treatment. In women undergoing ART procedures the risk of multiple pregnancy is mainly related to the number of embryos transferred. Multiple gestations are also mentioned as a possible adverse event related to ART treatment in the SmPC Section 4.8 (Undesirable effects).
Spontaneous abortion	None	Miscarriage is mentioned as a possible adverse event related to the ART procedure or subsequent pregnancy in the SmPC Section 4.8 (Undesirable effects).
Ectopic pregnancy	None	The following warning has been included in the SmPC Section 4.4 (Special warnings and precautions for use): Since infertile women undergoing ART, and particularly IVF, often have tubal abnormalities, the incidence of ectopic pregnancies might be increased. It is important to have early ultrasound confirmation that a pregnancy is intrauterine, and to exclude the possibility of extrauterine pregnancy. Ectopic pregnancy is also mentioned as a possible adverse event related to the ART procedure or subsequent pregnancy in the SmPC Section 4.8 (Undesirable effects).
Ovarian torsion	None	Ovarian torsion is mentioned as an uncommon adverse drug reaction in the SmPC Section 4.8 (Undesirable effects).
Venous thromboembolism	None	The following warning has been included in the SmPC Section 4.4 (Special warnings and precautions for use): In women with generally recognized risk factors for thromboembolic events, such as a personal or family history, severe obesity (Body Mass Index > 30 kg/m2) or thrombophilia, treatment with gonadotropins may further increase this risk. In these women the benefits of gonadotropin administration need to be weighed against the risks. It should be noted, however, that pregnancy itself also carries an increased risk of thrombosis.
Malignant neoplasm	None	The following warning has been included in the SmPC Section 4.4 (Special warnings and precautions for use): There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the baseline risk of these tumours in infertile women.

Important Missing / Limited Information		
Use of Org 36286 in combination with a GnRH agonist protocol	None	Restricted indication: Controlled Ovarian Stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program. The following text has been included in the SmPC Section 4.2: • The recommended doses of Org 36286 have only been established in a treatment regimen with a GnRH antagonist (see also section 4.4). In section 4.4 of the SmPC (Special warnings and precautions for use), the following additional information is included: • There are limited data on the use of Elonva in combination with a GnRH agonist. Results of a small uncontrolled study suggest a higher ovarian response than in combination with a GnRH antagonist. Therefore, Elonva is not recommended in combination with a GnRH agonist (see also section 4.2).
Use of Org 36286 in patients with renal impairment	None	In section 4.2 of the SmPC (Posology and method of administration), the following information is included: • Special populations: Renal impairment: No clinical studies have been performed in patients with renal insufficiency. Since the elimination of corifollitropin alfa might be impaired in patients with renal insufficiency, the use of Elonva in these women is not recommended (see section 4.4 and 5.2). The following warning has been included in the SmPC Section 4.4: • In patients with mild, moderate or severe renal insufficiency the excretion of corifollitropin alfa might be impaired. Therefore, the use of Elonva in these women is not recommended. In section 5.2 of the SmPC (Pharmacokinetic properties), the following information is included: • Distribution, metabolism and elimination of corifollitropin alfa are very similar to other gonadotropins, such as FSH, hCG and LH. After absorption into the blood, corifollitropin alfa is distributed mainly to the ovaries and the kidneys. Elimination of corifollitropin alfa predominantly occurs via the kidneys and may be impaired in patients with renal insufficiency (see section 4.2 and 4.4).
Use of Org 36286 in patients having risk factors for high ovarian response	None	The following contraindications have been included in the SmPC Section 4.3 (Contraindications): • Ovarian cysts or enlarged ovaries. • A history of Ovarian Hyperstimulation Syndrome (OHSS). • A previous COS cycle that resulted in more than 30 follicles > 11 mm on ultrasound scan. • A basal antral follicle count > 20. The following warning has been included in the SmPC Section 4.4: • Elonva has not been studied in patients with PCOS. In these women the use of Elonva is not recommended. • The ovarian response was shown to be higher after treatment with Elonva than after treatment with daily recFSH. Therefore, women with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with Elonva. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, careful monitoring for potential ovarian hyperresponse is recommended.
Use of Org 36286 during pregnancy and lactation	None	The following text has been included in the SmPC Section 4.6: *Pregnancy* No teratogenic risk has been reported, following controlled ovarian stimulation, in clinical use with gonadotropins. When inadvertent exposure to corifollitropin alfa during pregnancy occurs, clinical data are not sufficient to exclude an adverse outcome of pregnancy. In animal studies reproductive toxicity has been observed (see preclinical safety data in Section 5.3). The use of Elonva during pregnancy is not indicated. *Breast-feeding* The use of Elonva during breast feeding is not indicated.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the drug substance are adequately described, controlled and validated. The drug substance is well characterised, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the drug product has been satisfactorily described and validated. The quality of the drug product is controlled by adequate test methods and specifications. Viral safety and safety concerning other adventitious agents including TSE have been sufficiently assured. Except for a number of points, which will be addressed as part of post-approval follow-up measures, the overall Quality of Elonva is considered acceptable.

Non-clinical pharmacology and toxicology

An adequate non-clinical programme has been conducted for corifollitropin alfa. The preclinical observations did not raise major concerns against the use of corifollitropin alfa in humans at the proposed clinical use.

Preclinical data from conventional studies of single and repeated dose toxicity and safety pharmacology revealed no special hazard for humans. Reproduction toxicology studies in rats and rabbits indicated that corifollitropin alfa does not affect fertility. Administration of corifollitropin alfa to rats and rabbits, prior to and directly after mating, and during early pregnancy, resulted in embryotoxicity. In rabbits, when administered prior to mating, teratogenicity has been observed. Both embryotoxicity and teratogenicity are considered a consequence of the superovulatory state of the animal not able to support a number of embryos above a physiological ceiling. The relevance of these findings for the clinical use of Elonva is limited.
This information has been added to the SPC (section 5.3).

Efficacy

Justification of the dose
The dose-finding trial 38826 failed to demonstrate an optimal dose. Subsequently, an extensive PK-PD modelling has been performed taking into account pharmacodynamic and efficacy parameters. Based on its outcome, it was concluded that the recommended dose for the Phase III clinical program of Elonva was 100 µg for subjects with body weight ≤ 60 kg and 150 µg for subjects with body weight > 60 kg. Drug exposure was expected to be similar by the applicant in these predefined body weight groups. Dose selection is adequate, though it might be argued that instead of 150 µg, a 125 µg could have been chosen for subjects with body weight > 60 kg as it is predicted to be only slightly less efficacious (mean number of oocytes 12.4 for 150 µg and 13.2 for 125 µg).

Key efficacy findings

- In the **controlled phase III study 38819**, performed in females of couples with an indication for COS and IVF or ICSI with a body weight > 60 and ≤ 90 kg, 1509 subjects were randomized and embryo transfer was performed in 1367 subjects. The primary endpoint 'ongoing pregnancy rate assessed at least ten weeks after embryo transfer' was 38.9% for 150 µg Elonva and 38.1% for 200 IU recFSH (Puregon). Non-inferiority was adequately shown for the primary endpoint, as the 95% CI of the difference in pregnancy rates 0.9% [-3.9;5.7] between Elonva and recFSH excludes the predefined non-inferiority margin of -8%.
  The co-primary endpoint 'number of oocytes retrieved' was 13.7 for 150 µg Elonva and 12.5 for recFSH (Puregon). Equivalence for the co-primary endpoint was adequately shown, as the 95% CI of the difference in number of oocytes retrieved 1.2 [0.5;1.9] fell entirely within the predefined equivalence margin of -3; +5 oocytes.

The primary endpoint was requested by the FDA and the co-primary endpoint by the EMEA. Both endpoints are considered acceptable as well as the corresponding predefined non-inferiority margin and equivalence margin.
The starting dose of 200 IU recFSH in the comparator group, the possibility of dose adjustment from stimulation day 6 onwards and the maximum dose of 200 IU are considered acceptable.
No clinically relevant differences were observed between both treatment groups regarding secondary efficacy endpoints: the number of metaphase II oocytes, fertilization rate, mean number of good quality (Grade 1 and 2) embryos, mean number of good quality embryos transferred and mean implantation rate. The secondary efficacy analyses were supportive of the primary and co-primary endpoint.

- In the **controlled phase III study 107012**, performed in females of couples with an indication for COS and IVF or ICSI with a body weight ≤ 60 kg, 396 subjects were randomized and embryo transfer was performed in 367 subjects. The primary endpoint 'number of oocytes retrieved' was 13.3 for 100 µg Elonva and 10.6 for 150 IU recFSH (Puregon). Equivalence for the co-primary endpoint was adequately shown, as the 95% CI of the difference in number of oocytes retrieved 2.5 [1.2; 3.9] fell entirely within the predefined equivalence margin of -3; +5 oocytes. The primary endpoint was acceptable, although preferably 'ongoing pregnancy rate' would have been incorporated as primary endpoint as well. The rationale of the applicant to power only one study for pregnancy rate is understandable, and agreed as the EMEA asked for 'number of oocytes retrieved'. Including 'ongoing pregnancy rate' as primary endpoint would have led to a sample size at least 3-4 fold higher.
  The starting dose of 150 IU recFSH, the maximum dose of 200 IU recFSH and the possibility of dose adjustment from stimulation day 6 onwards are considered acceptable.
  The clinically most relevant secondary endpoint 'ongoing pregnancy rate' was 25.4% for 100 µg Elonva and 34.4% for 150 IU recFSH. The difference is 9.2% [-18.9; 0.5] in favour of 150 IU recFSH, and this difference is considered substantial. The applicant discussed differences in patient history and baseline characteristics, stimulation characteristics and fertilization procedures and embryo transfer between the two treatment groups. None of these factors could explain the observed difference in pregnancy rates. Thus, the observed difference is most likely a chance finding. Reassuring is the larger 38819 trial, with similar variables as 107012, which revealed a similar pregnancy rate for Elonva and Puregon.
  No clinically relevant differences were observed between both treatment groups in the number of metaphase II oocytes, fertilization rate, mean number of good quality (Grade 1 and 2) embryos and mean number of good quality embryos transferred. The implantation rate, biochemical and clinical pregnancies, vital pregnancy rates and miscarriage rate are in line with the difference in ongoing pregnancy rate in favour of recFSH treatment.

Safety

The overall incidence in subjects experiencing at least one AE and subjects with drug-related AEs was comparable between the treatment groups in the two Phase III trials. However, the subjects who discontinued due to AEs in trial 38819 were higher for the 150 µg Elonva group versus the 200 IU recFSH group. No clinically relevant differences were detected for the frequently reported AEs between the treatment groups (pelvic pain, pelvic discomfort, headache and nausea). In addition, the overall incidence of subjects with SAEs was also comparable between the treatment groups within each study. No clinically relevant differences were observed in these SAEs, apart from the slightly higher incidence of OHSS after Elonva treatment.

Drug-related AEs that were most frequently reported were Pelvic discomfort, OHSS, Headache, Pelvic Pain, Nausea and Fatigue. The incidences were very similar between the four treatment groups; 100 µg Elonva, 150 IU recFSH, 150 µg Elonva and 200 IU recFSH, except for a slightly higher incidence of OHSS.

OHSS represents one of the most serious complications in ART. The incidence of early-onset OHSS, which is associated with an excessive ovarian response, was higher after Elonva treatment in both completed Phase III studies: 3.0% vs. 1.6% for subjects treated with 100 µg Elonva and 150 IU

recFSH (trial 107012), respectively, and 5.2% vs. 4.0% for subjects treated with 150 µg Elonva and 200 IU recFSH (trial 38819), respectively. In addition, the OHSS observed is more severe after Elonva compared to Puregon, and more often led to discontinuation (1.6% vs. 0.1% in trial 38819).
The slightly higher incidence of OHSS with Elonva treatment is considered acceptable, taking into account the results of the ongoing Phase III study (3.5% OHSS), the fact that all women had recovered by the end of the trials, and the fact that there is no relation between race and OHSS, nor body weight and OHSS. In addition, the difference in absolute numbers was small between the Elonva and Puregon treatment groups, and the incidence of OHSS was comparable to what has been reported in public literature. Appropriate measures, in line with the measures taken in the Phase III studies, have been taken by the applicant in order to minimise the risk for OHSS:
1) All women with a history of Ovarian Hyperstimulation Syndrome are included in the list of contra-indications for use (SPC Section 4.3).
2) A previous COS cycle that resulted in more than 30 follicles >11 mm on ultrasound scan" has been added in the list of contraindications (SPC Section 4.3);
3) In line with the indication "Controlled Ovarian Stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program" the SPC (SPC Section 4.4) includes a warning that combined use with a GnRH-agonist is not recommended as the available data are insufficient to support efficacy and safety of Elonva in a long GnRH agonist protocol.

It is acceptable that the condition of PCOS is mentioned only in section 4.4. With the inclusion of the contra-indications "A basal antral follicle count > 20" and "Ovarian cysts or enlarged ovaries", women with PCOS with polycystic ovaries, who are at risk, are excluded for Elonva treatment.

Full pregnancy and neonatal follow-up information is available of the pivotal Phase III studies. Data was collected on 342 (expectant) mothers and 440 foetuses after Elonva treatment and on 312 (expectant) mothers and 381 foetuses after recFSH treatment. The data do not suggest any specific safety concern for the offspring of Elonva treatment. The other full study reports (38817, 38827 and 38834) and the interim study report of the ongoing Phase III study (38829) are in support of these conclusions. The applicant will provide the full study reports of the ongoing pregnancy and neonatal follow-up trial 38829 (including pregnancy and neonatal outcome) and the FTET trials 107015 and 38831, as soon as these studies are finished. The company has accepted a post-approval commitment to provide the full study reports as soon as these become available.

Immunogenicity was specifically assessed in the ongoing Phase III trial 38825 after repeated administration. It is concluded that three patients are positive for anti-corifollitropin antibodies, but that these antibodies are of low affinity and are not neutralizing. Therefore, these antibodies do not have a clinically relevant effect. Review of the AEs within the SMQ Anaphylactic reactions as well as local tolerance scores, and vital sign values 30 minutes after Elonva injection, revealed no clinically relevant observations.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 2.5 adequately addressed these.

- User consultation

The readability test was performed in July-August 2008. In the period between September-November 2008 some changes have been made to the package leaflet which was used in the readability test. These changes were mainly editorial (linguistic) improvements and some small changes to the lay-out.
The applicant included a bridging report in the dossier comparing the version of the leaflet used in the readability test and the final leaflet included in the dossier to support a justification for not testing the improved leaflet, which was developed in a later stage, after the performance of the readability test; however the contents, format, design and layout of the leaflets are similar. The bridging report is accepted as a justification for not testing the improved leaflet.

The user testing of the PL was performed and judged as acceptable.

Risk-benefit assessment

Benefits

The advantage of Elonva is that a single injection of corifollitropin alfa replaces 7 daily (rec) FSH administrations in Controlled Ovarian Stimulation, thereby improving patients` convenience. The efficacy of Elonva is considered comparable to Puregon, as in both trials equivalence was adequately shown for the (co-)primary endpoint 'number of oocytes retrieved'. In addition, non-inferiority for the primary endpoint 'ongoing pregnancy rate' was established in the largest pivotal trial.

Risks
The safety profile of Elonva and daily Puregon was comparable, except for a slightly higher incidence of OHSS in the Elonva treatment group. This slightly higher incidence is considered acceptable, taking into account that the difference in absolute numbers was small between the treatment groups, and that the overall incidence of OHSS was low, and comparable to what has been reported in published literature. Also, in line with measures taken in the Phase III studies, appropriate restrictions in its use are included in the SPC to minimise the risk for OHSS as much as possible.

In summary, it is concluded that the B/R balance of Elonva is considered positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Routine pharmacovigilance was adequate to monitor the safety of the product.
- No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of corifollitropin alfa for use in Controlled Ovarian Stimulation (COS) in combination with a GnRH antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) program was favourable and therefore recommended the granting of the marketing authorisation.