SCIENTIFIC DISCUSSION

1. Introduction

This is a centralised procedure for the marketing authorisation application for Pergoveris, which is a fixed dose combination of recombinant human follicle stimulating hormone (r-hFSH; INN: follitropin alfa) and recombinant human luteinising hormone (r-hLH; INN: lutropin alfa) presented as a powder and solvent for solution for injection. The strength of the active ingredients of Pergoveris is 150 IU for follitropin alfa and 75 IU for lutropin alfa. In this application, the results from the following clinical trials have been presented: two Phase II/III efficacy studies (GF6253 and GF6905), two biopharmaceutical studies (IMP23718 and IMP23722). Additional data from the following studies has been summarised: five clinical pharmacology studies (GF5007, GF5117, GF6135, GF6136, GF6137), one pharmacokinetic study (GF6137), four additional efficacy studies (GF7798, GF8297, IMP21008 and IMP21415).

Hypogonadotropic hypogonadism (HH) is a rare disorder of reproductive function and describes absent or decreased function of the gonads in both men and women. The dysfunction is characterized by the absence of effective hypothalamic occurring -pituitary secretory activity resulting in stopped or attenuated gonadal function. In women, the disorder may therefore be characterised by the failure to undergo the usual physical and reproductive changes of puberty or, if occurring after puberty, may by secondary amenorrhea (absence of menses). Amenorrhea is a manifestation of low oestrogen production and is associated with similar adverse health conditions as those seen in postmenopausal women: bone mineral abnormalities, altered lipid profiles and accelerated cardiovascular disease. The additional consequence of stopped ovarian function is anovulation and infertility. From the clinical perspective, the diagnosis of HH is confirmed by endocrine testing that demonstrates low gonadotropin serum levels and low oestrogen levels. Ovulation is the result of a well-defined sequence of events that includes the combined effect of pituitary gonadotropins FSH and LH. Any functional disorder of the hypothalamic-pituitary ovarian axis may lead to absence or inadequate ovulation, resulting in infertility. Anovulation is estimated to account for up to 24 % of human infertility problems.

The product will be marketed in a vial containing 150 IU of follitropin alfa and 75 IU of lutropin alfa in a fixed ratio. The approved indication for Pergoveris is the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/L. It should be noted that follitropin alfa and lutropin alfa are marketed as individual products by the same Company.

2. Quality aspects

Introduction

Pergoveris is a new fixed combination product whose active substances, follitropin alfa and lutropin alfa are also individually marketed as part of the centrally authorised products Gonal-f and Luveris respectively.
Follitropin alfa and lutropin alfa are produced from genetically engineered CHO cells. They are manufactured using a continuous perfusion mode and purified by a series of chromatography and filtration steps (different steps for follitropin alfa and lutropin alfa). The resulting active substances are combined and formulated, and then lyophilised to obtain Pergoveris finished product.

Pergoveris is intended to be administered by subcutaneous injection following reconstitution with sterile water for injections (supplied with Pergoveris).

Active Substances

Nomenclature

INN Name:	Follitropin alfa/lutropin alfa
Compendial Name:	Not Applicable
Chemical Name:	Recombinant human follicle stimulating hormone (r-hFSH) Recombinant human luteinising hormone (r-hLH)
Laboratory Code:	Not applicable
USAN/BAN/JAN Name:	Follitropin alfa/lutropin alfa
CAS Registry Number:	R-hFSH: 146479-72-3; r-hLH: 152923-57-4
WHO Number:	8313

Description of the active substances

Follitropin alfa and lutropin alfa are glycoprotein hormones 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 specific beta subunit (111 amino acids for follitropin alfa, 121 amino acids for lutropin alfa) leading to specific biological properties.
The alfa subunit contains two N-linked glycosylation sites (Asn 52 and Asn 78) and five disulphide bonds. The beta subunit contains six disulphide bonds and one (lutropin alfa) or two (follitropin alfa) N-linked glycosylation sites.
The oligosaccharides attached to the alfa and beta subunits of r-hFSH and r-hLH are of complex type, with bi-, tri-, tetra- or penta-antennary forms containing N-acetylglucosamine, mannose, galactose, sialic acid (at variable rates) and fucose residues.
The molecular masses of the alfa and beta subunits are approximately 14 kDa and 17 kDa (follitropin alfa)/15 kDa (lutropin alfa) respectively.

- Manufacture

Follitropin alfa and lutropin alfa are manufactured at Laboratoires Serono, Z.I de l'Ouriettaz, Aubonne, Switzerland. This facility is operated according to current Good manufacturing Practices, with standard operating procedures in place to describe all procedures and controls.

Development genetics
The genomic DNA fragments encompassing sequences for the α- and β-units of human FSH and human LH were isolated from a gene library carrying DNA from cells from human fetal liver.
The host cell line used for the production of follitropin alfa and lutropin alfa is an anchorage dependent CHO cell line isolated from a CHO-K1 cell line with deficient dihydrofolate reductase (DHFR) activity. The CHO cells were co-transfected with two plasmids, one containing the α-hFSH or α-hLH gene and a DHFR selective marker gene, and the other containing the β-hFSH or β-hLH gene and an ornithine decarboxylase selectable marker.
A subclone was selected as the cell line to be expanded for the preparation of the Master Cell Bank (MCB) and Working Cell Bank (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.

For each active substance, the MCB was prepared from a single vial of the above-mentioned subclone which was thawed and expanded by subcultivation in a growth medium. The WCB was prepared from one vial of MCB, based on the same principles as for the MCB.
MCB and WCB are stored in the vapour phase of liquid nitrogen.
Procedures followed in the preparation of MCB and WCB were appropriately described. An extensive range of tests was performed for their characterisation, in accordance with ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Fermentation process

One vial from the WCB is thawed and seeded into roller bottles or tissue culture flasks. Following sub-passages, the expanded cells are transferred into a bioreactor. Microcarriers are introduced into the bioreactor and are used as cell support during the bioreactor expansion and production phases. Harvests are collected and stored for the purification process.
Cell culture conditions and in-process controls (IPC) were sufficiently described and are considered appropriate.

Purification process
Follitropin alfa and lutropin alfa are purified using a series of chromatography and viral filtration steps.
Each step has been sufficiently described, including description of the elution buffers, exchange buffers, column regeneration and storage conditions of both columns and product after each step. Suitable IPCs are in place, with acceptable limits.

Manufacturing process development and process validation

Between the authorisation of Gonal-f and Luveris and the submission of the marketing authorisation application for Pergoveris, a number of changes to the manufacturing process of follitropin alfa and lutropin alfa active substance were implemented. Major changes concerned follitropin alfa and consisted in the introduction of a scaled up cell culture and purification process.

The scaled up process for follitropin alfa was validated and the results of four production runs were consistent. The outcome of the comparability exercise between the two follitropin alfa processes was satisfactory. The overall performance of the two fermentation scales is similar.
The two follitropin alfa purification processes were adequately validated. Column lifetimes are defined according to relevant performance criteria.

Validation of the lutropin alfa process was performed by analysing relevant parameters of four consecutive full-scale batches throughout the cell culture process and purification process.

Process validation for follitropin alfa and lutropin alfa is acceptable. It was demonstrated that the follitropin alfa and lutropin alfa processes are capable of consistently producing the active substances and consistently removing the product- and process-related impurities.

Characterisation
Extensive characterisation was undertaken, including peptide mapping, mass spectroscopy, carbohydrate content analysis, sialylation, N-terminal sequencing, iso-electric focusing, biological and immuno-activity. Follitropin alfa and lutropin alfa are complex molecules existing in a variety of different glycosylated and truncated forms. However, batch data showed consistency with respect to physico-chemical characteristics, immunological and biological activity.

The impurity profile of the active substances has also been assessed with respect to
- Potential process-related impurities, which includes host cell DNA, cell culture-derived protein contaminants, potential microbiological contaminants, potential viral contamination, purification-derived impurities;
- Product-related impurities, which includes oxidised forms, aggregates, free α- and β-subunits.

The data provided is acceptable, giving confidence that the product structure is well understood and that the impurity profile is adequately controlled.

- Specification

The release specifications of follitropin alfa and lutropin alfa active substances are unchanged compared to the currently authorised specifications for follitropin alfa in Gonal-f and lutropin alfa in Luveris.

- Stability

Stability data confirmed the 36-month 60-month shelf life for follitropin alfa and lutropin alfa respectively

Finished Product

- Pharmaceutical Development

The excipients used in Pergoveris formulation are sucrose, polysorbate 20, L-methionine, a phosphate buffer.
The pharmaceutical development of the finished product is based on the experience gained from Gonal-f and Luveris finished products. The excipients used in Pergoveris formulation are those found in these two medicinal products: sucrose, polysorbate 20, L-methionine, a phosphate buffer.

The results of the compatibility studies of the combined r-hFSH and r-hLH with the container closure adequately justify the proposed overages in the final formulation of both follitropin alfa and lutropin alfa.

- Manufacture of the Product

The manufacturing process of Pergoveris finished product include the preparation of the compounded solution including excipients solution and the calculated amount of active substances, which is subsequently sterile filtered and filled into vials under aseptic conditions before freeze-drying, stoppering and capping, labelling and packaging of the vials.

Process validation was completed by carrying out 3 manufacturing runs with different batches of finished product, at full manufacturing scale. The data provided were generally considered acceptable. However, the applicant committed to provide Quality Control release data from the first drug production batch at full scale to support the validation of the lyophilisation process.

The manufacturing process for water for injections was adequately described and appropriately controlled.

- Product Specifications

The specifications that have been set are based on the requirements of the Ph. Eur. monograph for parenteral products, the impurity profile with respect to product degradation, active substance content and biological activity, as well as the microbial purity and sterility. The specifications for all release tests are in general suitably justified.

The specifications for the solvent water for injections meet the Ph. Eur. requirements.

- Stability of the Product

Stability data of accelerated and long-term studies have been provided and confirmed that the finished product corresponding to the combined follitropin alfa and lutropin alfa active substance is stable over the proposed 36 month shelf-life. All results are within the required specifications.

Adventitious Agents

The raw materials of animal origin used in the manufacturing process of follitropin alfa and lutropin alfa active substances are FBS at different stages of the cell culture process and for which TSE certificates were provided, microcarrier beads (porcin collagen) and porcine trypsin. These raw materials are provided from qualified suppliers.
Adequate process controls are in place to ensure virological control (on the bulk harvest) and microbial control (throughout the manufacturing process). Both purification processes have been suitably validated for their ability to remove and/or inactivate potential viral contaminants.

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. IPCs are in place, ensuring consistency of the follitropin alfa and lutropin alfa manufacturing processes.

The purification process includes a membrane filtration step shown to reproducibly remove viruses based on size exclusion and not adsorption.
Non-viral and viral safety of follitropin alfa and lutropin alfa is considered to be assured.

The active substances were thoroughly characterised using state-of-the-art methods, giving confidence that structure of follitropin alfa and lutropin alfa is well understood.
The impurity profile is adequately controlled.

The active substance release specifications are unchanged compared to those of follitropin alfa contained in Gonal-f and of lutropin alfa contained in Luveris.

Stability data support the 36-month shelf life for follitropin alfa and the 60-month shelf life for lutropin alfa, and the 36-month shelf life for the finished product.

The manufacturing process and IPCs for Pergoveris finished product and WFI have been adequately described. Process validation is considered satisfactory.

The excipients used in the formulation of Pergoveris are of pharmacopoeial quality. There are no excipients of human or animal origin.

The finished product specifications have been adequately justified. The applicant committed to review these specifications when a statistically significant number of batches will have been manufactured.

3. Non-clinical aspects

Introduction
The two biotechnological drug substances follitropin alfa and lutropin alfa have been characterised separately by the applicant with non-clinical tests appropriate to the nature, the intended dosage and duration of administration of follitropin alfa/lutropin alfa. Human bioavailability studies have shown that there is no discernable change of the pharmacokinetics of the individual follitropin alfa and lutropin alfa when administered in combination. In addition, clinical experience using co-administered follitropin alfa and lutropin alfa did not give rise to any safety or efficacy concerns. Therefore, it is considered unlikely that a full non-clinical testing program conducted with drug product would extend the scientific knowledge already gained with the individual hormones in the claimed therapeutic indication. Repeating the same studies by exposing a large number of animals is considered unethical. However, as follitropin alfa/lutropin alfa is a new product, a new local tolerability study was performed with the intend-to-market formulation. Detailed descriptions of results obtained in the non-clinical programs conducted with the individual constituents of the Pergoveris formulation are given in the appropriate sections of the present application.

Pharmacology
The pharmacology of follitropin alfa and of lutropin alfa has been extensively described by the applicant. The patient population targeted by the product benefits from the presence of both constituents in the product and this population is presently treated with each constituent given separately. CHMP was of the opinion that no additional pharmacology studies in animals are required.

- Primary pharmacodynamics

In normal, sexually mature women the sex hormones are released in a cyclical manner under the control of the hypothalamo-pituitary axis. Hypothalamic neurones secrete Gonadotrophin Releasing

Hormone (GnRH) that, in turn, stimulates the anterior pituitary to release follicle-stimulating hormone (FSH) into the systemic circulation (Catt and Pierce 1986). FSH binds to a specific transmembrane receptor located on the ovarian granulosa cells that surround the oocyte and activates a receptor-associated adenylate cyclase system, which in turn, increases cyclic AMP (cAMP) production. This change in cAMP levels is responsible for the activation of protein kinases and the phosphorylation of regulatory protein substrates involved in hormone action. Receptor activation triggers granulosa cell mitosis, induction of oestradiol (E2) -producing enzymes and the acquisition of luteinising hormone (LH) receptors on the granulosa cells. Concomitantly, LH activity leads to maturation of the Graafian follicle and the ripening and release of a single oocyte per menstrual cycle. The corpus luteum formed after extrusion of the oocyte releases additional growth factors and steroids (including progestogens) that control the progestational phase of the reproductive cycle. The majority of female HH patients have an LH deficiency that precludes optimal follicular development and steroidogenesis unless LH is co-administered with FSH. Inadequate E2 secretion leads to impaired endometrial growth and the follicles do not form a functional corpus luteum when exposed to Chorionic Gonadotropin (hCG). Administration of FSH and LH has been used successfully to treat infertility problems in women. In fact, complete or partial deficiency in LH and FSH or dysynchrony of LH and FSH secretion may lead to absent or abnormal ovulation (i.e., dysovulation). Anovulation and dysovulation are common causes of infertility in women. Dysovulation probably accounts for up to 20% of human infertility problems.

A series of pharmacology studies intended to fully characterise the pharmacodynamics of the two active substances, including receptor binding affinity and activity in rodents and primate models of ovulation, have been conducted by the applicant with the individual recombinant hormones follitropin alfa and lutropin alfa. Non-clinical studies allowed confirming that follitropin alfa and lutropin alfa do exert the normal expected pattern of biological responses in relevant animal model systems. The primary pharmacodynamic response after concomitant exposure to follitropin alfa and lutropin alfa was assessed through two pharmacodynamic studies. These studies demonstrate that follitropin alfa and lutropin alfa exerted an additive effect on maturation of ovarian follicles *in vitro* (rats) and on the promotion of follicle growth and E2 production *in vivo* (monkeys). This finding is consistent with clinical experience on the efficacy of the combined administration of follitropin alfa and lutropin alfa for achieving adequate follicular development, follicular E2 production, endometrial growth and formation of a functional corpus luteum in response to hCG in the target population of women with severe FSH and LH deficiency.

- Safety pharmacology programme

Extensive experimental work has been conducted with the individual follitropin alfa and lutropin alfa active substances contained in final product, through the standard battery of safety pharmacology tests including cardiovascular, central nervous and respiratory systems. Additional safety pharmacology screening was performed: body temperature, sleeping time, locomotor activity, anticonvulsant activity, gastrointestinal motility, effects on isolated ileum, uterine motility and urine electrolyte excretion. These later tests allowed concluding that except for the predicted pharmacological effects related to interactions with the appropriate specific receptor expressed on the target cells, no other effect is expected. This finding is consistent across the preclinical and clinical experience gained.

- Pharmacodynamic drug interactions

Potential pharmacokinetic interactions when follitropin alfa and lutropin alfa are co-administered are assessed by the clinical pharmacology studies. Comparison of the pharmacokinetic parameters for each of the active substances when administered in combination, as compared to separate administrations has been established in humans. Based on the results obtained, it was considered that no additional information would be gained by repetition of such tests in animals with Pergoveris.

Pharmacokinetics

The pharmacokinetic profile of each individual recombinant hFSH and hLH has been fully characterised by the applicant following single and 7-day repeat administration in the monkey. Disposition of the radio-labelled (125I) gonadotropins has been assessed through rat ADME studies. In summary, mean absolute bioavailability in the monkey was 71% (follitropin alfa) and 48% (lutropin alfa) after single SC dosing and slightly higher to 77% (follitropin alfa) and 61% (lutropin alfa) after single IM dosing. Elimination half-life was around 20 h (follitropin alfa) and 11 h (lutropin alfa).

Upon repeat dosing FSH Cmax on day 7 was about twice the one after the first administration; there was no accumulation of lutropin alfa. Tissue distribution studies showed presence or significant concentrations of radioactivity in the ovaries and in organs like the kidney consistent with expected route of elimination. There was no radioactivity pattern suggesting extensive binding to or accumulation in tissues not expressing the relevant receptors (with the exception of the thyroids). Although no metabolism data were obtained from these studies, clearance of both gonadotropins is expected to occur through the common mechanisms in which glycoprotein hormones (like the naturally occurring FSH and LH) are cleared from the body. Most of the radioactive material was excreted in urine as low molecular weight fractions, which means that it is no longer composed of intact molecules. Since no differences were observed in the human PK profile of the two active substances when administered in combination compared to separate administrations, it is considered unnecessary to repeat animal PK studies.

Toxicology

Gonadotropin receptor expression is strictly restricted to gonads and highly cell-specific. Expression of the FSH receptor is limited to granulosa cells in ovaries and Sertoli cells in testis while that of the LH/HCG receptor is restricted to differentiate granulosa cells, theca cells and corpus luteum in ovaries and Leydig cells in testis. Therefore, each gonadotropin will exert its full range of biological activities without any other direct effects on cells devoid of specific receptor. Co-administration of the two gonadotropins is thus expected to result in biological effects related to their binding to the specific membrane-bound receptor and their pharmacodynamic actions. Findings in the toxicological experiments follitropin alfa and lutropin alfa as individually assessed are consistent with the predictable extension of their pharmacodynamic activities. However, it was shown that long-term animal experimentation has limits related to the development of antibodies to the human proteins injected. Although this resulted in decreased exposures, the expected pharmacodynamic actions were not prevented.

Historical experience with human menopausal gonadotropin containing FSH and LH include two four-weeks toxicity studies conducted in rats and monkeys with one parallel group receiving hMG (human menopausal gonadotropin) at a very high dose level, 1000 IU/kg/day. These experiments showed that hMG-induced changes were as expected from the high dose and prolonged administration period and were consistent with its combined FSH/LH pharmacodynamic activities. In rats, the overall pattern of effects observed was consistent with an extension of the combined FSH/LH activities on the gonads and their secondary endocrinological consequences. In females there was an increase in follicular cysts and corpora lutea and, most probably due to the consequential steroid production, hyperplasia of uterine mucosa, anterior pituitary and mammary gland acini. In males, interstitial cell hyperplasia and seminiferous tubule degeneration were the prominent histological finding in testes. The latter could again be ascribed to negative feedback mechanisms induced by the secondary production of sex steroids, which reflected in the observed epithelial hyperplasia of the prostate gland. In monkeys the ovary weights of all treated animals exceeded the control values. At the microscopic level these changes correlated with an increased number of follicular cysts (sometimes haemorrhagic) and with an increased incidence of degenerated corpora lutea (sometimes with haemorrhages). The testes showed a treatment-related increase in weight. Microscopically this correlated with a slight increase in tubular diameter.

- Single and repeat dose toxicity

The safety of Pergoveris is supported by an extensive toxicity programme performed by the applicant with the individual drug substances follitropin alfa and lutropin alfa present in the drug product formulation. In these studies encompassing single dose, subacute and subchronic toxicity experiments, no signs of intrinsic toxicity were detected in the relevant rodent and non-human primate species with either hormone at doses up to 1000 IU/kg/day (follitropin alfa) or 5000 IU/kg/day (lutropin alfa) for 4 weeks or 1000 IU/kg/day (both gonadotropins) for 13 weeks; these doses are several hundred times higher than those planned to be administered in women.

- Genotoxicity

The complete series of genetic toxicology testing following *in vitro* exposure (bacterial and mammalian cells) and *in vivo* administration (mouse) did not reveal any potential to induce genetic damage.

- Carcinogenicity

With respect to carcinogenicity, in accordance with ICH S6, no *in vivo* studies have been conducted with either the follitropin alfa/lutropin alfa combination product or each of the individual recombinant hormones because as for products of biotechnological origin these assays are generally regarded as inappropriate. Moreover, carcinogenicity testing of such human gonadotropins in animals would be extremely difficult to perform because as shown in the subchronic toxicity tests, antibodies against the human proteins developed by rodents following prolonged exposure are likely to affect the activity of the hormone. Carcinogenicity bioassays in rodents are therefore considered irrelevant. In addition, there are a number of good reasons why the combination product is not expected to cause an increased risk of reproductive tumours in patients: (1) follitropin alfa and lutropin alfa are both recombinant form of the corresponding native glycoprotein hormones, (2) comprehensive programme of genotoxicity studies was performed, (3) these studies showed that, even at conditions of extremely supraphysiological exposure to follitropin alfa or lutropin alfa there was no evidence of mutagenicity or clastogenicity, (4) the repeated dose toxicity and pharmacokinetic studies did not indicate any potential for accumulation or the presence of any premonitory changes, despite the use of doses that exceeded the proposed clinical use by a very large margin, (5) the proposed clinical use of the product envisages only short-term use.

- Reproduction Toxicity

The full set of reproductive toxicity experiments carried out in rats and rabbits highlighted the predictable consequences of the hormonal imbalance induced by the untimely administration of high doses of such potent gonadotropins affecting fertility, implantation, parturition and foetal viability, though no teratogenicity was observed. However the No Observed Adverse Effect Level (NOAEL) could be set in rats for each individual gonadotropin to at least 5 IU/kg/day. Within the reproductive toxicity experiments, hMG, 320 IU/kg/day was administered to parallel groups of rats (Segment I, II and III) and rabbits (Segment II). In this case the negative effects resulting from the association of the two gonadotropins were largely superimposable to those already known for each of the individual recombinant hormones and with the published literature on HMG in rat pregnancy (Espey et al. 1997). In the fertility and early embryonic development study (Segment I), hMG-related effects were seen on both male and female parent gonads i.e. in males: interstitial cell hyperplasia and tubule atrophy reflecting on decreased or degenerated spermatic elements in epidydimides, and in females: increased number of corpora lutea with degenerative aspects and uterine atrophy. And hormonal imbalance was clearly produced in dams (high frequency of females with irregular estrous cycles) and none of the dams was found to be pregnant at term. In the embryo-foetal development studies (Segment II), increased number of corpora lutea, post-implantation losses (most of the dams had only resorptions and none delivered any pup) were seen in rats. Only resorptions, increased number of corpora lutea, and follicle haemorrhages and corpora lutea degeneration were found at ovary histology in rabbits. In the pre- and post-natal development study (Segment III) there was a prolonged gestational period, dystocic parturition and intrauterine death.

The observed adverse events are the predictable consequences of inappropriate exposures of animals to high doses of FSH and LH leading to deep interferences on the hormonal balance from which occurrence of pregnancy in the studied animal species depends. However, these findings are of a limited value in terms of human risk assessment as it would be irrelevant to administer r-hFSH and lutropin alfa either alone or in combination during pregnancy. Monitoring of the follicular development and hormonal changes during the ovarian stimulation therapy is a well consolidated practice ensuring that treatment is initiated and discontinued in a timely manner according to the patient's response.

- Toxicokinetic data

Concerning the animal studies, reference is made to two single dose pharmacokinetic studies in the monkey, taking into account that for rats no kinetic studies with follitropin alfa other than those obtained with the radio-labelled compound were performed, and that exposure is complicated by the inconsistent and generally low concentrations of the gonadotropins in serum after multiple doses.

Follitropin alfa: assuming dose-proportional exposures, the single dose comparison clearly shows that the peak serum levels in monkeys at the NOAEL identified in the 13-weeks toxicity study (1000 IU/kg/day) were over 150-fold higher than a clinically relevant plasma level in human subjects. However, the clinical regimen considered for the intend-to-market product is 150 IU. Using the above calculation this would still indicate a margin of about 150-fold (as AUC) between this and the primate toxicity study. This multiple indicates that a substantial safety margin exists with regard to human subjects given follitropin alfa therapeutically.

Lutropin alfa: the data indicates a difference of about 10-fold between exposure in humans and exposure in primate, suggesting a reasonable margin of safety. In the human clinical pharmacology study 23722 a dose of 450 IU was used, whereas in the intended clinical formulation a dose of 75 IU of LH will be administered. The safety margin is thus increased by a further 5 to 6-fold. In addition, the NOEL in the 13-week primate study was set at 1000 IU/kg, which increases the apparent safety margin of a further 2.5-fold. It therefore seems reasonable to define the safety margin as higher than 150-fold, assuming that exposures would remain linear with dose over these ranges. Biological actions of follitropin alfa or lutropin alfa are consequent to binding to their specific receptor. There is no experience or knowledge that activation by concomitant administration would represent a specific, new risk to human subjects.

- Local tolerance

Although follitropin alfa and lutropin alfa drug products were already shown to be devoid of irritating potential, the local tolerability of Pergoveris was investigated in order to support the planned human bioavailability study to be carried out at high dose levels (900 IU follitropin alfa + 450 IU lutropin alfa), to offer reassurance on the tolerability after repeat dosing at the dose/volume and concentration of the new product as foreseen in human therapy (150 IU follitropin alfa + 75 IU lutropin alfa in 1 mL of Water for Injection). A local tolerance study was conducted in the rabbit using Pergoveris. This study showed no evidence of an adverse local effect.

- Other toxicity studies

Allergenic and Immunogenic potential have been evaluated for the individual recombinant hormones. These studies showed that the gonadotropins are able to act as moderate sensitizers after intradermal challenge in the guinea pig maximization test; lutropin alfa is mildly allergenic in guinea pig and mouse anaphylaxis models. Such results are expected from the administration of a foreign (human) protein to animals. Considering the homology of the recombinant and natural human gonadotropins, the relevance of these findings in animals for the human clinical context is limited. Furthermore, there have been no reports in the clinical studies of antibodies to either follitropin alfa or lutropin alfa. Therefore, no studies intended to address the potential allergenicity and immunogenicity were performed with Pergoveris.
With respect to bioavailability, in order to allow comparative exposure assessment between animals and humans, two studies were performed that evaluate the bioavailability of follitropin alfa and lutropin alfa in healthy female subjects following single s.c. injection of the combination product (IMP23718, IMP23722). In the first study the human subjects received doses of 300 IU of follitropin alfa in combination with 150 IU lutropin alfa. In the second study, the human subjects received doses of 450 IU lutropin alfa in combination with 900 IU of follitropin alfa. As an approximation, in the case of a 50 kg subject this would be equivalent to a r-h FSH dose of 6 IU/kg (first study) and to a lutropin alfa dose of 9 IU/kg.

Ecotoxicity/environmental risk assessment

An ERA has been submitted. Due to the nature of Pergoveris, and in accordance with the CHMP guideline (CHMP/SWP/4777/00draft), no risk to the environment is expected.

Conclusions on the non-clinical aspects

It is concluded that clinical use of Pergoveris product would not expose patients to any undue risk. This is supported by the safety profile showed through the post-marketing experience gained by the applicant with both follitropin alfa and lutropin alfa. It was therefore considered that additional toxicological studies with r-hFSH/r-hLH would have added little value to the clinical risk-benefit assessment, especially when so much is already known about the pharmacology and toxicology of the individual hormones in man and in animals. Due to the extent of preclinical and clinical experience with the individual recombinant hormones and to the documented safety of the simultaneous administration of follitropin alfa and lutropin alfa as shown from the clinical trials, it is considered as not justifiable to conduct additional toxicology studies with the intend-to-market product. Additional non-clinical studies are not expected to result in new information useful for human risk assessment, and are considered as unethical, as they would lead to unnecessary use of animals. The non-clinical sections of the proposed SPC are in line with the SPCs of the two individual substances.

4. Clinical aspects

Introduction

Pergoveris is a new product containing a fixed combination of 150 IU of follitropin alfa and 75 IU of lutropin alfa intended for the stimulation of follicular development in women with severe LH and FSH deficiency (WHO type I anovulation, Hypogonadotropic Hypogonadism, HH). These patients are characterized by the absence of effective hypothalamic-pituitary activity resulting in arrested or attenuated gonadal function, and they do not have the necessary threshold levels of endogenous LH required to achieve optimal follicular development and steroidogenesis when given FSH alone, and therefore a combination therapy that ensures adequate doses of both FSH and LH in an optimal ratio is beneficial in order to restore fertility. Based on the data from clinical trials of ovulation induction in the WHO group I population, the addition of lutropin alfa to follitropin alfa in patients with profound LH deficiency is aimed at increasing ovarian sensitivity to follitropin alfa, promoting E2 secretion by the pre-ovulatory follicle, resulting in normal endometrial growth, and promoting later luteinisation of follicles resulting in normal luteal phase progesterone levels. The clinical experience has shown that the level of efficacy achieved is clinically and statistically above that of h-rFSH alone. The clinical studies have demonstrated that the 2:1 ratio (150 IU r-hFSH/75 IU r-hLH) is the most appropriate for this indication. Both follitropin alfa and lutropin alfa are currently individually available on the market. At present r-hFSH is approved for co-reconstitution with reconstituted lutropin alfa and co-administered as a single injection. Likewise lutropin alfa is approved for mixing with r-hFSH as an alternative to injecting each product separately. A new product which simplifies the reconstitution procedure is likely to reduce the risk of errors during manipulation, as well as it may provide a more convenient procedure for patients, hence increasing the chance for good compliance.

To support the registration of Pergoveris, the relative bioavailabilities of the constituent gonadotropins were compared to their currently marketed counterparts: follitropin alfa and lutropin alfa in biopharmaceutical studies (IMP23718 and IMP23722). The pharmacokinetics of healthy volunteers was studied in key clinical pharmacology studies of follitropin alfa (GF5007 and GF5117) and separately of lutropin alfa (GF6135, GF6136 and GF6137) submitted to support this application. Clinical efficacy and safety of lutropin alfa administered in free combination with follitropin alfa in HH women were demonstrated in two phase II/III studies (6253 and 6905). Study 6253 is the pivotal study with a study patient population representative of the targeted population for this application. Study 6905 is a supportive study in which a broader population was assessed, including patients with less severe LH and FSH deficiency. The two studies had a similar prospective, randomised, dose-finding design. Both studies investigated three doses of lutropin alfa and included a placebo-control group. Additionaly safety data has been summarised from four additional efficacy studies (GF7798, GF8297, IMP21008 and IMP21415).

GCP

The applicant declares that the two clinical efficacy studies presented in this submission were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The standards of Good Clinical Practice (GCP) were applied with respect to IRB/IEC procedures, informed consent, protocol adherence, administrative documents, drug accountability, data collection, patient records (source documents), adverse event reporting, inspection and audit preparation and record detention.

BIOPHARMACEUTICAL STUDIES

Bioavailability

To support the registration of Pergoveris, the relative bioavailabilities of the constituent gonadotropins were compared to the individually approved products containing separately follitropin alfa and lutropin alfa in biopharmaceutical studies (IMP23718 and IMP23722). These two new clinical studies were run in healthy female subjects to allow separate investigations of bioavailability for follitropin alfa and lutropin alfa. In study IMP23718 the relative bioavailability of 300 IU of follitropin alfa in combination with 150 IU of lutropin alfa was compared to that of 300 IU of follitropin alfa. The relative bioavailability of lutropin alfa at a dose of 450 IU in combination with 900 IU of follitropin alfa was compared to 450 IU of lutropin alfa in study IMP23722.

Study IMP23718

Study IMP23718 was conducted in order to assess the relative bioavailability of FSH when administered as the combination of follitropin alfa/lutropin alfa compared to r-hFSH. This was a randomized, double-blind, 2 way cross-over study in which 36 healthy female subjects were down-regulated using the GnRH-agonist goserelin (one subcutaneous injection of 3.6 mg). Each down-regulated subject received, in a randomised order, a single injection of r-hFSH (300 IU) and a single injection of the fixed combination product containing: 300 IU of follitropin alfa and 150 IU of lutropin alfa. Treatments were separated by a washout period of at least 7 days. Blood samples for determination of the concentrations of FSH in serum were taken at predetermined time-points. The measured FSH serum concentration versus time profiles after subcutaneous administration of 300 IU of follitropin alfa alone (reference) or as follitropin alfa in fixed combination with 150 IU of lutropin alfa (test) were assessed using non-compartmental analysis and the following parameters were computed: (1) Area under the serum concentration vs. time curve from zero to the last measurable concentration by using the log-linear trapezoidal rule (AUClast), (2) Peak serum concentration (Cmax), (3) Time of peak serum concentration (tmax). No AUC to infinity was calculated as endogenous concentrations were present at baseline for all subjects and many profiles approached a flat line towards the end of the profile, indicating that endogenous FSH levels were increasing in response to the loss of down-regulation over time. After administration of 300 IU follitropin alfa as r-hFSH (reference) or in combination with 150 IU of r-hLH (test), the median FSH profiles were very similar for both treatments. The mean Cmax was identical (10.3 IU/L), the mean AUClast was comparable (918 IU·h/L and 925 IU·h/L for R-hFSH and the combination, respectively). The median tmax values were comparable for both treatments (12 h). Total variability (CV %) was around 20 % for both Cmax and AUClast for both treatments. One subject in the analysis data set showed a 5 to 10 fold higher peak than all other individuals following administration of the fixed combination, with a typical profile for LH. No explanation could be found for this unexpected occurrence; neither in the clinical unit nor in the laboratory at sample analysis was anything unusual noted. A repeated analysis of the back-up samples for that subject confirmed the measured serum concentrations. This subject was excluded from the bioequivalence analysis. In conclusion, bioequivalence of the dose of 300 IU of r-hFSH received from r-hFSH 150 IU / r-hLH 75 IU fixed monodose combination (test) and R-hFSH 150 IU (reference) is concluded as the 90% confidence interval of the ratios of their means for both AUClast and Cmax, calculated from the ANOVA (or ANCOVA), were within the range (0.8,1.25).

Study IMP 23722

Study IMP 23722 was conducted in order to assess the relative bioavailability of LH when administered as the fixed combination of r-hFSH/r-hLH compared to r-hLH. This was a 2 arm-cross-over, open-label study in which 81 healthy female subjects were down-regulated using a GnRH-agonist (3.6 mg of goserelin). Each down-regulated subject received, in a randomised order, a single injection of r-hLH (450 IU) and a single injection of the fixed combination product containing 900 IU r-hFSH and r-hLH, separated by at least 21 days. The administration of GnRH-agonist was repeated prior to the second study period in order to ensure the maintenance of down-regulation throughout the study. A total of 40 evaluable subjects were planned in one investigational site, however due to slow recruitment this was raised to 55 – 60 evaluable subjects over two investigational sites. 81 healthy pre-menopausal female subjects entered the treatment phase over the two investigational sites and were included in the safety analysis. 18 subjects were withdrawn from the study prior to Period 2, mainly due to failure of down-regulation. A total of 63 subjects successfully completed the study and were

included in the evaluation of bioequivalence. All available data from all subjects were included in the pharmacokinetic analysis. The median LH serum profiles were similar in shape for both investigational products but with a lower Cmax for the fixed combination (mean 8.6 vs 9.3 mIU/mL for r-hLH). AUC0-last was also lower for the fixed combination (mean 208 vs 235 mIU·h/mL for R-hLH). The median tmax was shorter for the fixed combination (6.13 vs 8.92 h for R-hLH). Variability was rather high with 35.5 % (R-hLH) / 37.1 % (combination) for Cmax and 58.3 % (R-hLH) / 56.8 % (combination) for AUC0-last.
In conclusion, bioequivalence of 450 IU r-hLH in fixed combination with 900 IU r-hFSH (test) and 450 IU r-hLH as R-hLH (reference) is concluded, as the 90% confidence intervals of the ratios of their means for both AUC0-last and Cmax, calculated from the ANOVA (or ANCOVA), were within the range 0.8,1.25.
CHMP was of the opinion that the bioequivalence after a single injection of Follitropin alfa (300 IU) and a single injection of the fixed combination product containing: 300 IU of follitropin alfa and 150 IU of lutropin alfa is identical (Study IMP23718). CHMP believed that the bioequivalence after a single injection of lutropin alfa (450 IU) and a single injection of the fixed combination product containing 900 IU follitropin alfa and 450 IU lutropin alfa is identical (Study IMP23722). A dose of 450IU was chosen for Study 23722 as at this dose serum LH concentrations lie in the optimal range of the method used to determine serum LH levels and stay in the range long enough to adequately characterize the serum LH concentration-time profile to enable bioequivalence comparisons to be made. The same reason was behind the choice of a dose of 300IU of rhFSH for study 23718. CHMP was of the opinion that it was reasonable to assume that results from these doses can be extrapolated to the dosing applied for.

- Analytical methods

In studies IMP23718 and IMP23722 LH and FSH bioanalysis was performed using the commercially available assays respectively MAIA clone immunoradiometric (Manufacturer: Adaltis Italia, Italy) and SPAC-S (Manufacturer: Daiichi Radioisotope Labs Ltd, Tokyo, Japan). These same assays have also been used to support the individual recombinant gonadotropin clinical pharmacology and biopharmaceutics programs. Reports of Bioanalytical and Analytical Methods were not given. In order to assess the relative bioavailability of the respective hormones in question, larger doses were given than the ones intended for the final formulation. This design was due to difficulties in measuring the low serum values.

- Comparison and analyses of results across studies

R-hLH shows linear pharmacokinetics after i.v. doses ranging from 300 IU to 40,000 IU, as assessed by the AUCs which are directly proportional to the dose administered and the clearance which remains almost constant throughout studies. Around 5 % of the dose is excreted unchanged in the urine. This is not shown for s.c. injection. The terminal half-life of r-hLH administered s.c. is around half a day. This is best estimated when high doses are injected, as those obtained with much lower doses are less precise given the larger impact of fluctuations in baseline. However, this makes it more difficult to evaluate the impact of the results. Study GF6137 demonstrates that there is no pharmacokinetic interaction between r-hLH and r-hFSH. After repeated s.c. administration, the pharmacokinetics of lutropin alfa are comparable to those found after single s.c. administration. When administered s.c. concomitantly at the dose of 150 IU per day, lutropin alfa does not markedly affect the response to follitropin alfa. This was confirmed in study IMP 23722 where in the fixed dose combination of r-hFSH / r-hLH formulation, r-hLH has no effect on the PK of r-hFSH.

CLINICAL PHARMACOLOGY

- Pharmacokinetics in healthy volunteers

The pharmacokinetics of follitropin alfa and lutropin alfa have been described in studies that were conducted as part of their respective development programmes. The clinical study pharmacology programme consists of five clinical pharmacology studies in healthy volunteers (GF5007, GF5117, GF6135, GF6136, GF6137).

Study GF5007

Study GF5007, was a Phase I, balanced, random-order, cross-over study to determine the pharmacokinetics of urinary human FSH 150 IU, highly purified human FSH 150 IU and r-hFSH

150IU given intravenously. The study was performed in 12, pituitary desensitised, healthy, female volunteers. During the clinical phase of the study, each subject received by i.v. route, separated by a washout period of one week, the following four treatments: urinary human FSH 150 IU; highly purified human FSH 150 IU, r-hFSH 150IU, and r-hFSH 300 IU in random order. The study lasted eight weeks and included four treatment weeks, each separated by a washout period of one week. The mean serum FSH concentration-time profiles after a single 150 IU dose i.v. of urinary human FSH 150 IU, highly purified human FSH 150 IU, r-hFSH 150IU were superimposable and the mean profile after a single 300 IU dose IV of r-hFSH was double that of the 150 IU dose. The data for the FSH preparations, following i.v. administration, were well described by a biexponential equation. Total clearance of the preparations was comparable, judging from the immunoassay (0.5 Lh-1) and bioassay (0.15 Lh-1) data. Based on the immunoassay data, renal clearance of u-hFSH was 0.1 Lh-1 while for follitropin alfa it was slightly lower, 0.07 Lh-1, indicating that less than one-fifth of the administered dose was excreted in the urine. Immunoassay data showed that the FSH preparations were similar in terms of initial and terminal half-lives (2 hours and 17 hours respectively). The volumes of distribution at steady state (11 L) were similar. The results of the *in vitro* bioassay confirmed this pharmacokinetic analysis. This study indicates that (i) the pharmacokinetic characteristics of follitropin alfa are similar to those of u-hFSH, (ii) the terminal half-life of exogenous human FSH is about one day.

Study GF5117

Study GF5117, was a Phase I study to evaluate single and repeated administration of r-hFSH in twelve healthy pituarity down-regulated female volunteers and was performed in two stages. Part I: balanced, random-order, cross-over administration to determine the pharmacokinetics of a single r-hFSH dose given via i.v., i.m., and s.c. routes. Part II: daily s.c. administration over one week to determine the steady-state pharmacokinetics and pharmacodynamics of r-hFSH. R-hFSH was administered in a balanced, random-order, cross-over sequence as a single dose (150 IU) on three occasions: i.v., i.m. and s.c., each separated by a one week washout period. This was followed by a daily s.c. administration for seven days. The study lasted three weeks and each subject received the study medication on three successive occasions, separated by a washout period of one week, plus a daily administration over one week (fourth treatment week). After single administration, the pharmacokinetics of follitropin alfa were well described by a two-compartment model following i.v. administration and by a one-compartment model with first-order absorption following i.m. or s.c. administration. After i.v. administration, FSH total clearance was approximately 0.6 Lh^{-1} and renal clearance accounted for one-tenth of the total elimination. The distribution half-life was around two hours and the terminal half-life was nearly one day when estimated either by modelling the i.v. data set or from analysis of the terminal phase of the steady state pharmacokinetic curve or from the time taken to reach steady state after repeated s.c. administrations. After a single i.m. or s.c. injection, around two-thirds of the administered dose was available systemically. The accumulation factor after repeated s.c. administration was around three when steady state was reached. The *in vitro* FSH bioassay data confirmed these estimations. Two thirds of volunteers developed significant follicular growth, inhibin and E2 secretion. The first pharmacodynamic marker of the ovarian response to FSH was serum inhibin, followed by plasma E2 and then follicular growth (measured in this case by total volume of follicles >10 mm in diameter). When FSH administration was stopped, inhibin levels dropped, while E2 continued to rise for one day and follicle size further increased during four days. No correlation was found between maximal serum FSH concentrations during r-hFSH administration and the maximal E2 responses, inhibin responses and follicular growth responses. This study shows that a fixed dose of r-hFSH administered during a limited period of time, stimulated ovarian follicular development in a majority of female volunteers. The observed large inter-individual variability in response to treatment is related to differences in individual ovarian sensitivity to FSH rather than to differences in FSH pharmacokinetics. This study indicates that the s.c. and i.m. routes of administrations are suitable for clinical use of r-hFSH.

The two clinical pharmacology studies of follitropin alfa (GF5007 and GF5117) have demonstrated that the pharmacokinetic characteristics of r-hFSH are very similar to the pharmacokinetic characteristics of u-hFSH when given in the described doses. Subcutaneous administration is a suitable route of administration for r-hFSH since it is associated with an absolute bioavailability of 70 %.

Study GF6135

Study GF6135, was a Phase I study to assess the pharmacokinetics of r-hLH after single i.v. administration of increasing doses compared to a single dose of hMG in twelve healthy female volunteers down regulated with goserelin. This study was carried out to characterize the clinical pharmacology profile of r-hLH over a range from 75 IU to 40,000 IU, using contemporary assay methodology. hMG and increasing doses of r-hLH (75, 300, 10,000 and 40,000 IU) were administered as single injections in twelve down-regulated healthy female volunteers, according to an open, non-randomised, dose-escalating and comparative design. To determine the pharmacokinetics characteristics and linearity of lutropin alfa in 12 healthy female volunteers following administration of four doses of lutropin alfa given by i.v. bolus. To perform a comparison with u-hLH (contained in the hMG preparation). To assess the safety of lutropin alfa in hMP and increasing doses of r-hLH (75, 300, 10,000 and 40,000 IU) were administered as single injections, according to an open, non-randomised, dose-escalating and comparative design. Study drug was administered as a single i.v. bolus once per week separated by a period of one week. Five treatments were administered during the course of the study. The pharmacokinetic profiles of the two compounds are superimposable and no statistically significant difference is observed between them when parameters which do not require the dose for their computation (such as half-life), are considered. A difference was observed between u-hLH and lutropin alfa in the fraction excreted unchanged into the urine with less than 5% of the administered dose excreted unchanged following lutropin alfa administration and around 25% of the dose excreted unchanged into the urine following treatment with u-hLH.

Following i.v. injections of increasing doses of lutropin alfa, LH pharmacokinetics were described by a biexponential model which incorporated a baseline correction function. Lutropin alfa was eliminated with a half-life of approximately 10 hours, following a rapid distribution phase with an initial half-life of about one hour. Total body clearance was approximately 2 $L \cdot h^{-1}$ with less than 5 percent of the dose being excreted in the urine. The steady-state volume of distribution was around 8 L. The pharmacokinetics of lutropin alfa were linear over the 300 to 40,000 IU dose range. A statistically significant difference was observed between the dose (determined by immunoassay) normalised AUC of u-hLH and r-hLH (300IU dose). No statistically significant difference was observed however between the half-lives of the two compounds. The pharmacokinetics of FSH following i.v. administration of hMP were well described by a biexponential model incorporating a baseline correction function. Following a distribution phase with an initial half-life of approximately two hours, u-hFSH was eliminated with a terminal half-life of approximately 17 hours. Total body clearance was approximately 0.3 $L \cdot h^{-1}$ with approximately 30% of the dose being excreted renally. The steady state volume of distribution was approximately 6l. This study indicates that irrespective of the dose, r-hLh is well tolerated and that the pharmacokinetics of r-hLH are linear over the 300 to 400 IU dose range.

Study GF6136

Study GF6136 was a phase I study to assess the pharmacokinetics of r-hLH, after single i.v., i.m., and s.c. administration in twelve healthy female volunteers down-regulated with goserelin. Twelve healthy female volunteers received a nominal dose of 10,000 IU r-hLH by intravenous, intramuscular and subcutaneous routes, after pituitary desensitisation. The study was conducted according to an open, balanced, random-order, cross-over design, with wash-out periods of one week. Twelve healthy female volunteers received a nominal dose of 10,000 IU r-hLH by i.v., i.m. and s.c routes, after pituitary desensitisation. The study ran for three months and study treatment was administered as a single dose on three occasions, separated by a period of one week. A two-compartment model was chosen, with elimination from the central compartment for the i.v. data. There was no significant difference of the immunoassay data for the i.m. and s.c. routes. Estimates of V_{ss} and $t_{½}$ were larger from the bioassay data than from those of the immunoassay data possibly due to a wider distribution of bioactive LH. The results obtained with bioassay data generally confirmed those issued from the immunoassay. The immunoassay data can therefore be used with confidence in the characterisation of r-hLH pharmacokinetics.

Study GF6137

Study GF6137 was a phase I study to assess the pharmacokinetics of r-hLH after single and repeated subcutaneous administration with or without r-hFSH in twelve healthy female volunteers down regulated with goserelin. This was an open, balanced, randomised, cross-over study in which twelve volunteers were down-regulated to maintain endogenous LH and FSH level to basal levels. In a first phase, volunteers received each of the following three treatments separated by a one week wash-out. The treatment sequence was allocated at random: 150 IU of r-hLH, 150 IU of r-hFSH, 150 IU of r-hLH/150 IU of r-hFSH as a single injection ("combined treatment"). The volunteers received thereafter the combined treatment as a daily s.c. dose for 7 days. As soon as down-regulation was confirmed, a 24-hour baseline assessment of the LH and FSH serum and urinary levels was performed. There were following objectives of the study: (1) to determine the pharmacokinetics of r-hLH with and without r-hFSH in twelve healthy down-regulated female volunteers following s.c. administration of r-hLH, (2) to determine the pharmacokinetics of r-hFSH with and without r-hLH in twelve healthy down-regulated female volunteers following SC administration of r-hFSH, (3) to determine the steady state pharmacokinetics and pharmacodynamics following daily repeated s.c. administration of r-hLH combined with r-hFSH for one week. The study ran for three and a half months and volunteers received single doses of either r-hLH, r-hFSH or r-hLH/r-hFSH combined on three successive occasions separated by a washout period of one week. Subsequent to randomisation administration of the three single s.c. doses, all volunteers received repeated daily administration of the r-hLH/r-hFSH combination over a one week period. Lutropin alfa and follitropin alfa pharmacokinetics are adequately described by a one-compartment pharmacokinetic model with first-order absorption following s.c. administrations. Following single dose administration of lutropin alfa or follitropin alfa, mean values for baseline corrected parameters were not different from those obtained following combined administration. Statistical analysis showed no differences for both LH and FSH following single dose administration alone or in combination, indicating that there is no pharmacokinetic interaction between lutropin alfa and follitropin alfa. After multiple dosing, there was a low accumulation of LH whereas FSH accumulated around threefold. The pharmacokinetics of both lutropin alfa and follitropin alfa were comparable to those found in the single dose phases. Serum concentrations were corrected for baseline. The data was described by a one compartment pharmacokinetic model with 1st order absorption. No statistically significant differences were observed in Cmax or AUC_{0-24} for either lutropin alfa or follitropin alfa when comparing administration alone with that in combination. This was also found for tmax, indicating that there is no pharmacokinetic interaction between s.c. lutropin alfa and s.c. follitropin alfa, nor clinically relevant biopharmaceutical interaction. After multiple s.c. administration of lutropin alfa and follitropin alfa given simultaneously, the pharmacokinetics of lutropin alfa and follitropin alfa were comparable with those found following single dose administration. No correlation was found between maximal serum concentration of FSH (steady-state values) and any of the four effects recorded. No relationship was observed between maximal LH serum concentration and any of the pharmacodynamic markers. Estradiol as well as inhibin serum levels were found to be early markers of the follicle development. When administered concomitantly at the dose of 150 IU per day, lutropin alfa does not markedly affect the response to follitropin alfa. The pharmacokinetics of r-hLH and r-hFSH were comparable to those found following single administration. The interference of endogenous hormone was less marked following multiple dosing as the accumulation of recombinant product, especially r-hFSH, led to adequately high concentrations.

In the opinion of CHMP these additional studies indicate that: the pharmacokinetic characteristics of follitropin alfa are similar to those of u-hFSH, the terminal half-life of exogenous human FSH is about one day, the s.c. and i.m. routes of administrations are suitable for clinical use of r-hFSH, the pharmacokinetics of r-hLH are linear over the 300 to 400 IU dose range, immunoassay can be used in the characterisation of r-hLH pharmacokinetics, and repeat dose pharmacokinetics of r-hLH and r-hFSH were comparable to those after a single dose.

- Special populations

The co-administration of follitropin alfa and lutropin alfa were assessed in study GF6137, IMP 23718 and IMP 23722 as described above. No additional special studies with the fixed dose formulation were deemed as necessary in line with current regulatory and ethical considerations. Therefore, the results of studies previously performed with applicant's follitropin alfa and lutropin alfa are considered applicable to the product under evaluation.

Pharmacodynamics

- Primary and Secondary pharmacology

Study efficacy data from studies GF6253 and GF6905, described below, provided evidence that LH administration facilitates the action of FSH in a dose-dependent manner. This is suggestive of a significant pharmacodynamic interaction between lutropin alfa and follitropin alfa.

CLINICAL EFFICACY

- Dose response studies and main studies

Efficacy data included in this application are from two pivotal studies performed by the applicant using for the first time lutropin alfa along with follitropin alfa. The two phase II/III studies in this population used follitropin alfa 150 IU along with three different doses of lutropin alfa administered in free combination. The aim of both studies was to evaluate the efficacy of lutropin alfa and identify the minimal effective dose, in the treatment of women with HH. Both of these studies were submitted for recombinant human luteinising hormone registration. The first trial, Study GF6253, is the primary study, as the study patient population represents the targeted population for this application. The second, Study GF6905, is a supportive study in which a broader population was assessed, including patients with less severe LH and FSH deficiency

Study 6253

Study GF6253 was an open, randomised, dose-finding, multicentre, pivotal Phase II/III study to determine the minimal effective dose and assess the safety of lutropin alfa to support follitropin alfa-induced follicular development in LH and FSH deficient anovulatory women (WHO Group I). Thirty-eight patients were enrolled

The objectives were: to assess the need for and efficacy of lutropin alfa for inducing ovulation in women with HH, to determine the minimal effective dose of lutropin alfa to be administered during follitropin alfa stimulation of follicular development, to assess the safety of lutropin alfa administered subcutaneously (s.c.) to women for up to 20 days per cycle for a maximum of three cycles at a dose of up to 225 IU/day.

- Patient population

Women with HH, aged 18-35 years, with a negative progesterone challenge test, serum LH<1.2 IU/L and FSH <5 IU/L, an ultrasound showing (i) a uterus with a midline echo, (ii) no ovarian tumor or cyst and (iii) ≤ 13 (if using a vaginal probe) or ≤ 10 (if using an abdominal probe) small follicles (mean diameter ≤ 10mm) on the largest section through each ovary, a BMI between 18.4 and 31.4, no systemic diseases, using mechanical contraception if not wishing to conceive, having signed informed consent form.

The mean age of the 38 patients was 28.7 years, with a range of 20 to 35 years; the majority of the patients was Caucasian (97.4 %) not current smokers (84.2 %). Amenorrhoea was primary in the majority of patients (73.7 %); 10 patients (26.3 %) had secondary amenorrhoea. Age of menarche for the 10 patients with secondary amenorrhoea ranged from 11 to 16 years. Infertility was primary in 23 of the 28 patients (82.1 %) wishing to conceive and secondary in 17.9 %. Duration of infertility for the primary and secondary infertility patients ranged from 0.25 to 15 years and 1-5 years, respectively. A past pregnancy was reported by 23.7 % of patients.

- Method

The FSH daily dose was fixed at 150 IU based upon clinical experience and to ensure that all patients would be above their threshold needs. Patients were to administer two daily s.c. injections, one of lutropin alfa (25, 75 or 225 IU) and one of follitropin alfa (150IU). Recombinant-hLH was to be injected into the right side of the abdomen and follitropin alfa into the left side. Patients assigned to 0 IU lutropin alfa were to receive only a daily injection of 150 IU r-hFSH. According to the protocol, patients were to be treated for one cycle (cycle A). If consenting, patients could be treated for a further optional one or two cycles with different doses of lutropin alfa (cycle B and C). The lutropin alfa dose

for cycle A was randomly allocated. The lutropin alfa dose for cycles B and C depended on the patient response during the previous cycle.

- Endpoints

The study's primary efficacy endpoint was follicular development as defined by three parameters (all of which were to be fulfilled): i. at least one follicle with a mean diameter of ≥ 17 mm, ii. preovulatory serum E2 level of ≥ 400 pmol/L, iii. mid-luteal phase serum P4 level of ≥ 25 nmol/L. Secondary efficacy endpoints included: estradiol levels per follicle at mid-cycle, number of follicles at mid-cycle, endometrial thickness at mid-cycle and pregnancy. The safety assessment was based on the incidence and severity of adverse events, local tolerance at injection sites, anti-LH antibodies, pathological changes in clinical laboratory parameters, and pregnancy outcome. The study tested four doses of lutropin alfa, 0IU, 25IU, 75IU, and 225IU per day.

- Sample size

Thirty-eight patients were enrolled and randomised and treated for up to three cycles for a total of 52 cycles (38 cycle A, nine cycle B, and five cycle C). The primary efficacy analysis was conducted on the A cycles. It included 34 A cycles: ten patients treated with 225 IU, nine treated with 75IU, seven treated with 25IU and eight treated with 0 IU r-hLH. Four patients were excluded from the efficacy analysis for major protocol violations. All patients were included in the safety analysis. Of the 38 patients at cycle A, 17 of them received hCG and 21 patients did not receive the hCG injection (5 presented a risk of OHSS, 14 failed to develop a follicle with a mean diameter of at least 17 mm and two withdrew consent after a few days of treatment). Out of the 17 patients who completed cycle A and received hCG, nine entered the optional cycle B. During this cycle, three patients received the hCG injection and six did not due to insufficient follicular development. Five of the nine patients entered and completed the optional cycle C.

- Results

Primary efficacy analysis

During cycle A, 17 patients received hCG, five did not receive hCG because of risk of OHSS, 15 did not receive hCG because of insufficient follicular development and two withdrew consent. Four of these patients were excluded from the eligible patients analysis. Primary efficacy analysis was conducted on cycle A results and included 34 evaluable patients: eight patients in the 0 IU/day dose group, seven in the 25 IU/day group, nine in the 75 IU/day group and ten in the 225 IU/day group. In the low LH groups four patients had good or excessive follicular growth contrasting with the higher LH groups in which fifteen patients had good or excessive follicular growth. The proportion of patients who fulfilled the primary efficacy endpoint criteria (≥ 1 follicle ≥ 17mm; E_2 ≥ 400 pmol/L; mid-luteal phase P_4 ≥ 25 nmol/L) was related to the dose of r-hLH both when excessive follicular development was not included as a success (0.0%, 14.3%, 44.4% and 50.0% for treatment with 0, 25, 75 and 225 IU r-hLH respectively; p=0.0124) and when excessive follicular development was included as a success (0.0%, 14.3%, 66.7% and 80.0% for treatment with 0, 25, 75 and 225 IU r-hLH respectively; p=0.0001). When only patients who received hCG are considered, optimal steroidogenesis as defined in the protocol (i.e. preovulatory E_2 and P_4 values) was observed in 0.0%, 33.3%, 80.0% and 100.0% for treatment with 0, 25, 75 and 225IU r-hLH respectively; p=0.0210).

Secondary endpoint analyses

Secondary endpoint analyses confirm the strong influence of r-hLH dose on E_2 secretion, resulting in very different endometrial growth between the treatment groups.

Estradiol per follicle at mid-cycle

The E2 level per follicle ratio was highest in the 75 and 225 IU/day dose groups: 855 and 1598 pmol/L per follicle, respectively. Results in the 0 and 25 IU/day dose groups were 60 and 89, respectively.

Follicle number at mid-cycle

On the day of hCG administration, the number of follicles >10 mm in diameter was 1.0, 3.5, 5.0 and 3.2 for the 0, 25, 75 and 225 IU/day dose groups respectively. Similarly, the number of follicles ≥15 mm on the day of hCG administration were 1.0, 3.0, 2.0 and 2.0 for the 0, 25, 75 and 225 IU/day dose groups.

Endometrial thickness at mid-cycle

On the day of hCG administration, median endometrial thickness was 2.0, 4.0, 9.0 and 9.0 mm in the 0, 25, 75 and 225 IU/day dose groups, respectively.

Patient pregnancy rates

Twenty-eight of the 38 patients enrolled in the study desired pregnancy and ten were volunteers. These 28 patients initiated a total of 39 treatment cycles, three of which resulted in pregnancy (7.7 % per cycle). No pregnancies occurred in the 0 or 25 IU dose groups. In the 75 and 225 IU dose groups, pregnancy occurred in 16.6 and 11.1 % of the patients, respectively. Two of the three clinical pregnancies resulted in live births and one in a spontaneous abortion. Of the two live births, one was a singleton and the other a set of twins.

In terms of safety, the study showed that LHadi is safe at a dose up to 225IU per day and is not immunogenic. Reported AEs are those usually recorded when stimulating follicular development with FSH alone. Recombinant-hLH does not appear to modify the safety profile or r-hFSH. The data showed an excellent local tolerance to s.c. administration of LHadi.

Conclusions of the primary study

This study demonstrated the efficacy of the first preparation of pure hLH available for clinical use, for supporting FSH-induced follicular development prior to triggering ovulation in WHO Group I anovulatory women. R-hLH promoted in a dose-related manner, E_2 secretion and luteinisability of FSH-induced follicles. It enhanced ovarian sensitivity to FSH. Although individual requirement for r-hLH varied, a daily dose of 75 IU r-hLH was effective in the majority of WHO Group I anovulatory patients. A dose up to 225IU/day could be necessary in a minority of patients. The study data suggest that a conservative dosage of r-hFSH should be used in association with r-hLH. This study demonstrates a clinically and statistically significant relationship between the dose of lutropin alfa administered and follicle development. This finding is further confirmed when the risk of OHSS is accepted as evidence of LH efficacy. The study also shows that a majority of HH patients respond adequately to a daily dose of 75 IU lutropin alfa, achieving sufficient but not excessive follicular development and steroidogenesis with this dose. In summary, the data demonstrate that lutropin alfa is well-tolerated and, when co-administered with follitropin alfa, does not appear to modify the safety profile of follitropin alfa. In addition it demonstrates that women with HH associated with severe LH-deficiency who are seeking conception will benefit in a dose-response manner to co-administration of lutropin alfa with follitropin alfa.

Study GF6905

This was a prospective, randomised, parallel group, dose-ranging study to determine the minimal effective dose and the efficacy and safety of r-hLH administered s.c. at doses up to 225 IU/day to support stimulation of follicular development with a fixed dose of 150 IU/day of r-hFSH in anovulatory women with HH.

- Objectives

The objectives were: to assess the need for and efficacy of r-hLH for inducing ovulation in women with HH, to determine the minimal effective dose of r-hLH to be administered during follitropin alfa stimulation of follicular development, to assess the safety of r-hLH administered s.c. to women for up to 21 days per cycle for a maximum of three cycles at a dose of up to 225 IU/day.

- Patients population

Premenopausal women with HH, aged 18-40 years, with low serum values of FSH ($\leq 50^{th}$ percentile of the normal range (≤10.85 IU/L), LH$\leq 50^{th}$ percentile of the normal range for the follicular phase (≤13.3 IU/L)), and oestradiol (E2<60pg/mL); an ultrasound showing (i) a uterus with a midline echo, (ii) no ovarian tumour or cyst and (iii) ≤13 small follicles (mean diameter ≤10mm) on the largest section through each ovary; BMI between 18 and 35, no systemic disease, using mechanical contraception if not wishing to conceive, having signed informed consent form were eligible. Patients were randomised to one of four dose groups of r-hLH: 0 (control), 25 IU, 75 IU and 225 IU in cycle A. Two further treatment cycles were optional. Dose adjustment of r-hLH was to be considered for subsequent cycles based on the patient's individual response. All patients received a fixed daily dose of 150 IU r-hFSH for all cycles, A, B and C administered s.c. every day at approximately the same time as the lutropin alfa. Lutropin alfa at doses of 25, 75 or 225 IU and follitropin alfa at 150 IU were to be administered once daily at the same time, as two separate s.c. injections into the anterior abdominal

wall. Patients assigned to the 0 IU/day lutropin alfa dose group were to receive only the daily injection of 150 IU follitropin alfa. Administration of r-hLH and r-hFSH was not to exceed 21 days in any cycle unless increased E_2 levels and/or follicular growth (follicle >10mm) indicated imminent follicular maturation. Patients could be treated for up to three cycles (cycles B and C were optional).

- Endpoints

The primary efficacy endpoint was follicular development as defined by: i. at least one follicle with a mean diameter of ≥17mm, ii. (pre-ovulatory serum E_2 level ≥160 pg/mL, iii. mid-luteal phase P_4 level ≥10 ng/mL. Secondary efficacy endpoints included: estradiol levels per follicle of >15 mm on the day of hCG administration, number and size of follicles on the day of hCG administration, mid-luteal phase serum P4 levels, endometrial thickness and pregnancy. Safety: Incidence and severity of adverse events, local tolerance at injection sites, anti-LH antibodies, pathological changes in clinical laboratory parameters, and pregnancy outcome.

Sample size

Forty-three patients were randomised and 40 patients were treated for up to three cycles for a total of 61 cycles (40 cycle A, 16 cycle B, and 5 cycle C). As planned, the primary efficacy analysis was conducted on the results of cycle A, the randomised cycle, and included all 40 patients: 11 patients in the 0IU/day dose group, nine in the 25 IU/day group, 11 in the 75 IU/day group and nine in the 225 IU/day group. Safety analyses included data from all 40 patients treated and for all 61 treatment cycles. Three patients were withdrawn from the study during the pre-treatment period, two of them were not eligible for inclusion and the third one chose to withdraw prior to treatment. The median age of the 40 patients was 30.5 years, with a range of 22 to 40 years; the majority of the patients were Caucasian (77.5%) and not current smokers (90.0%). Amenorrhea was secondary in the majority of patients (23/40, 57.5%); 17 patients (42.5%) had primary amenorrhea. A family history of the condition was reported by 10.0% of patients. Median age of menarche for the 23 patients with secondary amenorrhea was 14.0 years. Infertility was primary in 57.5% of patients, secondary in 32.5% and unknown in 10% of patients (volunteers). Median duration of infertility was 28.0 months and a past pregnancy was reported by 37.5% of patients.

- Results

Primary efficacy analysis

All patients were included. The primary efficacy endpoint in this study was follicular development, as defined by the three parameters described below. In cycle A, the follicular development rate was lowest in the 19IU/day r-hLH dose group, with 63.6% of the 11 patients meeting the criteria for follicular development. All nine patients in the 25 IU/day dose group, eight (72.7%) of 11 patients in the 75 IU/day dose group and six (66.7%) of nine patients in the 225IU/day dose group achieved follicular development. A statistically significant dose-related trend was not observed. Because of the limited number of patients continuing into the second and third cycles of treatment, no conclusion regarding the minimal effective dose per patient was possible.

There was not a statistically significant trend in the proportion of patients achieving at least one follicle with a mean diameter of ≥17 mm (p = 1.000). The proportion of patients who had serum E2 levels ≥160 pg/mL during cycle A was lowest in the 0 IU lutropin alfa/day dose group (63.6 %). Among the 29 patients in the 25, 75 and 225 IU/day dose groups, all nine (100 %) patients in the 25 IU/day dose group, nine (81.8 %) of 11 patients in the 75 IU/day dose group and six (66.7 %) of 9 patients in the 225 IU/day dose group had a serum E2 level ≥160 pg/mL. There was not a statistically significant trend in the proportion of patients achieving this endpoint (p = 0.458). For mid-luteal serum P4 levels, there was not a statistically significant trend in the proportion of patients achieving this endpoint (p = 0.442).

Secondary endpoint analyses

Oestradiol per follicle at mid-cycle

There was a statistically significant difference among the dose groups for the assessment of median E_2 level (pg/mL) per follicle ≥15mm on the day of hCG administration (p=0.042), with the highest levels occurring in the 75 and 225IU dose groups (189.5 and 339.3 pg/mL, respectively).

Follicle number at mid-cycle

There were no statistically significant differences among the dose groups for the number of follicles >10 mm in diameter or for those ≥15 mm on day of hCG administration.

Endometrial thickness at mid-cycle

On the day of hCG administration, there was a statistically significant difference observed among the r-hLH dose groups for endometrial thickness with the highest median endometrial thickness of 10.0mm observed in the 225IU/day dose group (p=0.041).

Patient Pregnancy Rates

Cycle A total pregnancy rates for all treated patients willing to conceive increased across the r-hLH dose groups. The total pregnancy rates were 20.0%, 25.0%, 30.0% and 33.3% in the 0, 25, 75, and 225IU/day dose groups, respectively. During the entire course of the study, pregnancy occurred in 14 (26.9%) of the 52 treatment cycles completed by patients wishing to conceive and clinical pregnancy in 12. Nine clinical pregnancies (75.0%) resulted in live birth and two (16.6%) spontaneous abortions were reported. Pregnancy outcome data were not available for one patient. Five of the nine clinical pregnancies resulted in singleton birth and four patients had twins.

Safety

A higher proportion of patients who received r-hLH at doses of 25, 75, or 225 IU/day in combination with r-hFSh (84.4%) experienced adverse events as compared to those patients who received r-hFSH alone (65.0%). However, there did not appear to be a relationship between the dose of r-hLH administered and the adverse event rate with 83.3% of patients who received 25IU/day, 75.0% of patients who received 75IU/day and 69.2% of patients who received 225IU/day reporting at least one adverse event. Over the entire course of the study a total of 91 adverse events were reported. The most commonly reported events included ovarian cyst, abdominal pain, breast pain, dysmenorrhea, headache and nausea. Over 96% of all events were judged to be mild or moderate in severity. No serious adverse events were reported during the study and none of the patients discontinued the study due to adverse events. Local tolerance at the injection site was good with 98% or more of the r-hLH injections having no or only mild itching, redness, swelling, bruising or pain reported. There were no clinically significant changes from baseline to post-treatment observed in clinical chemistry, haematology or urinalysis parameters. No study patients developed antibodies to LH or FSH.

- Conclusions

Study GF6905 demonstrated that r-hLH is well-tolerated and, when co-administered with r-hFSH, presents a similar profile of safety to r-hFSH administered alone. In this study, although some efficacy trends were apparent, no statistically significant effect of addition of r-hLH was demonstrated on follicular development in HH patients. The overall study results confirm that some patients with HH may respond to FSH alone, however, an LH deficiency was evident in some of the secondary efficacy parameters consistent with the two-cell theory of gonadotropins and follicle function. When the population of HH patients with a more severe endocrine deficiency was analysed, the need for co-administration of r-hLH with r-hFSH was clear. In this population patients randomised to r-hFSH-alone, the 0 IU/day r-hLH dose, were non-responders. In conclusion, Study GF6905 confirms the heterogeneity of baseline characteristics and response patterns of patients with HH and supports the need for co-treatment with LH and FSH in patients with severe gonadotropin deficiency.

- Analysis performed across trials (pooled analyses and meta-analysis)

Due to differences in inclusion criteria for study GF6905 and those of the pivotal study GF6253, the patient population investigated in study GF6905 included HH women with less severe LH and FSH deficiency compared to those enrolled in Study GF6253. Thirty-eight patients were treated in study GF6253, and 40 in study GF6905. At screening, 36 patients in study GF6253 had LH levels below 1.2 IU/L. In study GF6905, only 15 out of the 40 treated patients had a LH value <1.2 IU/L.

These differences are shown in the table below:

Regarding the demographics, both study populations fulfilled the criteria for HH, but study GF6253 patients presented a more severe deficiency as documented by lower LH, FSH and E_2 levels, a higher proportion of patients with LH <1.2 IU/L at baseline, and thinner endometrium.

Primary and Secondary Efficacy Variables - Data Sets Analyzed

Study GF6253
For efficacy analysis, the data set (n=34) included all patients who received at least one dose of FSH/LH except four patients who presented major deviations from the eligibility criteria and / or the treatment regimen / study procedures described in the protocol: one patient did not receive the prescribed dose of follitropin alfa, one discontinued treatment for personal reasons before any efficacy and safety assessments were carried out, and two had LH values well above the protocol limit at baseline and throughout treatment. For safety analysis, all 38 patients who received at least one dose of FSH/LH were included.

Study GF6905
For efficacy analysis two data sets were analyzed: the first of these was the data set including all 40 patients who received at least one dose of FSH/LH. This set was used for analysing the primary and secondary efficacy endpoints, the second was the data set formed by patients with pre-study LH level <1.2 IU/L. This set was used only for analyzing the primary efficacy endpoint. For safety analysis, all 40 patients who received at least one dose of FSH/LH were included.

A highly significant statistical and clinical difference in patient response related to the dose of lutropin alfa was seen in study GF6253. No difference was observed, however, between treatment groups in study GF6905, with a majority of patients fulfilling the primary efficacy endpoint criteria.

Analysis of the secondary efficacy endpoints supports the conclusion that LH promotes E2 secretion by the growing follicles in a dose-dependent manner. This dose effect is highly significant in study GF6253. It is also apparent in study GF6905, especially when the E_2 per follicle ratio is compared between treatment groups (p=0.042). In agreement with this observation, the endometrial growth in patients who received 75 and 225 IU/day lutropin alfa is maximal and comparable with the endometrial thickness observed during normal, spontaneous cycles. In study GF6905 only three patients in the control and 0-LH groups (9 %) had a clinical pregnancy, compared with eight patients in the 75 and 225 IU/day lutropin alfa groups (24 %).

- Supportive studies

Four additional studies have been conducted utilizing lutropin alfa combined with follitropin alfa in women with severe LH and FSH deficiency. These studies support the recommendations for a daily administration of 75 IU lutropin alfa with 150 IU follitropin alfa in HH patients.

- Discussion on clinical efficacy

In the opinion of CHMP study GF6253 provided sufficient evidence to support the proposed dose of 75 IU of lutropin alfa in the combined product. However, study GF6905 did not provide adequate evidence to differentiate between doses of lutropin alfa, in that, there is clear evidence of efficacy for all doses studied (25, 75 and 225 IU/day) in patients with LH < 1.2 IU/L. Nevertheless, overall, it is reasonable to accept that a starting dose of 75 IU is appropriate. An analysis of the secondary endpoints, including pregnancy rates supports this position. CHMP was of the opinion that there were no methodological concerns regarding this application. Sufficient evidence of bioequivalence of the two active components of when given in combination, to the individual components, when given alone, has been provided.

CLINICAL SAFETY

Safety data for this application is mainly from two key clinical studies (GF6253 and GF6905) and the post-marketing experience for each of the two recombinant gonadotropins. Additional safety data from a further seven studies, four efficacy (GF7798, GF8297, IMP21008 and IMP21415), two

biopharmaceutic (IMP23718 and IMP23722) and one pharmacokinetic study (GF6137) on follitropin alfa co-administered with lutropin alfa, were also summarised.

- Patient exposure

A total of 38 patients from study GF6253 and 40 from study GF6905 were included in the main safety analysis, representing a total of 114 cycles overall. During 83 of the 114 cycles at least one dose of r-hLH was administered (42 cycles in study GF6253 and 41 cycles in study GF 6905).

- Adverse events

Study GF6253

The incidence of adverse events according to r-hLH treatment groups are shown in the table below. A total of 42 AEs were reported with 32 AEs in 11/42 (26.2 %) lutropin alfa treatment cycles and ten AEs in 3/11 (27.2 %) control (lutropin alfa 0 IU) cycles. A total of 78.6% events were reported as mild and 19.0% events were reported as moderate in severity. One event of severe back pain (2.4 %) was reported in a patient receiving follitropin alfa only (control). The most frequent were headache, pelvic and abdominal pain, breast pain, nausea, somnolence and ovarian disorder. No symptoms suggesting immune reactions were reported. Two SAEs were reported, one was a patient in shock after a road accident, and the other was a patient who suffered a miscarriage. Three further patients presented with symptoms and ultrasound scans that suggested a risk of OHSS and were discontinued from the study.

Study GF6590

A total of 91 AEs were reported over the course of the study and are presented in the table below**.** Of the 32 patients who received at least one dose of lutropin alfa during the study, 27 (84.4 %) reported a total of 65 AEs. No apparent relationship, however, was seen between the lutropin alfa dose and AE rate, with 83.3 %, 75.0 % and 69.2 % of patients who had received 25, 75 or 225 IU respectively, reporting at least one AE. The most commonly reported events included ovarian cyst, abdominal pain, breast pain, dysmenorrhea, headache and nausea. Of these 61.5% were reported as mild, and 35.2% were reported as moderate in severity. Three events, reported by three patients, were judged to be severe: two (pelvic pain and abdominal pain) in patients receiving follitropin alfa alone, and one (pelvic pain) in a patient receiving follitropin alfa in combination with lutropin alfa 25 IU. No SAEs were reported during the study and none of the patients discontinued the study because of AEs. Seven patients were at risk of OHSS but completed the study. Five patients discontinued the study: four of the five withdrawals were due to patients' decision after completing cycle A (two each at lutropin alfa doses of 75 IU and 225 IU) and the fifth was due to protocol violation (pregnancy started before study treatment).

Study GF7798

A total of six AEs were reported by 4 (26.7 %) patients. Four AEs were cases of OHSS in three patients (all of whom required hospitalisation) and were considered to be probably related to treatment and moderate or severe in intensity. The OHSS led to the discontinuation of two of the patients from the study. The remaining two AEs comprised mild dizziness (possibly treatment-related) and Klebsiella fever (unrelated to treatment). Local tolerance to the injections was good with only mild bruising (four cases) and redness (one case) reported. During the study, clinical pregnancy occurred in seven patients and of these, five resulted in live births. No congenital malformations were reported.

Study GF8297

Nine patients experienced a total of ten AEs, all of which were mild or moderate in severity. Three patients experienced OHSS, of which two cases were moderately severe SAEs; the remaining case was considered mild and non-serious. All of the other AEs were considered to be unrelated to treatment, except for one case of headache. Over 90 % of the injections were not associated with local reactions. Seven patients experienced mostly mild or moderate local reactions at the injection site. Only one of the seven patients reported severe symptoms (itching and pain). During this study, there were 15 clinical pregnancies and of these, 13 resulted in live births. The only congenital malformation reported was inguinal hernia in a couple of twins, which necessitated surgical repair.

Study IMP21008

A total of 44 AEs were reported by 13 patients: 33.3 % patients in the active lutropin alfa group and 33.3 % patients in the placebo group. The most commonly reported AEs were abdominal pain,

flatulence, nausea, headache, injection site reaction, and ovarian cyst. A possible or probable relationship to the study drugs was determined for 12 AEs in each treatment group (active, 44.4 %; placebo, 70.6 %). The majority of AEs were considered to be mild or moderate in severity and no SAEs were reported. One AE judged to be severe but non-serious was a case of OHSS in a pregnant patient in the placebo group.

Study IMP21415
A total of 65 AEs were recorded in 15 (48.4 %) patients. The most frequently reported AEs were flatulence, constipation, abdominal pain, nausea, breast pain and headache. Most AEs were mild or moderate in severity, however three (4.6 %) were judged to be severe: two non-serious (abdominal pain and injection site inflammation) and one serious (OHSS). All three severe AEs were considered to be possibly or probably related to the study drug. In total, 61.6 % AEs were considered to be possibly or probably related to the study drug. Of the 16 clinical pregnancies achieved during this study, 14 resulted in live births with no congenital malformations. The outcome of the remaining two pregnancies is unknown.

Study IMP23718
Twenty AEs were reported in each treatment group, the most common of which was headache. All AEs were mild or moderate in intensity.

Study IMP23722
The majority of AEs from both treatment groups were mild or moderate. There were two severe AEs; one patient experienced a vasovagal episode and one patient experienced severe labile emotions. Headache was the most common AE and was reported by 32.4 % and 46.6 % of subjects in the R-hLH and fixed combination product groups respectively.

Study GF6137
Single dose subcutaneous administration of follitropin alfa and lutropin alfa both alone and in combination was well tolerated in the 12 healthy subjects at the dose studied. The most common AEs were hot flushes and headaches and all were mild in intensity. Multiple dose administration of follitropin alfa/lutropin alfa was also well tolerated at the doses studied, although more of the subjects experienced hot flushes.

Immunological events
Study GF6253 and Study GF6905: no study patients developed antibodies to either LH or FSH. Study GF7798: no study patients developed antibodies to either LH or FSH. Mild systemic allergic reactions and serious cases of allergic reactions including anaphylactic reactions have been reported with a frequency rated as “very rare”. In the case of separate use of R-hLH, no reports of hypersensitivity have been reported in clinical trials. In two efficacy studies, no potentially immune-mediated events were reported and in study GF6253 patients did not develop antibodies to either LH or FSH. The applicant searched the Serono adverse event database for clinical trial adverse event reports with regard to immunogenicity and its related reactions. All trials discussed in the Gonovel file were searched and no cases were retrieved from these trials that would suggest a potential immunogenicity induced by the use of R-hFSH or R-hLH. No post-marketing data are available with regard to the immunogenicity of R-hFSH or R-hLH, while used separately. Cases of allergic reactions reported with R-hFSH are listed in the Core Safety Information and labelled in the SPC of the product.

- Serious adverse event/deaths/other significant events

Study GF6253
Two SAEs were reported which led to hospitalisation of the patients: (1) the first was mild shock from a road traffic accident, which occurred 14 days after the patient completed her third cycle of treatment (lutropin alfa 25 IU). The investigator considered this event to be unrelated to the study drugs, (2) a 28-year-old woman with Kallman’s syndrome became pregnant as a result of study treatment (last cycle lutropin alfa 75 IU). Miscarriage occurred 69 days after receiving hCG injection. The investigator considered the relation of the event to the study drugs to be unknown.

Study GF8297
Two cases of OHSS were reported as moderately severe SAEs.

Study IMP21415
One SAE of OHSS was reported as serious.

Study GF6137
No SAEs were reported in studies GF6950, GF7798, IMP21008, IMP23718, IMP23722 and GF6137.

- Laboratory findings

No clinically significant changes from baseline in laboratory values were detected at the end of studies GF6253, GF6905, GF7798, GF8297, IMP21415, IMP23718 and IMP23722.

Study IMP21008
No clinically relevant differences were seen between treatment groups in laboratory values. Two patients had clinically significant abnormal laboratory values: one patient from the placebo group had elevated values at the study endpoint compared with baseline for AST/SGOT and ALT/SGPT (recorded as non-serious AEs) and a second patient, from the active group, had abnormal baseline cholesterol values. All vital signs parameters showed no clinically significant changes from baseline.

- Safety in special populations

Study GF6253 and Study GF6905

Pregnancy
Following controlled ovarian hyperstimulation using gonadotropins, no teratogenic risk has been reported, however, insufficient clinical data exists to exclude a teratogenic effect of follitropin alfa. The SmPC for r-hLH states that lutropin alfa should not be administered during pregnancy or lactation. R-hFSH/r-hLH should not be administered during pregnancy or lactation.
Intrinsic Factors
A subset analysis was performed to assess follicular development in a population of 15 patients in study GF6905 with screening LH levels of <1.2 IU/L. The incidence of AEs among these patients was higher than in the overall study population: the 27 (44 % of total) treatment cycles undergone by this subset were associated with more than half (56 %) of the AEs. The incidence of AEs was higher in study GF6905 which may be due to the difference in the number of cycles, 27 in study GF6253 and 53 in study GF6905.
Extrinsic Factors
No safety data available.

- Safety related to drug-drug interactions and other interactions

Study GF6137
No pharmacokinetic interaction between lutropin alfa and follitropin alfa was observed. The pharmacokinetics of lutropin alfa after repeated subcutaneous administration was comparable with those after a single subcutaneous dose.

Study GF6253
The proportion of patients developing at least one follicle in response to a fixed dose of follitropin alfa (150 IU/day) increased in relation with the dose of co-administered lutropin alfa. This suggests that lutropin alfa administration increases ovarian sensitivity to FSH. Conservative dosage of FSH should therefore be used in association with lutropin alfa. Other than with each other, lutropin alfa and follitropin alfa should not be administered as a mixture in the same injection with other medicinal products.

- Discontinuation due to adverse events

Study GF6253
Three patients discontinued the study due to symptoms and ultrasound scans which suggestive of OHSS. All symptoms resolved within eight days of discontinuation of the study drug (lutropin alfa 75

IU for one patient and 225 IU for two patients). The total duration of lutropin alfa/follitropin alfa treatment in each of these three cases was nine or ten days. The investigator considered the relationship of these events to the study drug as possible in two of the three cases, and probable in the remaining case.

Study IMP21008
One non-serious AE (delayed hypersensitivity reaction) led to the discontinuation from the study of one patient in the active group.
There were no patient discontinuations in studies GF6905, GF7798, GF8297, IMP21415, IMP23718, IMP23722 and GF6137.

- Discussion on clinical safety

Clinical safety data for this application is mainly provided from two key clinical studies (GF6253 and GF6905) and the applicant's post-marketing experience for each of the two recombinant gonadotropins. Additional safety data from a further seven studies, four efficacy (GF7798, GF8297, IMP21008 and IMP21415), two biopharmaceutic (IMP23718 and IMP23722) and one pharmacokinetic study (GF6137) on follitropin alfa co-administered with lutropin alfa, have also been summarised. A total of 38 patients from study GF6253 and 40 from study GF6905 were included in the main safety analysis, representing a total of 114 cycles overall. During 83 of the 114 cycles at least one dose of lultropin alfa was administered (42 cycles in study GF6253 and 41 cycles in study GF 6905). A total of 42 AEs were reported in study GF6253 and the most frequent were headache, pelvic and abdominal pain, breast pain, nausea, somnolence and ovarian disorder. No symptoms suggesting immune reactions were reported. Two SAEs were reported. A total of 91 AEs were reported in study GF6590 the most frequent of which included ovarian cyst, abdominal pain, breast pain, dysmenorrhea, headache and nausea. No SAEs were reported. From the additional safety data, six AEs were reported in study GF7798, ten in study GF8297, 44 in study IMP21008, 65 in study IMP21415 and 20 in study IMP23722. One SAE of OHSS was reported as serious in study IMP21415 and two cases of OHSS were reported as moderately severe SAEs in study GF8297. Three patients discontinued in study GF6253 due to scans and symptoms suggestive of OHSS and one patient discontinued from study IMP21008due to delayed hypersensitivity reaction. The applicant has adequately addressed the potential for immunogenicity with acceptable reasoned arguments. Overall, no new safety concerns have been raised and the recommendation from a clinical point of view is favourable.

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
The CHMP, having considered the data submitted in the application, is of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product and no additional risk minimisation activities were required beyond those included in the product information.

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 substances are adequately described, controlled and validated. The drug substances are well characterised with regard to their physicochemical and biological characteristics, 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. The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured. Except for a number of quality points, which will be addressed as part of post-approval follow-up measures, the overall quality of Pergoveris is considered acceptable.

Non-clinical pharmacology and toxicology
The two biotechnological drug substances follitropin alfa and lutropin alfa have been characterised separately by the applicant with non-clinical tests appropriate to the nature, the intended dosage and duration of administration of Pergoveris. Human bioavailability studies have shown that there is no discernable change of the pharmacokinetics of the individual follitropin alfa and lutropin alfa when administered in combination. CHMP considered that based on the extent of preclinical and clinical experience gained with each individual recombinant hormone and the documented clinical efficacy and safety of the simultaneous administration of r-FSH and lutropin alfa, conducting additional preclinical studies with the combination would be unethical as they would unnecessarily use additional animals. Additional non-clinical studies are unlikely to extend scientific knowledge on the pharmacology of the applicant's follitropin alfa and lutropin alfa and the results of such studies would not impact r-hFSH/r-hLH risk balance. Therefore, the CHMP was of the opinion that no additional pharmacology studies were required. However, as Pergoveris is a new product, a new local tolerability study was performed with the intend-to-market formulation. A local tolerance study was conducted in the rabbit using the new Pergoveris product. This study showed no evidence of an adverse local effect.

Efficacy
No new efficacy studies were provided with this application. The applicant performed however two phase II/III studies (6253 and 6905) in order to demonstrate the clinical efficacy of lutropin alfa administered in free combination with follitropin alfa in HH women. Both of them were submitted for lutropin alfa registration. The two studies had a similar prospective, randomised, dose-finding design. Both studies investigated three doses of lutropin alfa and included a placebo-control group and provided sufficient evidence to support the proposed dose of 75 IU of lutropin alfa in the combined product. CHMP was of the opinion that there were no methodological concerns regarding this application. Sufficient evidence of bioequivalence of the two active components when given in combination and when given alone, has been provided. The adequate evidence of bioequivalence with the applicant's registered single components for the same indication in the same target population in the opinion of CHMP obviates the need for new efficacy data. Further, the clinical data on lutropin alfa and follitropin alfa support the proposed posology for this Pergoveris.

Safety
No new safety studies were provided with this application. The applicant performed however two phase II/III studies (6253 and 6905) in order to demonstrate the clinical safety of lutropin alfa administered in free combination with follitropin alfa in HH women. A total of 38 patients from study GF6253 and 40 from study GF6905 were included in the main safety analysis, representing a total of 114 cycles overall. A total of 42 AEs were reported in study GF6253 and 91 AEs in study GF6590. The most frequent were headache, pelvic and abdominal pain, breast pain, nausea, somnolence and ovarian disorder. No symptoms suggesting immune reactions were reported. Two SAEs were reported in study GF6253 and none in study GF6905. The applicant has adequately addressed the potential for immunogenicity with acceptable reasoned arguments. Overall, no new safety concerns have been raised and the recommendation from a clinical point of view is favourable.

- User consultation

A user test was presented as a summary, nevertheless enough information was available to assess the test, and to be assured that the package leaflet had been tested in an appropriate way.

The package leaflet is found to be acceptable and so is the user test.

Risk-benefit assessment

HH is a rare disorder of reproductive function and describes absent or decreased function of the gonads in both men and women and is characterized by the absence of effective hypothalamic occurring -pituitary secretory activity resulting in arrested or attenuated gonadal function. In women, the disorder may therefore present as failure to undergo the usual physical and reproductive changes of puberty or, if occurring after puberty, may present as secondary amenorrhea. Amenorrhea is a manifestation of low oestrogen production and is associated with similar adverse health conditions as the ones seen in postmenopausal women: bone mineral abnormalities, altered lipid profiles and accelerated cardiovascular disease. The additional consequence of arrested ovarian function is anovulation and infertility. From the clinical perspective, the diagnosis of HH is confirmed by endocrine testing that demonstrates low gonadotropin serum levels and low oestrogen levels. Anovulation is estimated to account for up to 24 % of human infertility problems. There are no major quality or pre-clinical issues. The data from the clinical studies are supportive of the proposed dose of 75 IU of lutropin alfa in the combined product. The registered starting dose of follitropin alfa is between 75-150 IU. This provides sufficient justification for the starting daily dose of 150 IU FSH. No methodological concerns were raised and sufficient evidence of bioequivalence of the two active components of Pergoveris, when given in combination, to the individual components, when given alone, has been provided. Clinical data on lutropin alfa and follitropin alfa support the proposed posology for Pergoveris. Although adverse events were fairly common, serious adverse events were not and the safety profile did not raise any new safety concerns. Immunologically, there were also no concerns. All the data provided support a positive risk/benefit.

A Risk Management Plan was provided as per the CHMP Guideline on Risk Management Systems for medicinal products for human use.
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.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Pergoveris in the stimulation of follicular development in women with severe LH and FSH deficiency was favourable and therefore recommended the granting of the marketing authorisation.