EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2014
EMA/65507/2013 rev.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bemfola

International non-proprietary name: Follitropin alfa

Procedure No. EMEA/H/C/002615

Note

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

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Product information

Name of the medicinal product:	Bemfola
Applicant:	Finox Biotech AG Gärten 71 FL-9496 Balzers Liechtenstein
Active substance:	rhfsh, follitropin alfa
International Non-proprietary Name:	rhfsh, follitropin alfa
Pharmaco-therapeutic group (ATC Code):	Follitropin alfa (G03GA05)
Therapeutic indications:	<u>In adult women</u> • Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate. • Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT). • Bemfola in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level <1.2 IU/l. <u>In adult men</u> • Bemfola is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic

	Gonadotrophin (hCG) therapy.
Pharmaceutical form:	Solution for injection
Strengths:	75 IU/0.125 ml, 150 IU/0.25 ml, 225 IU/0.375 ml, 300 IU/0.50 ml and 450 IU/0.75 ml
Route of administration:	Subcutaneous use
Packaging:	cartridge (glass) in pre-filled pen
Package size:	1 pre-filled pen and 1 injection needle

Table of contents

List of abbreviations

AE	Adverse Event
AEX	anion exchange chromatography
AFC	Antral Follicle Count
APP	All Patient Population
ART	Assisted Reproductive Technology
ASRM	American Society for Reproductive Medicine
AUC	Area Under the Curve
BVDV	bovine viral diarrhea viruses
BMI	Body Mass Index
CD	Circular Dichroism
CFU	Colony Forming Units
CI	Confidence interval
CHO	Chinese Hamster Ovary
Cmax	Maximal Concentration
CPP	Critical Process Parameter
CRS	Chemical Reference Standard
CRF	Case Report Form
DIGE	Difference gel electrophoresis
E2	Estradiol
EC	Ethics Committee
EOPC	End of Production Cell
EOPCB	End of Production Cell Bank
ELISA	Enzyme Linked Immunosorbent Assay
ESI-MS	Electrospray Ionization Mass Spectrometry
ESI-TOF-MS	Electrospray Ionization Time-of-flight Mass Spectrometry
EU	Endotoxin Units
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GlcN	N-Acetylglucosamine
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-Releasing Hormone
HAC	Ceramic Hydroxyapatite Chromatography
Hcg	Human Chorionic Gonadotropin
HEENT	Physical Examination of Head, Ears, Eyes, Nose and Throat
HIC	Hydrophobic interaction chromatography
HCP	Host Cell protein
HDPE	High Density Polyethylene
^{1}H NMR	Proton nuclear magnetic resonance
HPAEC-PAD	High-Performance Anion-Exchange Chromatography with Pulsed Amperometric Detection
HPLC	High-Performance Liquid Chromatography
HMW	High molecular weight

ICH	International Conference on Harmonization
ICSI	Intracytoplasmic Sperm Injection
IEF	Isoelectric Focusing
IPC	In process control
IRB	Institutional Review Board
IU	International Unit
IVF	In Vitro Fertilization
kD	Kilo Dalton
KNB	Klosterneuburg
KPP	Key Process Parameter
LAL	Limulus Amebocyte Lysate
LC-ESI-MS	Liquid Chromatography Electrospray Ionisation Mass Spectrometry
LH	Luteinizing Hormone
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MESA	Micro-epididymal sperm aspiration
MS	Mass Spectrometry
MS/MS	Tandem Mass Spectrometry
MMV	Murine Minute Virus
MuLV	Murine leukemia virus
NeuAc	N-Acetylneuraminic acid
NeuGc	N-Glycolylneuraminic acid
NF	Nanofiltration
NGNA	N-Glycolylneuraminic acid
NKPP	Non-Key process parameters
NMT	Not More Than
NOR	Normal Operating Ranges
OR	Operating ranges
OHSS	Ovarian Hyperstimulation Syndrome
P	Probability
PAR	Proven Acceptable Range
Ph. Eur.	European Pharmacopoeia
pmol	Pico mol
PP	Per-Protocol
PBB	Polar Body Biopsy
PGS	Preimplantation Genetic Screening
PGD	Preimplantation Genetic Diagnosis
PMT	Premature Termination
QC	Quality Control
rhFSH	Recombinant Human Follicle Stimulating Hormone
RP-HPL	Creversed phase High-Performance Liquid Chromatography
RS	Reference Standard
RP-HPLC	Reversed Phase High-Performance Liquid Chromatography
SAE	Serious Adverse Event
SAS	Safety Analysis Set

SD	Standard Deviation
SDS-PAGE	Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis
SEC	Size-exclusion chromatography
SUSAR	Suspected Unexpected Serious Drug Reaction
TESA	Testicular sperm aspiration
TESE	Testicular sperm extraction
TSE	Transmissible Spongiform Encephalopathy
TSH	Thyroid-Stimulating Hormone
U	Unit
UV	Ultraviolet
V	Visit
VIE	Vienna
WCB	Working Cell Bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant, Finox Biotech AG submitted on 30 October 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Bemfola, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the CHMP on 21 July 2011.

The applicant applied for the following indication:

In adult women

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

In adult men

- *Bemfola is indicated in the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotrophin (hCG) therapy.*

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice in November 2008 (EMEA/CHMP/SAWP/593346/2008). The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

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

1.2. Manufacturers

Manufacturer of the active substance

Polymun Scientific Immunbiologische Forschung GmbH
Donaustraße 99,
Klosterneuburg, 3400,
Austria

The GMP certificate issued by AGES indicates that the facility was inspected on 4 October 2011.

Manufacturer responsible for batch release

Finox Biotech AG
Gärten 71
FL-9496 Balzers
Liechtenstein

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Bart van der Schueren

- The application was received by the EMA on 30 October 2012.
- The procedure started on 21 November 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 February 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2013.
- During the meeting on 21 March 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 March 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 September 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 October 2013.

- During the CHMP meeting on 21 November 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 13 December 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 3 January 2014.
- On 31 January 2014, the CHMP, in the light of the overall data submitted issued a positive opinion for granting a Marketing Authorisation to Bemfola.

2. Scientific discussion

2.1. Introduction

Follicle stimulating hormone (FSH) is a gonadotropic hormone produced by the anterior lobe of the mammalian pituitary gland. It is indispensable for normal female and male gamete growth and maturation, and normal gonadal steroid production. Deficient endogenous production of FSH is a known cause of infertility and administration of exogenous gonadotropins is used to treat this condition.

About the product

Bemfola is presented as an aqueous solution intended for subcutaneous administration. The product is available in a pre-filled pen. There are 5 different pre-filled pens available (75 IU/0.125 ml (5.5 micrograms/ 0.125 ml) solution for injection, 150 IU/0.25 ml (11 micrograms/ 0.25 ml) solution for injection, 225 IU/0.375 ml (16.5 micrograms/ 0.375 ml) solution for injection, 300 IU/0.50 ml (22 micrograms/ 0.5 ml) solution for injection and 450 IU/0.75 ml (33 micrograms/ 0.75 ml) solution for injection).

The concentration of follitropin alfa is identical for all pre-filled pens, i.e. 600 IU follitropin alfa/1 ml solution for injection. The cartridges have the same concentration as the solution for injection in the pre-filled pens of Gonal-f, i.e. 600 IU/1 ml. The Bemfola pen is for single-use application only. Therefore, there are no preservatives present in Bemfola. In contrast, the reference product Gonal-f is multi-use and includes the preservative m-cresol in the formulation.

The Bemfola pen offers fine-tuning of dosing of 12.5 IU increments. This is similar to the new Gonal-f pen that was approved in 2011 with type II variation EMEA/H/C/000071/II/0109/G. The Applicant states that benefits of the single use pen are volume and injection control mechanisms and visual aids that enhance therapy compliance. Additionally, an inbuilt lock prevents re-use of the pen device, which enhances patient safety.

The dossier is submitted to support the approval of Bemfola with the same indications as Gonal-f. The indications requested are as follows:

In adult women

— *Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate.*

— *Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).*

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

In adult men

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

The clinical development program was based on relevant guidelines particularly EMEA/CHMP/BMWP/42832/2005 (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues).

The clinical program consists of a Phase I study in healthy subjects and a Phase III study in infertile ovulatory women undergoing ART.

Currently approved recFSH

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

- Gonal-f (EU/1/95/001/001-035, MAH: Serono Europe Ltd.), the reference product in this biosimilar application.
- Puregon (EU/1/96/008/001-041, MAH: N.V. Organon). Puregon has the same indications as Gonal-f, except for the indication concerning the *"stimulation of follicular development in women with severe LH and FSH deficiency in association with a luteinising hormone (LH) preparation"*, which is only approved for Gonal-f. In section 4.2 the starting dose for the Assisted Reproduction Techniques (ART) indication is 100-225 IU.

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

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

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

FSH is essential for normal female gamete growth and maturation, and induction of normal gonadal steroid production. In the first protocols used in ART (standard "long" protocol), a GnRH agonist was used to suppress the hypothalamic-pituitary ovarian axis (pituitary down-regulation) for controlled ovarian stimulation and additionally to prevent a premature LH surge. When desensitization has been achieved, controlled (= exogenous) ovarian stimulation with gonadotropins (FSH alone or FSH

+ LH) is started, while the use of the GnRH agonist is continued until the time when hCG will be administered. HCG is administered for final follicular maturation and triggering of ovulation after confirmation of adequate follicular development.

Another option to achieve desensitization is the use of a GnRH antagonist. In contrast to the long-acting GnRH-agonists that after an initial stimulation (flare-up effect) inhibit pituitary gonadotropin secretion by desensitizing gonadotropins to GnRH via receptor down-regulation, the antagonists block the GnRH receptor in a dose-dependent competitive fashion and have no flare effect[1]; gonadotropin suppression is almost immediate.

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

2.2. Quality aspects

2.2.1. Introduction

Bemfola contains recombinant human follicle-stimulating hormone (rhFSH; follitropin alfa) and was developed as a "similar biological medicinal product" using Gonal-f as a reference product, authorised in the EU (EMEA/H/C/71).

The finished product is a solution for subcutaneous injection and is supplied in five different volume presentations in 1.5 ml glass cartridges, i.e. between 75 IU (0.125 ml) and 450 IU (0.75 ml) of a solution of 600 IU FSH/ml. The glass cartridge is assembled into a disposable pen-injector device.

FSH is a glycoprotein hormone that is produced in the anterior lobe of the pituitary gland. FSH is indispensable for normal female and male gamete growth and maturation, and normal gonadal steroid production. Exogenous FSH is administered to stimulate multifollicular development in women undergoing assisted reproductive treatment (ART) or to induce ovulation in women with anovulatory infertility.

The mechanism of action involves binding of the hormone with a specific cell surface receptor present only in reproductive organs. In females, FSH initiates follicular growth, specifically affecting granulosa cells. FSH levels vary with the follicular phase, thus determining the maturation of follicles to ovulation, FSH stimulates follicular development via binding to a specific FSH receptor.

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

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

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

2.2.2. Active Substance

The active substance of Bemfola is follitropin alfa.

Follitropin alfa consists of two non-covalently linked, non-identical glycoproteins designated as the alfa- and beta-subunits. The alfa- and beta-subunits have 92 and 111 amino acids, respectively. The alfa-subunit is identical to that of human chorionic gonadotropin (hCG), luteinizing hormone (LH) and thyroid-stimulating hormone (TSH). The beta-subunit is specific, and confers its specific biologic action and is responsible for interaction with the FSH receptor. The molecular weight of the heterodimeric and glycosylated molecule is in the range of 30-34 KDalton, with the carbohydrate content being approximately 25-30%.

The alfa chain has two N-glycosylation sites (Asn 52 and Asn 78) and the beta chain has two N-glycosylation sites (Asn 7 and Asn 24).

Manufacture

The active substance is produced by Polymun Scientific Immunbiologische Forschung GmbH, Klosterneuburg (KNB), Austria.

Development genetics

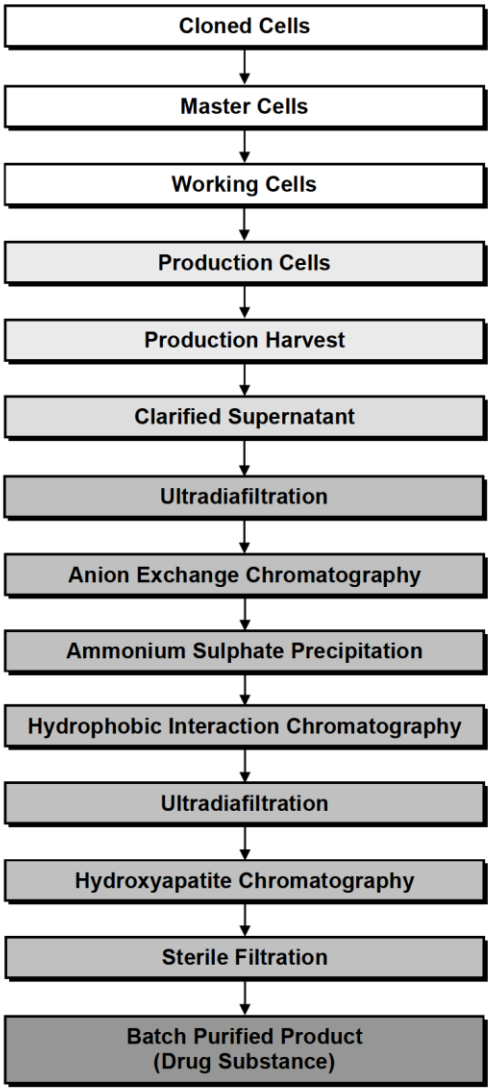
The transfection of the pre-adapted host cell line dihydrofolate reductase deficient Chinese Hamster Ovary cells (CHO DHFR-) with the plasmids coding for the alfa and beta-chain was performed under serum-free culture conditions, and was therefore free from materials of animal origin.

The manufacturing process from an ampoule of the working cell bank does not contain any starting materials of biological origin.

Cell banking system

A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed and maintained in accordance with current Good Manufacturing Practices (cGMP) and ICH guidelines. The preparation of the MCB and the current WCB is sufficiently described. A range of tests was performed for their characterisation, in accordance with ICH guidelines, including tests for identity, viability, stability, and adventitious agents.

Figure 1 General Overview of the active substance manufacturing process



Fermentation process

Each production run is carried out with production cells generated from one vial of the WCB. The cultivation system for cell propagation and production consists of two bioreactors, a first stirred tank bioreactor (up to 15 L) and a second perfusion bioreactor (up to 90 L) with an ultrasonic cell retention system.

The fermentation process is sufficiently described and consists of a two-step batch process followed by a continuous harvesting from the second bioreactor operated in cell retention mode. Collection of supernatant is initiated after a cell density of at least 2 x 10^6 cells/ml is reached. Harvesting is performed in three-day intervals. Clarification is performed with a depth filter followed by 0.2 µm filtration.

A sample of cell suspension, the end of production cells (EOPCs), is taken from the second bioreactor at the day of the last production harvest to generate the end of production cell bank (EOPCB). Genetic stability of the production cell line/ EOPCs is sufficiently addressed.

Purification process

The downstream process is sufficiently described and consists of ultradiafiltration, anion exchange chromatography, ammonium sulphate precipitation and filtration, hydrophobic interaction chromatography followed by a second ultradiafiltration, hydroxyapatite chromatography and a terminal nanofiltration and sterile filtration.

The purified active substance in 20mM sodium phosphate buffer pH 7.0 is stored under appropriate conditions until formulation into the finished product.

Critical steps and intermediates

The control strategy is based on parameters identified in a process parameter identification report, describing one (full-scale) pilot batch and three clinical batches, and a risk assessment report.

The control strategy has been brought in line with principles and definitions described in ICH Q8(R2). Process parameters have been adequately identified and appropriate ranges for Critical Process Parameters (CPPs) have been laid down in the dossier. These ranges are linked to the virus validation studies. The control strategy is acceptable.

The CHMP recommends conducting a full review of the CPPs and associated Normal Operating Ranges (NORs)/Proven Acceptable Ranges (PARs) when 30 batches have been manufactured, and to submit these updated data.

Process validation

Process validation is based on a traditional approach, comprising the successful manufacture of three validation batches. This validation is extensively described and actual numerical data are given for all CPPs, Key Process Parameter (KPPs), and Non-Key Process Parameters (NKPPs). All parameters are within the predefined (set) limits. The validation is acceptable.

Manufacturing process development

It is noted that this dossier is a 'traditional development' according to ICH Q8 terminology. No Design Space or other Quality-by-Design elements are claimed. One version of the process has been presented in the dossier. This process was transferred from one site (Vienna) to the other (Klosterneuburg) with technical adaptations only.

There were two production campaigns, where the first three consecutive batches were produced in the former facility located in Vienna and the second three consecutive batches were produced in the new facility located in Klosterneuburg, Austria. No significant changes were made to the production process other than the re-location to the new production site. An extensive comparability exercise was performed between active substance batches from both production sites and finished products thereof, including also new batches of reference medicinal finished product Gonal-f. No significant alterations to the product quality parameters were observed.

Characterisation and Impurities

The elucidation of structure of Bemfola rhFSH, both in absolute terms and in comparison with Gonal-f, has been extensively investigated in the context of a series of three independent comparability studies (see also section on comparability) using orthogonal state-of-the-art methods which demonstrate that the active substance is well characterised.

The following analytical methods were employed during characterisation:

- Identity: polypeptide structure analysis and sequence verification by proteolytic cleavage and MS analysis, polypeptide mass determination of both subunits prior to and after deglycosylation, C-terminus and N-terminus integrity by proteolytic cleavage and MS analysis, peptide mapping, Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (SDS-PAGE), Western Blotting, higher order protein structure by Circular Dichroism (CD) and Proton Nuclear Magnetic Resonance (^{1}H NMR).
- Glycans: isoform distribution profile by Isoelectric Focusing (IEF)-Western Blot, relative quantification of isoforms of the intact protein by IEF, comparison of isoforms for each subunit by 2-dimensional difference in gel electrophoresis (2D-DIGE), carbohydrate structures of individual subunits by mass spectrometry (MS), monosaccharide composition including sialic acid, sialic acid analysis (N-Acetylneuraminic acid (NeuGc), O-acetylated sialic acids), oligosaccharide composition by mass spectrometry, mapping of native oligosaccharide structures by High-Performance Anion-Exchange Chromatography with Pulsed Amperometric Detection (HPAEC-PAD), including calculation of z-number, mapping of neutral oligosaccharide structures by HPAEC-PAD, site-specific glycans by mass spectrometry.
- Content per container: quantitative Size-exclusion chromatography High-Performance Liquid Chromatography (SEC-HPLC), *in vivo* biological activity.
- Purity: aggregates and fragments by SEC-HPLC, oxidized species by Reversed Phase High-Performance Liquid Chromatography (RP-HPLC), deamidated forms by RP-HPLC/MS.
- Other physicochemical tests: pH, osmolality, endotoxins.
- Pharmacodynamics: (*in vivo*) dose-response curves in immature rats, specific biological activity (IU/mg), (*in-vitro*) cAMP response in CHO cell line transfected with human FSH receptor.

The process-related impurities include residual chemicals and buffer components present in the upstream and downstream operations, the contact surfaces in their respective unit operations and contaminants like Host Cell Protein (HCP), residual DNA, endotoxins and microbial contamination.

The product-related impurities range from modifications of the protein backbone (truncations, deamidation, oxidation), tri- and quaternary structures (aggregates and fragments) to modifications of the glycan structures (N-glycolylneuraminic acid (NGNA)).

Specification

The rhFSH active substance release specification include FSH content biological activity, purity, HCP, residual DNA, bacterial endotoxin, bioburden, identification, N-glycans, NGNA, oxidized forms, pH, osmolarity, and visual appearance.

Table 1 Bemfola rhFSH Active Substance Specification

Test	Method	Reference to Standard Method[1]	Acceptance Criterion
FSH Content	SEC-HPLC	FSH/SOP/004	2.50 ± 1.00 mg/ml
Biological Activity	*In-vivo* bioassay in rats	SOP: external (Ph. Eur. Monograph Urofollitropin)	10,000-17,000 IU/mg rhFSH
Purity	SEC-HPLC	FSH/SOP/008	Higher molecular weight substances ≤ 0.5%
Purity	Non-reducing SDS-PAGE	FSH/SOP/007	Free subunits ≤ 3%
Host Cell Protein	ELISA	221/SOP/009	≤ 0.05%
Residual DNA	Threshold System™	221/SOP/014	≤ 100.0 pg/mg rhFSH
Bacterial Endotoxin	Chromogenic endpoint method	221/SOP/001	< 0.1 EU/IU rhFSH
Bioburden	Viable Count	225/SOP/001 Ph. Eur. 2.6.12	< 10 CFU/10 ml
Identification	SDS-PAGE	223/SOP/002, 223/SOP/004	Protein band between 37 kD and 50 kD in concordance with reference standard
Identification	Western Blot	223/SOP/002 223/SOP/006	Positive reaction of protein band with specific antibody between 37 kD and 50 kD in concordance with reference standard
Identification	Isoelectric Focusing Pattern	FSH/SOP/002, 223/SOP/006	Isoform distribution profile between pI 3.5–6.0 in concordance with reference standard No relative shift of overall band pattern in comparison to reference standard
Identification	Peptide Map	FSH/SOP/005	Chromatogram in concordance with the chromatogram obtained with the reference standard
N-Glycans	HPAEC-PAD	SOP-AA-173-01	Z = 178-274
N-Glycolylneuraminic	HPAEC-PAD	SOP-AA-064-01	≤ 2.0%

acid (NGNA)			
Oxidized forms	RP-HPLC	SOP-AA-169-01	≤ 6.0%
pH value	Potentiometric Determination	224/SOP/016 Ph. Eur. 2.2.3	7.0 ± 0.5
Osmolality	Freezing Point Depression	224/SOP/009 Ph. Eur. 2.2.35	50 ± 20 mOsmol/kg
Visual Appearance	Visual Inspection	224/SOP/011 Ph. Eur. 2.2.1 Ph. Eur. 2.2.2	Clear and colourless

Upon request by the CHMP, the applicant has introduced active substance specifications for the N-glycolylneuraminic acid (NGNA) content with a limit of ≤ 2.0%, for oxidized follitropin with a limit of ≤ 6.0%, for distribution of sialylated species (Z-number) by HPAEC-PAD with a limit of 178-274, and for free subunits by non-reducing SDS-PAGE with a limit of≤ 3%.

Additional justification for the specifications was provided, and the limits for purity by SEC-HPLC, and for endotoxins were amended in line with the new Ph. Eur. monograph Follitropin concentrated solution (01/2014:2286).

Finally, the applicant has introduced Isoelectric Focus (IEF) as a routine test method for both identification and to control product-related impurities as already employed in the course of stability testing.

Analytical methods are deemed sufficiently described and validated.

Batch analysis data are limited to six batches, from two different facilities. At each facility, three batches were manufactured in one campaign. In addition, data from one full-scale pilot batch is available. This number does not constitute a firm basis for a statistical analysis. Therefore, it is recommended that the applicant submits updated batch analysis data and performs a full review of the active substance specifications when 30 batches have been manufactured.

Several issues were identified in relation to the establishment of the Reference Standards (RS), which were sufficiently addressed. It is recommended that the applicant performs a comparison of the reference preparation to the follitropin Chemical Reference Standard (CRS) and inform the EMA of the outcome.

Container closure system

The active substance container closure system, i.e. sterile High Density Polyethylene (HDPE) narrow mouth bottles with polypropylene closures, is sufficiently described.

Stability

Stability data are available for 60 months from three batches manufactured in Vienna stored at 2-8°C and ≤–20°C and 12 month data from three batches manufactured in Klosterneuburg stored

at 2-8°C. An accelerated stability study at 25 ± 2°C for 12 months was completed for the aforementioned six GMP-batches of active substance. Additionally, stress testing at 37 ± 2°C for 3 months was also completed for one GMP-batch of active substance from the first campaign and for one GMP-batch of active substance from the second campaign, where 6 months data are available.

The stability data provided were within the specifications and support a shelf-life for Bemfola rhFSH active substance of 48 months, when stored at 2-8°C.

Since stability studies are still on-going the applicant is obliged to finalise the stability studies and in accordance with EU GMP guidelines[4], any confirmed out-of-specification result, or significant negative trends, should be reported to EMA.

2.2.3. Finished Medicinal Product

Bemfola is presented as a solution for injection in cartridge available in five different volume presentations of an identical concentration of 600 IU (44 mcg)/ml, i.e. 75 IU/0.125 ml, 150 IU/0.25 ml, 225 IU/0.375 ml, 300 IU/ 0.5 ml and 450 IU/0.75 ml for subcutaneous administration (see Table below. The container closure system consist of a 1.5 ml Type I glass cartridges, sealed with a rubber disc with an aluminium over-seal (combi-seal) and containing a bromobutyl rubber plunger.

The cartridges are assembled into disposable pen-injector devices as the delivery system.

Pharmaceutical Development

The active substance is formulated with disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate (buffer components), phosphoric acid (pH adjustment), sucrose (stabiliser), L-methionine (antioxidant), poloxamer 188 (stabiliser), and water for injections. Bemfola finished product has a nearly identical composition to the reference product Gonal-f. The only formulation difference to Gonal-f is that Bemfola does not contain the preservative m-cresol as Bemfola is a single-dose liquid preparation and inclusion of a preservative for a single dose preparation is unnecessary. The choice and function of the excipients are clearly described and justified. The cartridges, combination seals and plungers are standard components that were already in use at the manufacturer.

Table 2 Composition the finished product

Ingredient	Quantity per ml	Function	Reference to standards
rhFSH	600 IU 44 µg	Active ingredient	In-house
Sucrose	60 mg	Protein stabiliser	Ph. Eur., NF
Disodium hydrogen phosphate dihydrate	1.1 mg	pH buffering agent	Ph. Eur., USP
Sodium dihydrogen phosphate dihydrate	0.52 mg	pH buffering agent	Ph. Eur., USP

[4] 6.32 of Vol.4 Part I of the Rules Governing Medicinal Products in the European Union

Ingredient	Quantity per ml	Function	Reference to standards
L-methionine	0.1 mg	Antioxidant	Ph. Eur., USP
Lutrol F-68*	0.1 mg	Solubiliser	Ph. Eur.
Phosphoric acid (1M)	0.05 µl	For pH adjustment	Ph. Eur., NF
Water for injections	q.s. to 1 ml**	Vehicle	Ph. Eur., USP

* *recently rebranded by the manufacturer (BASF) as 'Kolliphor P 188'*

** *weight/ml = 1.021 g/ml*

Adventitious Agents Safety Evaluation

Control of materials of biological origin

The manufacturing process starting from the WCB does not contain any starting materials of biological origin. The transfection of the CHO host cell line was performed under serum-free culture conditions. Only in the development of the cell line itself, thymidine purified from salmon sperm and porcine trypsin to disaggregate cells were used. The Transmissible Spongiform Encephalopathy (TSE) Risk Assessment Report summarizes all materials that are used in the production process. Most of the materials are from synthetic origin, from defined animal-free origin or from plant or microbial origin. No materials were derived from TSE-relevant animal species. The only materials derived from non TSE-relevant animal species are thymidine purified from salmon sperm and porcine trypsin.

Testing of cell banks for adventitious agents

The safety testing for adventitious agents in the MCB /WCB/ EOPCB is adequate and the results are satisfactory.

In-process testing during manufacture

In-process testing at appropriate steps in the manufacturing process for both the active substance and finished product are used to monitor for the presence of potential adventitious contamination that may be introduced from the manufacturing environment or raw materials used during manufacture. These controls are considered appropriate.

Viral clearance studies

For the viral clearance studies four model viruses according to guideline "Note for Guidance on Virus Validation Studies" (CPMP/BWP/268/95) were chosen and include: Murine Leukemia Virus (MuLV, ssRNA, enveloped), Bovine Viral Diarrhea Virus (BVDV, ssRNA, enveloped), Reovirus Type 3 (REO, dsRNA, non-enveloped) and Murine Minute Virus (MMV, ssDNA, non-enveloped).

For the evaluation of the capacity of the production process to remove or inactivate viruses, the following three production steps were validated:

- Virus removal by anion exchange chromatography (AEX) (DEAE Sepharose FF);
- Virus removal by combination of ammonium sulphate precipitation and hydrophobic interaction chromatography (HIC) (Phenyl-Sepharose 6FF);
- Virus removal by duplicate nanofiltration using a 20 nm virus filter.

The double nanofiltration step is deemed sufficiently validated using a downscaled process and is the main process step to assure viral safety of the product. Together with the anion exchange two orthogonal effective steps are present. Virus removal by ammonium sulphate precipitation and HIC relies both on partition and the effect of high pH. Cumulative reduction factors are presented and sufficiently assure viral safety. Additional information is still sought on the role of high pH in the inactivation of MuLV and BVDV, therefore it is recommended that the applicant conducts a well-designed study (post-approval) that demonstrates that high pH robustly inactivates MuLV and BVDV. If necessary, a validated hold time will be introduced in the manufacturing process to ensure that demonstrated viral clearance is achieved in the routine manufacturing process.

In conclusion, the safety of Bemfola in respect to viral contamination is adequately assured by the control materials, the chosen virus testing program and assessment of virus removal and inactivation by the manufacturing process.

Control testing for release of active substance and finished product

Following purification, the active substance is tested for bioburden and endotoxin and the finished product is tested for endotoxin and sterility.

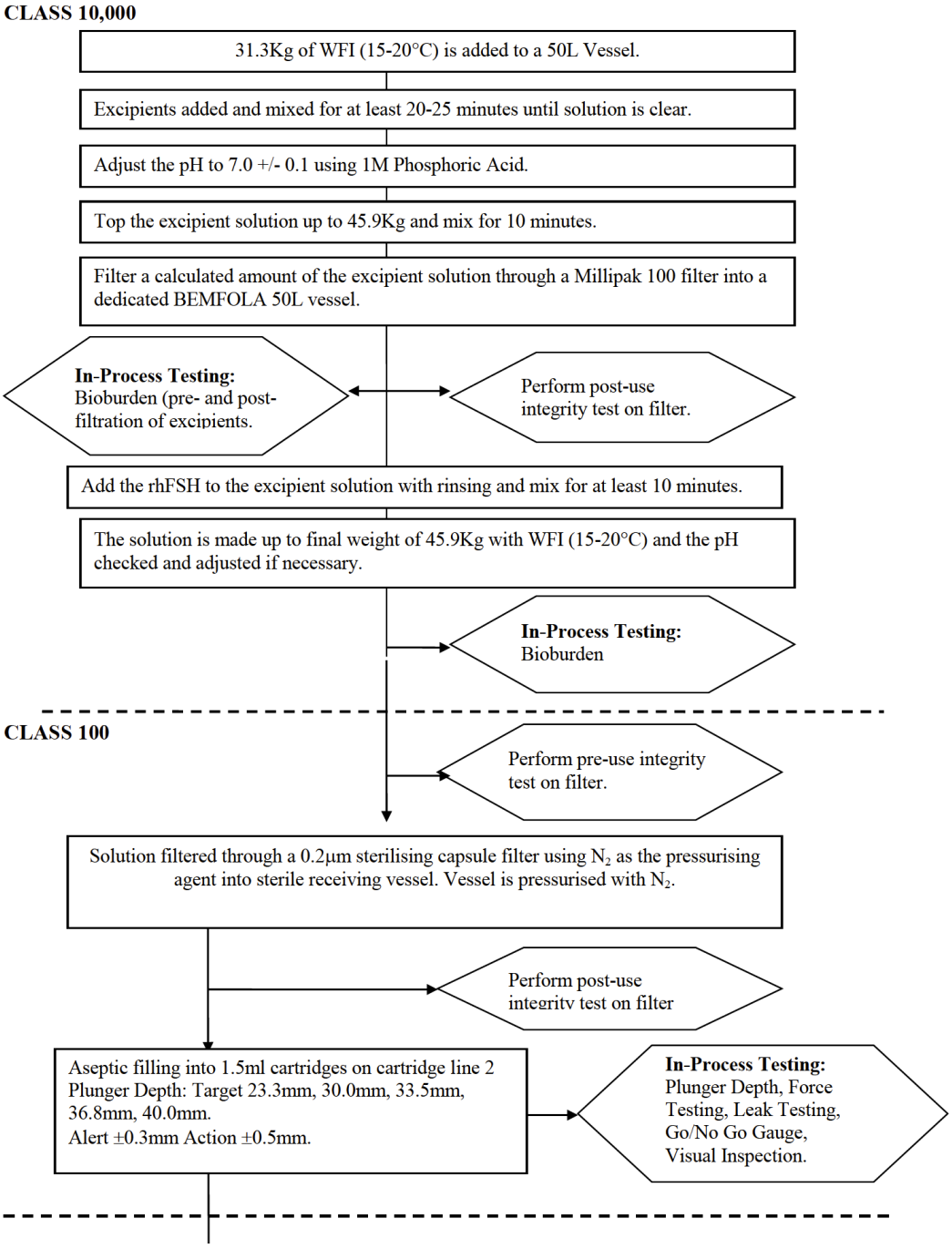
Overall, these controls assure that Bemfola finished product is free from adventitious agents and safe in its intended clinical use.

Manufacture of the Product

Finished product in cartridges is manufactured by CP Pharmaceuticals, Wrexham, UK. Assembly, labelling, packaging, testing and dispatching of pens is performed by AllPack AG, Reinach, Switzerland. The batch release for EU will be performed by Finox Biotech AG in Liechtenstein.

The finished product manufacturing process is typical for filling of a biological product and is done by adding the active substance to the formulation buffer, sterilization of the formulated final bulk by filtration and filling into cartridges. A risk assessment study of relevant parts of the aseptic manufacturing processes was performed in order to justify that the final sterilising filter is not placed directly before the filling point. Appropriate in-process controls are in place. The manufacturing process was satisfactorily validated using three batches manufactured at 40, 58 and 100% of the commercial batch size of 45 litres.

Figure 2 Process Flow Diagram for the Manufacture of BEMFOLA Solution for Injection in 1.5 ml Cartridges (45 Litre Scale)



Control of excipients

Excipients are well-known and of compendial (Ph. Eur.) grade. The control of excipients is sufficiently described and justified.

Product Specifications

The finished product release and shelf-life specification include FSH content, biological activity, purity, oxidized forms, bacterial endotoxin, sterility, identification, N-glycans, pH, osmolarity, identification of sucrose, identification and L-methionine content, visual appearance, visible and sub-visible particles, dose accuracy.

Table 3 Release and shelf-life specification for BEMFOLA rhFSH solution for injection in 1.5 ml Cartridges (75, 150, 225, 300, 450IU)

Test	Method	Reference to Standard Method[1]	Acceptance Criterion
FSH Content	SEC-HPLC	FSH/SOP/004 UFAG VM1443-3	39.6-48.4 μg/ml
Biological Activity	*In-vivo* bioassay in rats[1]	SOP: external (Ph. Eur. Monograph Urofollitropin)	480-750 IU/ml with fiducial limits of 384-936 IU/ml
Purity	SEC-HPLC	PY FSH/SOP/008 UFAG VM1443-3	Higher molecular weight substances ≤ 2.00%
Purity	Non-reducing SDS-PAGE	PY FSH/SOP/007 UFAG VM1451-4	Free subunits ≤ 5%
Oxidized forms	RP-HPLC	Glycothera SOP-AA-169-01	≤ 10%
Bacterial Endotoxin	Kinetic turbidimetric method	SOP: GTM/078 Ph. Eur. 2.6.14	< 12.0 EU/ml
Sterility	Membrane filtration method	SOP: GTM/090 Ph. Eur. 2.6.1	Sterile
Identification	SDS-PAGE	PY223/SOP/002, 223/SOP/004 UFAG VM1451-5	Protein band between 37 kD and 50 kD in concordance with reference standard
Identification	Western Blot	Western Blot PY 223/SOP/002, 223/SOP/006 UFAG VM1451-4	Positive reaction of protein band with specific antibody between 37 kD and 50 kD in concordance with reference standard

Identification	Isoelectric Focusing Pattern	PY 223/SOP/002, 223/SOP/006 UFAG VM1451-4	Isoform distribution profile between pI 3.5–6.0 in concordance with reference standard
N-Glycans	HPAEC-PAD	Glycothera SOP-AA-173-01	Z = 178-274
pH value	Potentiometric Determination	224/SOP/016 Ph. Eur. 2.2.3	7.0 ± 0.3
Osmolality	Freezing Point Depression	SOP: 224/SOP/009 Ph. Eur. 2.2.35	220 ± 20 mOsmol/kg
Identification of Sucrose	Ion Exchange Chromatography	SOP: UFAG VM1441-1	Retention time corresponds to reference
Identification of L-methionine	RP-HPLC	SOP: UFAG VM1440-1	Retention time corresponds to reference
L-methionine content	RP-HPLC	SOP: UFAG VM1440-1	0.09–0.11 mg/ml (90–110% of label claim)
Visual Appearance	Visual Inspection	SOP: GTM/115 Ph. Eur. 2.2.1 Ph. Eur. 2.2.2	Clear and colourless solution
Visible Particles	Visual Inspection	SOP: GTM/115 Ph. Eur. 2.9.20	Essentially free of particles
Sub-visible Particles I	Light obscuration particle count test	SOP: GTM/153 Ph. Eur. 2.9.19	≤6000 particles of ≥10 µm per container
Sub-visible Particles II	Light obscuration particle count test	SOP: GTM/153 Ph. Eur. 2.9.19	≤600 particles of ≥25 µm per container
Dose Accuracy	Ejection Volume	ISO11608-1 (TP30000-30004)	75 IU = <0.2 ml ± 0.01 ml (cf. ISO) ≥150 IU = >0.2 ml ± 5% (cf. ISO)

[1] The *in-vivo* bioassay is only performed on the first filling lot of a new final formulated bulk.

In general, the proposed specifications are sufficient to verify the quality of the finished product.

Tests for free-subunits, glycan mapping and dose accuracy after assembly of cartridge and pen have been added to the finished product specifications. The applicant has properly justified that the establishment of a release specification for deamidation is not needed for this product. As recommended by the CHMP, the limits for protein content have been narrowed to the stated content

of ± 10% and the *in vivo* bioassay will only be performed on the first filling lot of a new final formulated bulk instead of on each filling lot. In addition, it is recommended that the applicant reviews the limits of a number of specifications (Z-number, free subunits, purity by SEC-HPLC, oxidized rhFSH) after manufacturing batch formulations of finished product from 30 different active substance batches.

The analytical methods are clearly described and sufficiently validated.

Sufficient batch analysis data have been provided in order to demonstrate the consistency of manufacture of the finished product.

The same reference standards are used for the active substance and the finished product.

Container closure system

The finished product is filled into sterile Type I clear glass cartridges, sealed with a rubber disc with an aluminium over-seal (combi-seal) and containing a bromobutyl rubber plunger. Adequate information has been provided on the identity, properties and quality of the primary container/closure system. The components are manufactured from well-known materials and meet the Ph. Eur. criteria.

The closed cartridge is irreversibly integrated in a disposable pen injector for self-administration. Once the cartridge and the pen device are assembled, the resulting pen injector is a sealed unit that cannot be disassembled without physically destroying the pen-injector. Although the pen injector is not a medical device by definition, it has been developed in accordance with the ISO standards for medical devices.

Stability of the Product

Long-term stability data at 2-8° C are available up the 36 months for three 75 IU rhFSH batches, one 150 IU rhFSH batch and three 450 IU rhFSH batches manufactured with active substance from the Vienna facility at 22% of the proposed formulated bulk full-scale. The bracketing approach for testing stability of Bemfola is considered acceptable. Recently, production of active substance was relocated to a new facility in Klosterneuburg, Austria. Twelve months stability results are available for finished product batches manufactured with active substance from this new facility. Comparability of both materials is sufficiently demonstrated to allow a shelf life of 36 months at 2-8 °C. The experiments under stress conditions (37 ± 2°C) showed that Bemfola rhFSH solution for injection and Gonal-f alike are prone to deamidation and to lesser extent oxidation, but are otherwise stable for up to six months.

The storage of the finished product at or below 25°C for 3 months within its shelf life has been properly substantiated by real-time/real-temperature data.

In accordance with EU GMP guidelines[5], any confirmed out-of-specification result, or significant negative trend, should be reported to EMA.

[5] 6.32 of Vol.4 Part I of the Rules Governing Medicinal Products in the European Union

Comparability Exercise for Finished Medicinal Product

Bemfola is a biosimilar product with Gonal-f as a reference medicinal product throughout the entire development program. Since the disposable Bemfola injector-pen is designed for administration of a single-dose of rhFSH, compared to the multiple-use injector pen presentations of Gonal-f, Bemfola finished product does not contain m-cresol.

The applicant has clearly presented their analytical comparability exercises of Bemfola with Gonal-f. Three comparability exercises were performed. The first series of analyses were conducted in 2008, prior to the phase I clinical study on finished product formulated with m-cresol. This study encompasses only a limited number of analytical techniques. The second study was performed in 2009/2010 and was more extensive. Besides comparability with Gonal-f as discussed hereinafter, the results of this study indicate comparability between the finished product formulation with and without m-cresol. The third study was performed in 2012, after the relocation of the active substance manufacturer from its Vienna-based facility to a new facility in Klosterneuburg (KNB). Extensive state-of-the-art characterisation studies using orthogonal methods were conducted on three active substance batches manufactured in the Vienna facility, three active substance batches manufactured in the Klosterneuburg facility, and three batches of Gonal-f RFF pens, 900 IU/1.5 ml (66 µg/1.5 ml) liquid formulation, European source. In addition, three batches of Bemfola finished product manufactured from Klosterneuburg active substance and one finished product batch manufactured from Vienna active substance were included in this study, albeit characterisation of these finished product batches is less extensive than the active substance batches. In general, the choice of the samples and design of the analytical comparability studies are considered adequate.

The primary sequence of Bemfola and Gonal-f has been verified by proteolytic cleavage and ESI-ion trap-MS/MS analysis. Additional confirmation of comparability of the primary structure of Bemfola and Gonal-f was obtained by polypeptide mass determination of both subunits after deglycosylation and by peptide mapping of Lys-C digests. The alfa- and beta-subunits are each internally cross-linked with 5 disulphide bridges in the alfa-subunit and 6 disulphide bridges in the beta-subunit. The analysis of the disulfide bridges was hampered by the complex insoluble structures that were formed during analysis. Instead, indirect methods were used to confirm the conformational similarity, including CD-spectroscopy and Proton Nuclear Magnetic Resonance (^{1}H NMR) data.

N-terminal truncation of the FSH alfa-chain, lacking the first 2 amino acids AP, and N-terminal truncation of the FSH beta chain, lacking the first 2 amino acids NS, were observed for both Gonal-f and Bemfola batches. The level of truncation of the beta chain (around 55%) was similar for Gonal-f and Bemfola batches, irrespectively of the site of Bemfola active substance manufacture. The percentage of truncated alfa chain was similar for Bemfola active substance batches manufactured in the new KNB facility (4-5%) and Gonal-f (6-8%), but was higher in active substance batches manufactured in the Vienna location (11-22%), including the batch used in clinical trials (22%). According to the applicant it is unlikely that this difference has any impact on the efficacy and/or safety. No C-terminal truncation was observed.

The level of oxidized FSH species and the level of deamidated FSH were comparable for Bemfola batches manufactured in both facilities and Gonal-f. Circular dichroism (far-UV-CD) analysis of Bemfola batches of both manufacturing sites and Gonal-f batches showed identical spectroscopic features of all batches. No aggregates and no fragments were detected in Gonal-f batches and

Bemfola batches by SEC-HPLC. Also SDS-PAGE and Western blotting revealed no differences between Bemfola batches manufactured with active substance from the Vienna and KNB facilities. However, Bemfola active substances and corresponding finished products appear at a slightly higher molecular weight than Gonal-f batches in the SDS-PAGE analysis as a result of minor differences in the micro heterogeneity of the glycan profile (see below).

Isoform distribution profiles and a relative quantification of isoforms of the entire protein following fluorescent labelling showed batch-to-batch variability for both Bemfola and Gonal-f. Both methods reveal only minor differences in the IEF pattern of Bemfola Vienna, Bemfola KNB and Gonal-f with respect to relative distribution. This was also found by comparison of isoforms for each subunit by a sensitive two-dimensional difference in gel electrophoresis method. The slightly lower molecular weight of Gonal-f compared to Bemfola active substances and finished product was also observed by this method.

Determination of monosaccharide composition and sialic acid analysis (N-acetyl- and N-glycolyl neuraminic acid) clearly demonstrate a similar composition of monosacharides, NeuAc and NeuGC in both products. Glycan structures on the alfa- or the beta-chain were studied by mass spectrometry. Similar glycan structures were found in both products for the alfa-chain. For the beta-chain the fingerprint and glycan structures were also similar to Gonal-f, but higher antennarity detected for Bemfola. Analysis of isolated oligosaccharides from the protein backbone by HPAEC-PAD indicates a slight shift from disialo to tetrasialo structures for Bemfola KNB relatively to Gonal F (see Table below). Mapping of neutral sugars also indicates that Bemfola displays slightly more of higher antennary structures than Gonal-f. However, considering the batch-to-batch variation, these differences can be regarded as small. For instance, the differences in Z numbers (a measure of the relative amounts of asialo, mono- di-, tri, and tetrasialylated N-glycans) in the two comparability studies (study V02: Bemfola: Z = 229–233; Gonal-f: Z = 225–227; study V3: Bemfola 227-246; Gonal-f: 221 – 233) are much smaller than the variation allowed in the Ph. Eur. monograph for follitropin (178 – 274 when using the PAD method). Differences in the antennarity between the two products could be assigned to glycosylation site 2 (N78 on the alfa-chain) and glycosylation site 3 (N7 on the beta-chain). The most complex glycosylation site N7 also revealed the highest batch-to-batch variation within both product groups.

Table 4 Mapping of native oligosaccharide structures including calculation of z-number by HPAEC-PAD of Bemfola (left panel) and Gonal-f (right panel).

	Bemfola	***Gonal-f***	
V03	Asialo: **0.7 – 2.0%** Monosialo: **13.6 – 18.6%** Disialo: **42.0 – 43.8%** Trisialo: **22.4 – 24.2%** Tetrasialo: **11.7 – 16.6%** Pentasialo/sulphated: **1.0 – 1.5%** z-number: **227 - 246**	Asialo: **0.8 – 1.2%** Monosialo: **13.4 – 18.2%** Disialo: **48.6 – 50.1%** Trisialo: **21.2 – 23.7%** Tetrasialo: **9.7 – 11.6%** Pentasialo/sulphated: **0.0 – 0.2%** z-number: **221 - 233**	Slightly differences in antennarity between the two products were detected. Batch-to-batch variability was similar for the two products, the slightly shift in antennarity form disialo- to tetrasialo-structures for AFOLIA compared to Gonal-f could be confirmed, which is reflected also in the slightly higher z-numbers. No significant differences observed between batches from VIE vs. KNB.
V02	Asialo: **1.1 – 1.3%** Monosialo: **18.1 – 19.2%** Disialo: **41.8 – 42.9%** Trisialo: **23.0 – 23.6%** Tetrasialo: **12.6 – 13.8%** Pentasialo/sulphated: **0.9%** z-number: **229 - 233**	Asialo: **0.9 – 1.1%** Monosialo: **16.5 – 17.3%** Disialo: **46.6 – 47.7%** Trisialo: **23.0 – 23.4%** Tetrasialo: **10.3 – 11.0%** Pentasialo/sulphated: **0.2%** z-number: **225 - 227**	

The applicant pointed out that 2.5% of the sialic acid residues of the alfa-subunit of Gonal-f samples contain an O-acetyl group. This was based on a low signal in the ES I-MS spectrum of the Gonal-f FSH, whereas the signal for Bemfola was below the level of detection. The applicant sufficiently justified that this difference does not have any relevance.

No differences were observed on the stated biological activity of 600 IU/ml (526 – 648 IU/ml for Bemfola finished product, 555 – 595 IU/ml for Gonal-f and the specific biological activity, indicating an identical specific biological activity.

In many studies it was necessary to concentrate the (Gonal-f) finished product samples. The suitability of these systems in preserving the structural integrity and overall quality of rhFSH (extracted from finished product versus active substance) was satisfactorily addressed.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the evaluation procedure a number of Other Concerns has been raised related to the manufacture of active substance and the associated control strategy, active substance and finished product specifications and their justification, analytical method validation of both active substance and finished product, the Duopen and to the reference standards.

The applicant has provided responses and, with regards to the biological and pharmaceutical aspects of Bemfola, the CHMP considers that all issues have been satisfactorily addressed by the applicant and a list of recommendations has been agreed as listed below.

Conclusions on comparability exercise

The applicant has clearly presented their analytical comparability exercises of Bemfola with Gonal-f. The choice of the samples and design of the analytical comparability studies are considered adequate. Powerful modern techniques were employed for elucidating and comparing the polypeptide backbone, the heterogeneity of the backbone and its degradation products. Also the

complex carbohydrate structure of FSH was extensively studied in Bemfola active substance batches manufactured in the former Vienna facility and the current KNB facility and FSH isolated from Gonal-f batches using orthogonal techniques.

No qualitative differences in rhFSH were observed between Bemfola and Gonal-f and evidence for a highly similar physicochemical quality profile was obtained. Bemfola is not claimed to be fully identical to Gonal-f and, as can be expected for complex molecules manufactured by two processes, some minor differences were observed with regard to the glycosylation profile:

- the ratio of tetra-antennary to di-antennary structures is for Bemfola slightly higher compared to Gonal-f

- for the most complex glycosylation site 3 (beta subunit), slight differences in distribution of fucosyl residues in relation to antennarity were observed between Bemfola and Gonal-f.

- a small amount of the sialic acid residues of the alfa-subunit of Gonal-f samples contain an O-acetyl group, whereas the level in Bemfola was below detection.

These minor differences are in line with the similarity principle. A major impact on the efficacy and safety profile is not expected.

In summary, it is concluded that Bemfola and Gonal-f show a highly similar physico-chemical and biological quality profile.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

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

The overall quality of Bemfola is considered acceptable.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. To conduct a full review of the CPPs and associated NORs/PARs when 30 batches have been manufactured, and to submit these updated data.

2. To perform a review of the active substance specification (individual tests and limits applied) as soon as analytical data for the release of 30 batches of Bemfola rhFSH active substance are available.

3. To perform a comparison of the reference preparation to the follitropin CRS and inform the EMA/CHMP of the outcome.

4. To conduct at a well-designed study that demonstrates that high pH robustly inactivates MuLV and BVDV. If necessary, a validated hold time will be introduced in the manufacturing process to ensure that demonstrated viral clearance is achieved in the routine manufacturing process.

5. To perform a review of the finished product acceptance criteria for purity by SEC-HPLC, oxidised rhFSH forms, N-glycans (Z-number) and free subunits after manufacturing batch formulations of finished product from 30 different active substance batches.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant claims Bemfola to be similar to Gonal-f, used as the reference product and registered via the centralised procedure on 20 October 1995 by Merck Serono Europe Ltd.

The development strategy was based on demonstrating the physicochemical and biological comparability of Bemfola with Gonal-f.

The non-clinical testing includes a demonstration of similar receptor "binding" and activation properties of Bemfola and Gonal-f and induction of a functional response in human FSH-receptor bearing cells (study FSHR/DR/001-01). *In vivo* tests of biological activity by the Steelman-Polhey assay were used to compare both compounds. Pharmacokinetic (Study 23326), single-dose toxicity (Study 23325) and repeat-dose toxicity (Study 23327) studies were conducted in order to evaluate differences in the pharmacokinetic and toxicological profile of the two FSH formulations.

Scientific advice regarding the non-clinical evaluation program was obtained from the EMA (EMEA/CHMP/SAWP/ 593346/2008; Procedure EMEA/H/SA/1147/1/2008/SME/III) and from the Austrian Health Authority, AGES (31 July 2008).

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Receptor affinity was studied using a HEK293 cell line expressing the hFSHR. In this assay three batches of Bemfola (K_D 0.808 – 0.862) showed comparable affinity as three Gonal-f batches (K_D 0.687 - 0.962 nM). The Applicant conducted an *in vitro* study to compare the pharmacological activity of Bemfola and Gonal-f (Study report FSHR/DR/001-01) in which CHO cells stably expressing rhFSH receptor were used. Formation of cAMP was measured by a commercial competitive enzyme immunoassay. Three Gonal-f and three Bemfola batches were evaluated. Each batch was assayed over a range from 0.1 to 5000 mIU/mL. Four replicates for each concentration were assayed. A mean value of maximum cAMP concentration of 1189 fmol was obtained for Bemfola and 1130 fmol for Gonal-f, respectively. The mean value of ED_{50} was 94.4 mIU/ml for Bemfola and 73.7 mIU/ml for Gonal-f, indicating a similar binding to the hFSH receptor and triggering the second messenger cascade.

In vivo

The Applicant also conducted the Steelman-Pohley assay to determine the potency of three drug substance batches and 3 drug product batches. The same was done for Gonal-f (drug product) batches. The results from the Steelman-Pohley assay indicate that the potency of Bemfola drug substance is consistent and comparable to Gonal-f before and after the production site-switch.

Secondary pharmacodynamic studies

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

Safety pharmacology programme

No safety pharmacology studies have been conducted with Bemfola. No pharmacological effects on other organ systems except the gonads would be anticipated with Bemfola.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were conducted with Bemfola. Recombinant hFSH has been available clinically for a number of years and possible interactions based on its pharmacological activity are well recognised and reflected in the Summaries of Product Characteristics (SmPC) for the existing r-hFSH products, Gonal-f and Puregon (Merck-Serono, 1995; Organon, 1996).

2.3.3. Pharmacokinetics

Methods of analysis

Determination of FSH in application solutions and rat sera

The determination of Bemfola and Gonal-f concentrations in rat serum samples was performed with an FSH-specific solid phase enzyme-linked immunosorbent assay (ELISA). The FSH ELISA is based on the sandwich principle. The validation study showed acceptable accuracy, precision, sensitivity

and stability of samples after three freeze-thaw cycles or storage for 4 weeks at -20°C. The method was considered suitable for determination of Bemfola and Gonal-f in application solutions and rat sera.

Absorption

The single dose pharmacokinetics study comprised 4 groups, each with 5 female rats. The amounts of the test item and the reference item were adjusted to each animal's current body weight on the day of administration. Intravenous and subcutaneous routes of administration were selected because the subcutaneous route is the anticipated route for human clinical use, but also to assess the bioavailability.

Absorption of Bemfola was compared to Gonal-f after single subcutaneous application to rats. Cmax was reached after 6 h for both products and was 72.29 mIU/ml and 65.81 mIU/ml for Bemfola and Gonal–f, respectively. The absolute bioavailability of Bemfola and Gonal-f were 73.2 and 61.9%, respectively. No significant differences were detected in the absorption of the two products.

Distribution

No specific distribution studies have been conducted with Bemfola. Given the absence of any indication of differences in pharmacokinetic behaviour between Bemfola and Gonal-f, it is considered acceptable not to have conducted specific distribution studies with Bemfola.

Metabolism

No specific metabolism studies have been conducted with Bemfola. Given the absence of any indication of differences in pharmacokinetic behaviour between Bemfola and Gonal-f, it is considered acceptable not to have conducted specific metabolism studies with Bemfola.

Excretion

The excretion of follitropin alfa, including the half-lives after i.v. administration and after s.c. administration have been measured as a part of single dose pharmacokinetics study. The routes of excretion are not expected to be different from Gonal-f. The main mechanisms of clearance appear to be the hepatic or the renal routes [*Rose et al 2000*]. Excretion in milk has not been described, but r-hFSH will not be used during lactation.

Pharmacokinetic drug interactions

No specific pharmacokinetic drug interaction studies have been conducted with Bemfola. Given the absence of any indication of differences in pharmacokinetic behaviour between Bemfola and Gonal-f, it is considered acceptable not to have conducted specific drug interaction studies with Bemfola.

2.3.4. Toxicology

Comparative single dose and repeated dose toxicity studies with Bemfola and Gonal-f were performed in rats. The Applicant followed guidance in accordance with the original version (released in 2005) of the guideline CHMP/42832/05 (Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues), although

single dose toxicity studies are not advised in this document. Furthermore, the recently released Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH) (EMA/CHMP/BMWP/671292/2010) states that generally, separate repeated dose toxicity studies are not required.

Single dose toxicity

A single subcutaneous administration of 600 IU Bemfola/kg or 600 IU of Gonal-f/kg to rats did not reveal any signs of toxicity. No mortality occurred during the 14 day-observation period. All animals gained the expected body weight throughout the whole study period. There were no macroscopic findings during necropsy. No local intolerance reactions were noted.

Repeat-dose toxicity

In the repeated dose toxicity study in male and female rats no local or systemic adverse effects were noted after administration of either FSH up to 300 IU/kg/day for 28 days. Only minimal effects on the ovarian were noted (increased number of follicles). Also, at the end of the study 4 out 10 animals in the high dose Bemfola group showed vaginal tissue in proestrus, whereas placebo control animals showed none.

FSH serum levels were dose-dependently increased on the first day of dosing and no differences between Bemfola and Gonal-f were observed. At the end of the study FSH levels were generally very low, which is explained by the formation of anti-hFSH antibodies. The observed antigenicity in rats is not considered predictive for humans.

Genotoxicity, Carcinogenicity and Reproductive toxicity

Genotoxicity studies are not required for a biosimilar medicinal product. Genotoxic effects of gonadotropins are not expected because of their mechanism of action. This is in accordance with both the ICH S6 guideline on the development of biotechnology-derived pharmaceuticals (Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals; CPMP/ICH/302/95) and the CHMP guideline on the development of biosimilar products (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005).

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

Toxicokinetics

Toxicokinetic evaluation was carried in satellite rats of the 4 week-repeat dose toxicity study. Serum FSH concentrations were determined after the first administration of Bemfola or Gonal-f on day 1 – 2 and after the last administration of each compound on day 28. Toxicokinetic parameters following sc administration of Bemfola or Gonal-f on day 1-2 are given in the following table as mean values. On study day 28 serum FSH levels were extremely variable between animals and ranged from below the quantification limit (<12.5 mIU/mL) to 4208 mIU/mL. These differences were demonstrated to be connected to the development of immune response. There were a higher

number of male rats having undetectable FSH levels compared to female rats. The number of animals with low or undetectable serum FSH levels was comparable for Bemfola and Gonal-f in all study groups. The available data did not allow for calculation of PK parameter.

Local tolerance

Local tolerance was investigated in the course of the repeated dose toxicity study. In the repeated dose toxicity study in male and female rats no local adverse effects were noted after administration of either FSH up to 300 IU/kg/day for 28 days.

2.3.5. Ecotoxicity/environmental risk assessment

Bemfola has the same structure and activity as endogenous FSH. FSH is a pituitary hormone that controls the reproductive system in both males and females. Given the characteristics above, the performance of specific studies for Environmental Risk Assessment was not requested as proteins are biodegradable in the environment.

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

2.3.6. Discussion on non-clinical aspects

Bemfola and Gonal-f have been shown to have similar receptor binding. Similar pharmacological effects have been verified in an *in vitro* receptor activation assay in which CHO cells stably expressing the FSH receptor were used, where both FSH formulations showed equivalent activation after binding to the FSH receptor as measured by cAMP production.

Bemfola was shown to exhibit comparable *in vivo* biological activity to Gonal-f. These data were obtained in the *in-vivo* model according to the method published by Steelman and Pohley 1953, which measures the increase in ovary weights in female rats.

In summary, the pharmacology results thus far suggest that the pharmacological effects of Bemfola and Gonal-f are similar. Although it has not been resolved why it was not possible to demonstrate the presence of the hFSHR in the CHO cell line used to compare functional activity of Bemfola and Gonal-f, the Applicant provided evidence to accept this assay for a comparability exercise. Additional data from a HEK293 cell assay are less convincing, but in view of the CHO cell assay data which are in line with the quality data showing high similarity and other non-clinical and clinical data confirming biosimilarity we conclude that the issue needs not be pursued any further.

No significant differences in exposure were noted for Bemfola and Gonal-f following single dose subcutaneous or intravenous administration.

Comparative single dose and repeated dose toxicity studies with Bemfola and Gonal-f were performed in rats. The Applicant followed guidance in accordance with CHMP/42832/05 (Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues) and CHMP's Scientific Advice, although single dose toxicity studies are not advised in these documents. Furthermore, the recently released Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human

follicle stimulating hormone (r-hFSH) (EMA/CHMP/BMWP/671292/2010) states that generally, separate repeated dose toxicity studies are not required.

Single dose subcutaneous administration of 600 IU/kg of either FSH did not cause any toxicity in rats and in the repeated dose toxicity study in male and female rats no local or systemic adverse effects were noted after administration of either FSH up to 300 IU/kg/day for 28 days. Only minimal effects on the ovaria were noted (increased number of follicles), whereas a more prominent pharmacological effect was expected. Probably this is a consequence of the young age (36-38 days) of the rats at the start of dosing. FSH serum levels were dose-dependently increased on the first day of dosing and no differences between Bemfola and Gonal-f were observed. At the end of the study FSH levels were generally very low, which is explained by the formation of anti-hFSH antibodies. The observed antigenicity in rats is not considered predictive for humans.

No studies on genotoxicity, carcinogenicity, reproductive and developmental toxicity or other toxicity were conducted, which is considered acceptable for a biosimilar FSH.

The non-clinical data support the view that the active substance of Bemfola is the same or highly similar to the active substance of Gonal-f.

Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

GCP

According to the applicant, all clinical trials were conducted in compliance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, and Hong Kong, Somerset West, Edinburgh, Washington). All studies were performed in compliance with the CHMP/ICH "Note for Guidance on Good Clinical Practice" (CPMP/ICH/135/95). Additionally, the development program was carried out considering the CHMP "Guideline on Similar Biological Medicinal Products" (CHMP/437/04) and is consistent with the draft CHMP "Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH)".

The Applicant has filed two GCP serious breach reports to the MHRA about one of the UK sites (8200) in the FIN3001 study. The MHRA was notified on 31 October 2012. Protocol violations that were identified were inclusion of non-eligible patients, and the blind of the ultrasound scans was potentially compromised. Site 8200 included 42 patients. Based on these findings, the Applicant indicated that there was a potential impact to scientific value/data credibility.

A routine GCP inspection was agreed on by the EMA, investigating three sites, including Site 8200.

Site 8200
Several findings were identified by the inspectors during this GCP inspection that have an impact on the reliability and validity of the dataset for this site (a number of the areas of non-compliance presented in the inspection report for site 8200 had already been identified by the NHS Trust in an internal audit and associated report and/or the sponsor in their serious breach report submitted to MHRA prior to the inspection). The conclusion of the GCP inspection report is that the trial cannot be considered to have been conducted in accordance with ICH GCP at this site.
The Rapporteurs agreed with the IIR conclusions and the fact that the quality and integrity of the data might have been affected at site 8200.

As a result of the GCP inspection, the applicant was requested during the clockstop to provide a re-analysis of the Efficacy and Safety data of the Phase III study without the inclusion of site 8200 data (of 42 patients). The applicant was requested to submit the results of this new analysis along with the responses to the LOQ (D121).

Site 4000 and site 7000
The GCP inspection performed at site 4000 and site 7000 showed that the data recorded and reported by these sites are in general trustworthy and reliable and that the subjects did receive adequate information and that they were well taken care off. Therefore, in the Rapporteurs opinion, another GCP-inspection was not necessary, as the inspectors concluded that the data collected at the sites 4000 and 7000 could be used for evaluation and assessment of the application.

Due to GCP issues identified at the UK site 8200, it was decided to exclude the subjects from this site from all analyses. Without site 8200, 372 patients were randomized.

- Tabular overview of clinical studies

The clinical development program consists of a Phase I study in healthy subjects and a Phase III study in infertile ovulatory women undergoing ART. Table 5 gives an overview of these studies.

Table 5 Clinical development programme for Bemfola						
Study No.	**Phase**	**Subject/ Patient type**	**Bemfola**	**Comparator (Gonal-f)**	**Treatment duration**	**No. treated**
FIN1001	I	Healthy female volunteers	Single dose 225 IU	Single dose 225 IU	Single dose	24
FIN3001 Main Study	III	Infertile ovulatory women under-going ART	Fixed dose phase for 6 days: 150 IU/day Afterwards decrease was only allowed in case of risk of imminent OHSS	Fixed dose phase for 6 days: 150 IU/day Afterwards decrease was only allowed in case of risk of imminent OHSS	Up to 16 days	273
FIN 3001 Addendum	III	Infertile ovulatory women under-going ART for a 2nd cycle, not pregnant in Main Study	Fixed dose phase for 6 days: 150 IU/day Afterwards decrease was only allowed in case of risk of imminent OHSS.	Fixed dose phase for 6 days: 150 IU/day Afterwards decrease was only allowed in case of risk of imminent OHSS	Up to 16 days	123

2.4.2. Pharmacokinetics

The applicant characterised the pharmacokinetics of Bemfola in the phase I study FIN1001. Study FIN1001 was a comparative study to compare the pharmacokinetics of Bemfola and Gonal-f after single subcutaneous application, in healthy volunteers. In this study, the increase in 17ß-estradiol (E2) serum concentration and the immunogenicity of Bemfola and Gonal-f were also assessed and compared, safety was monitored descriptively. Repeat-dose PK studies have not been conducted because repeated administration of FSH to healthy volunteers would not be acceptable for ethical reasons. Such a study is also not required according to the guideline on biosimilar rFSH.

Study FIN1001 was conducted as a single centre study in Austria under the sponsorship of Polymun Scientific GmbH between January and August 2009. The study is a randomised, open label, two period, two treatment cross-over study in 24 healthy female volunteers, with a duration of 11 weeks. A single dose of the test product Bemfola and reference product Gonal-f, both containing 300 IU/0.5 ml, follitropin alfa were administered subcutaneously after down-regulation of the endogenous production of FSH. Down-regulation was performed with a GnRH agonist, leuprorelin (Enantone-Gyn). Eligible subjects received Enantone-Gyn (day 15-21 of contraception) for the down regulation of their endogenous FSH levels. After 10 days (study day 1) blood was collected and serum E2 and FSH were analysed to confirm down regulation.

In study FIN1001 the pharmacokinetic serum samples were collected until 192 hours after the first FSH injection. The analytical assessment of serum r-h FSH levels was performed at the central laboratory of the university hospital Vienna (KIMCL) using bioanalytical method FSH/V001R/0309. The r-hFSH concentrations in human serum were analysed with a COBAS test system.
The r-h FSH PK parameters were assessed by non-compartmental analysis. Standard pharmacokinetic variables AUC, C_{max}, t_{max} and $t_{1/2}$ were estimated for r-h FSH.
The statistical method used was the difference method.

The results of study FIN1001 are presented in table 6 and in Figure 3:

Table 6 Pharmacokinetic parameters FSH (arithmetic mean ± SD, t_{max} median, range)

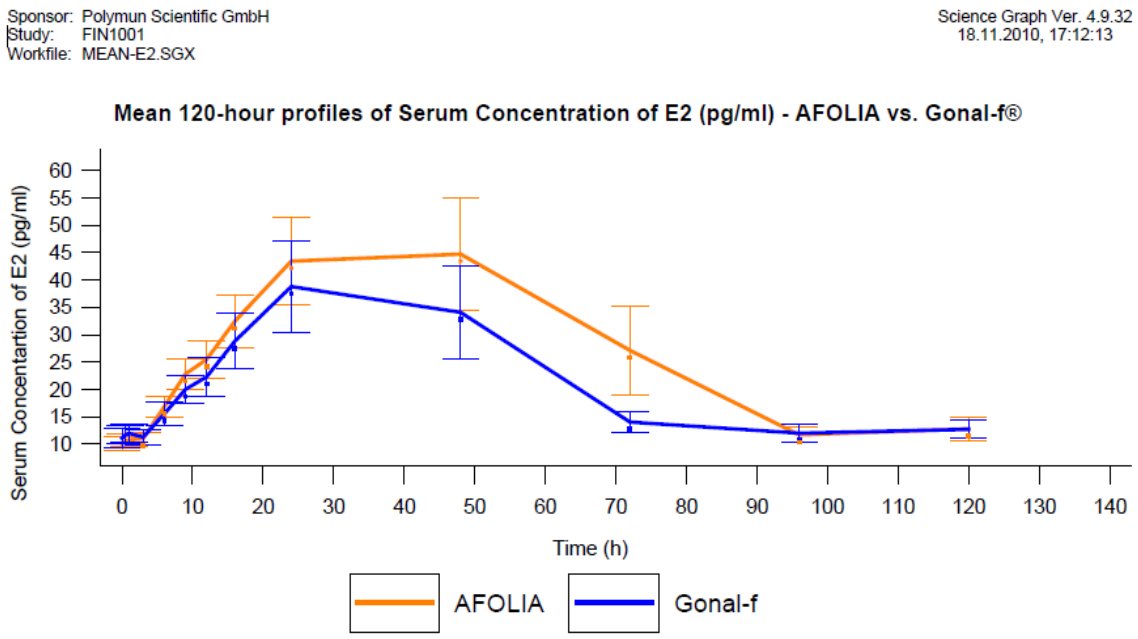
Treatment	N	AUC_{0-192} mIU*h/ml	C_{max} mIU/ml	t_{max} h	$t_{1/2}$ h	K_e 1/h
Bemfola	24	451± 114.6	5.86±1.37	24 (9-24)	43.58 ± 14.17	0.0075 ±0.003
Gonal f	23	456.8±122.1	6.18±1.319	24 (6-24)	42.58 ± 16.47	0.0077 ± 0.002
***Ratio (90% CI)**		98.2 (84.7-113.9)	94.7 (89.2-100.6			

AUC_{0-192} area under the plasma concentration-time curve from time zero to 192 hours>
C_{max} maximum plasma concentration
t_{max} time for maximum concentration (* median, range)
$t_{1/2}$ half life
K_e terminal elimination rate constant

**ln-transformed values*

In study FIN1001, the protocol was amended by an additional secondary study objective, namely the increase in 17ß-estradiol (E2) serum concentration (AUC) after single application of Bemfola and Gonal-f. The exposure (AUC_{0-120h}) to 17ß-estradiol (E2) were 3304.3 ± 2252.88 pg. h/ml after administration of a single dose of Bemfola compared to 2624 ± 1750.60 pg. h/ml after a single dose of Gonal-f. The results of the pharmacokinetic analysis of E2 are summarised in figure PK02.

Figure 3 Mean 120-hour profiles of serum concentration of E2 (pg/ml) – Bemfola (Bemfola) vs. Gonal-f



The administration of both follitropin alfa formulations was well tolerated, a total of 4 adverse events were assessed as related to either follitropin alfa or the combination of follitropin alfa and Enantone-Gyn. One adverse event (abnormal ultrasound) led to the discontinuation of a subject.

No specific antibodies to FSH were detected.

2.4.3. Pharmacodynamics

Mechanism of action

Follitropin alfa consists of two non-covalently linked, non-identical glycoproteins designated as the α- and β- subunits. The α- and β- subunits have 92 and 111 amino acids, respectively. The empirical formula is $C_{975}H_{1513}N_{267}O_{304}S_{26}$. The molecular weight of the heterodimeric and glycosylated molecule is in the range of 30000-34000 Dalton, with the carbohydrate content being approximately 25-30%. The basic building blocks of FSH are amino acids and sugars, which are chiral molecules. Bemfola is produced biologically and will only contain natural (L-)amino acids and sugars.

The mechanism of action of FSH is the same in all indications and FSH binds either to the ovarian or testicular FSH receptor. No separate pharmacodynamic study was conducted. The pharmacodynamic parameters were taken into account in one Phase III trial FIN3001 comparing Bemfola with Gonal-f in patients undergoing controlled ovarian stimulation. The measured serum levels were: FSH and estradiol.

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

In trial FIN3001 pituitary down-regulation was achieved with a gonadotropin-releasing hormone (GnRH) agonist. The GnRH-agonist was administered according to center's procedures (e.g. Decapeptyl 0.1 mg/day; other formulations were allowed by the protocol according to the corresponding SPCs. GnRH depot formulations or nasal sprays were not allowed). The patient received a fixed subcutaneous dose of 150 IU of rFSH (either Gonal-f or Bemfola) once daily for at least 6 days. This fixed dose of 150 IU was maintained throughout the study period unless there was a risk of imminent OHSS (as judged by the investigator, no definition was provided in the protocol for imminent OHSS). Following confirmation of adequate follicular development (at least 1 follicle ≥ 18 mm and 2 additional follicles ≥16 mm), hCG (Ovitrelle) was to be administered for final follicular maturation and triggering of ovulation.

Based on FSH levels, adequate down-regulation was achieved at baseline in both groups (see table below).

Table 7 FSH [IU/L] in Bemfola and Gonal-f at different times

FSH [IU/L]	Visit	Bemfola	Gonal-f
	Baseline, prior to FSH treatment		
	Mean (SD)	6.9 (1.37)	6.8 (1.52)
	Median	6.9	6.8
	Range	2.5 to 10.0	2.8 to 10.0
	Stimulation Day 8		
	Mean (SD)	12.1 (2.70)	10.8 (2.26)
	Median	11.9	10.8
	Range	6.0 to 22.5	5.8 to 16.4
	On the day of hCG administration		
	Mean (SD)	11.7 (2.87)	10.3 (2.31)
	Median	11.6	10.3
	Range	4.3 to 19.0	5.0 to 16.4

FSH concentrations were slightly higher in the Bemfola group compared to the Gonal-f group on Stimulation Day 8 and on the Day of hCG administration.

Estradiol concentrations are shown in the table below.

Table 8 Estradiol [pmol/L] in Bemfola and Gonal-f at different times

Estradiol [pmol/L]	Visit	Bemfola	Gonal-f
	Baseline, prior to FSH treatment		
	Mean (SD)	52.69 (29.27)	52.06 (25.64)
	Median	47.70	49.15
	Range	18.4 to 164.0	18.4 to 135.8
	Stimulation Day 8		
	Mean (SD)	3958.89 (3699.41)	3233.97 (2428.09)
	Median	2817.50	2869.60
	Range	37.1 to 22691.6	96.2 to 11971.5
	On the day of hCG administration		
	Mean (SD)	8982.29 (6535.33)	7704.17 (5345.84)
	Median	7090.40	6606.00
	Range	107.9 to 39669.0	566.6 to 29855.5

The results on estradiol concentrations show that:

- the median concentration at Stimulation Day 8 was comparable (2749 pmol/L for Bemfola vs. 2788 pmol/L for Gonal-f)
- the median concentration in the Bemfola group was slightly higher on the Day of hCG administration (7179 pmol/L for Bemfola vs. 6584 pmol/L for Gonal-f).

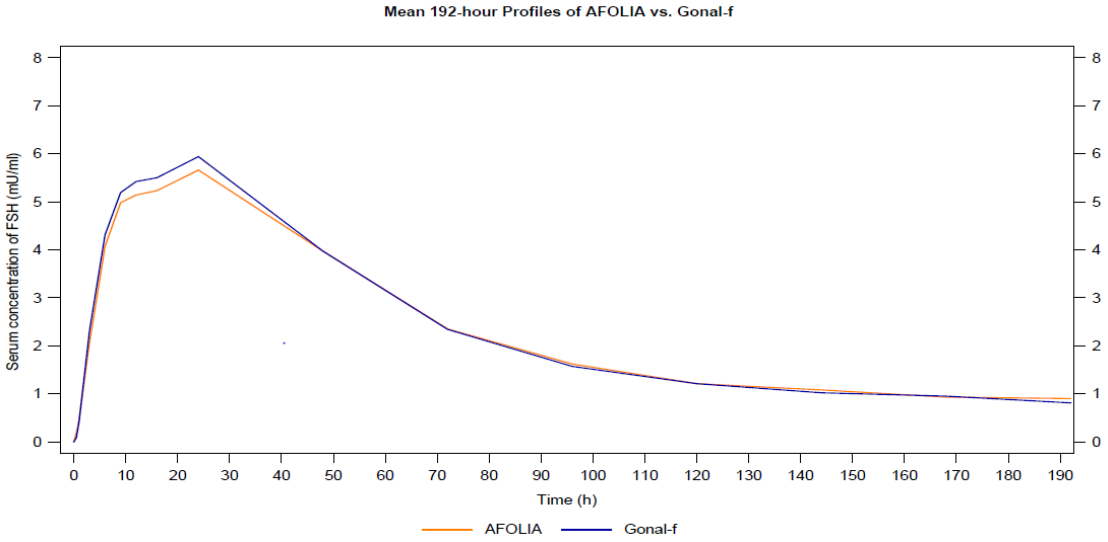
2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The relative pharmacokinetic properties of the Bemfola and Gonal-f were determined in a single dose cross-over study FIN1001. Based on study FIN1001 bioequivalence may be concluded.

The sampling scheme of study FIN1001 was not appropriate for a reliable estimate of peak exposure. Misspecification of the C_{max} may have occurred due to the fact that the there was a 8 hour interval around t_{max}. However, because both the shape of the concentration time curves (see figure PK02) and the total exposure (AUC_{0-192h}) to r-hFSH are similar in both treatment groups no major differences in C_{max} are expected. Therefore the potential misspecification of C_{max} is not expected to be an indication of clinical differences between Bemfola and Gonal-f.

Figure 4 Mean 192-hour profiles of Bemfola vs Gonal-f



The analytical report of study FIN1001 and the validation report for the analytical method FSH/V001R/0309 were submitted. The analytical method FSH/V001R/0309 has been validated according to ICH Guideline Q2R1 and ISO 5725. The applicant showed that there is no cross-reactivity to be expected from structurally related compounds, such as LH, TSH, hCG, hGH and hPL. An acceptable justification has been provided concerning the selectivity and carry-over: endogenous interferences have been tested during the IVD certification of the test kit with different types of plasma and as no concomitant medications were allowed, interference with exogenous compounds is excluded; carry-over was reduced to a minimum due to intensive washing steps in combination with the relatively low concentrations measured during this study. A certificate of analysis for Bemfola and Gonal-f was submitted in order to adequately document the reference material. Only one batch of FSH calibrator (#182187) was used for all assays and therefore the

analytical performance of the method when changing reagent batches have not been investigated. The precision and accuracy has not been evaluated according to the current guideline, however the applicant provided additional information showing that the accuracy of the applied assay is to be expected within acceptable limits. Furthermore the applicant has demonstrated that the results of study FIN1001 are in line with routine FSHs tests performed at the central laboratory of the university hospital Vienna (KIMCL). Parallelism has also not been tested in accordance with the current guideline; however, no interferences are to be expected and concentrations measured were relatively low.

Random fluctuations of the (endogenous) FSH concentrations are observed in the last three time points of the pharmacokinetic curve. Therefore the applicant also determined the AUC over the first 120h after administration and compared both treatments. The analysis of the $AUC_{0\text{-}120h}$ data supports the bioequivalence conclusions.

Endogenous FSH production has a circadian rhythm and is fluctuating throughout the day. The diurnal rhythm was not taken into account since all drug applications were performed at the same time of the day (± one hour) and therefore the variation in FSH concentration due to endogenous FSH production is expected to be similar for all subjects. The baseline FSH values subtracted for the calculation of PK parameter were obtained at visit 3 and visit 13 directly before drug administration.

The range of doses used in stimulation protocols is large and five presentations between 75 IU and 450 IU are proposed by the applicant. The bioequivalence study was conducted with the 225 IU dose, as the 225 IU dose is a commonly used, effective and safe dosage. The 225 IU dose was shown to lie within the linear dose range of the comparator product (Gonal-f) and is considered suitable to detect differences in the PK profiles between the test and reference product.

Plasmon Surface Resonance method used to detect antibodies to FSH is considered appropriate and the applicant sufficiently justified not complying with the guideline EMEA/CHMP/EWP/192217/2009 (especially for the determination of selectivity, dilutional linearity, parallelism and ISR).

Pharmacodynamics

Investigating the PD parameters as part of the phase III trial is acceptable, and in line with the 'Draft guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-FSH; EMA/CHMP/BMWP/671292/2010)'.

In the draft guideline EMA/CHMP/BMWP/671292/2010 also inhibin-B, luteinizing hormone (LH) and progesterone are indicated as one of the pharmacodynamics parameters that should be taken into account. The guideline, however, appeared after the Phase III trial was conducted by the Applicant. Inhibin-B, as well as estradiol, correlates with the number of follicles seen on an ovarian ultrasound. As sufficient other pharmacodynamic parameters were measured (estradiol levels, FSH levels, number and size of follicles), the lack of inhibin-B, LH and progesterone levels is not considered an issue.

Based on the estradiol and FSH concentrations, Bemfola is considered slightly more potent than Gonal-f, e.g. on the day of hCG administration the median estradiol level for Bemfola was slightly

higher compared to Gonal-f: 7090.4 pmol/L and 6606.0 pmol/L, respectively. However, these differences are considered small in light of the range of the estradiol concentrations on the Day of hCG administration varying from 107.9 pmol/L to 39669.0 pmol/L. Furthermore, on Stimulation Day 8 the median E2 levels were similar in both treatment groups.

The Applicant has provided the E2 serum concentration profiles for the Phase III trial for treatment cycle 1. The E2 serum levels are not statistically significantly different from each other in both treatment groups. The E2 measurements in the local and central laboratories were in agreement with each other.

2.4.5. Conclusions on clinical pharmacology

The applicant provided the analytical report in which the most relevant details on the methodology and the study results were presented. The applicant has also demonstrated that the results of study FIN1001 are in line with routine FSHs tests performed at KIMCL. The applicant provided the KIMCL proficiency testing data which were obtained for the intra-laboratory test program in 2009 and also compare these data to the results of study FIN1001.

FSH and estradiol concentrations were slightly higher on the day of hCG administration in FIN3001. However, these differences are considered small in light of the range of the estradiol and FSH concentrations on the Day of hCG administration, and are in accordance with the concept of biosimilarity.

2.5. Clinical efficacy

2.5.1. Dose response studies

No specific dose-response studies were undertaken in the light of this application. In general ART stimulation therapies take 7 to 19 days, and the dose of 150 IU / day FSH was chosen on the basis of the results of previous studies in which the differences in efficacy between lower and higher daily doses did not appear to negatively impact the outcome of treatment. Furthermore, this dose is consistent with the approved dose of the reference medicinal product (Gonal-f) in the studied indication. The Applicant also refers to the Phase 1 study results, were they feel that the safe use of the proposed dose and the bioequivalence of these two FSH formulations was demonstrated.

2.5.2. Main study

Proof of clinical efficiency was based on one phase III FIN3001 study to support efficacy and safety.

Study participants

Inclusion criteria

- infertile due to any of the following factors: tubal factor, mild endometriosis (ASRM stage 1-2), male factor, unexplained fertility;

- age between 20 and 38 years with regular menstrual cycles of 25-35 days;
- BMI between 18-30 kg/m2 inclusive;
- Basal FSH <10 IU/L (cycle day 2-5);
- E2 levels <50 pg/mL (<0.18 nmol/L) at the day of FSH administration;
- Antral follicle count (AFC) ≥ 10 to ≤ 25 follicles (sum of both ovaries)

Exclusion criteria

- history of ≥ 2 succeeding ART retrieval cycles (which includes fresh and frozen embryo transfers before the study cycle without clinical pregnancy (applies only for first treatment cycle);
- presence of polycystic ovaries (PCO);
- previous history or presence of severe ovarian hyperstimulation syndrome;
- presence of severe endometriosis (ASRM stage 3 or stage 4) and hydrosalpinx;
- presence or history of thrombophlebitis or thromboembolic disorders;
- history of extrauterine pregnancy in the previous 3 months;
- history of poor response to gonadotropin treatment (defined as fewer than 5 oocytes retrieved in a previous attempt).

Treatments

In eligible patients, the endogenous FSH production was down-regulated with a GnRH-agonist (Figure 1). The GnRH-agonist was administered according to center's procedures (e.g. Decapeptyl 0.1 mg/day; other formulations were allowed by the protocol according to the corresponding SPCs. Depot formulations or nasal sprays were not allowed).

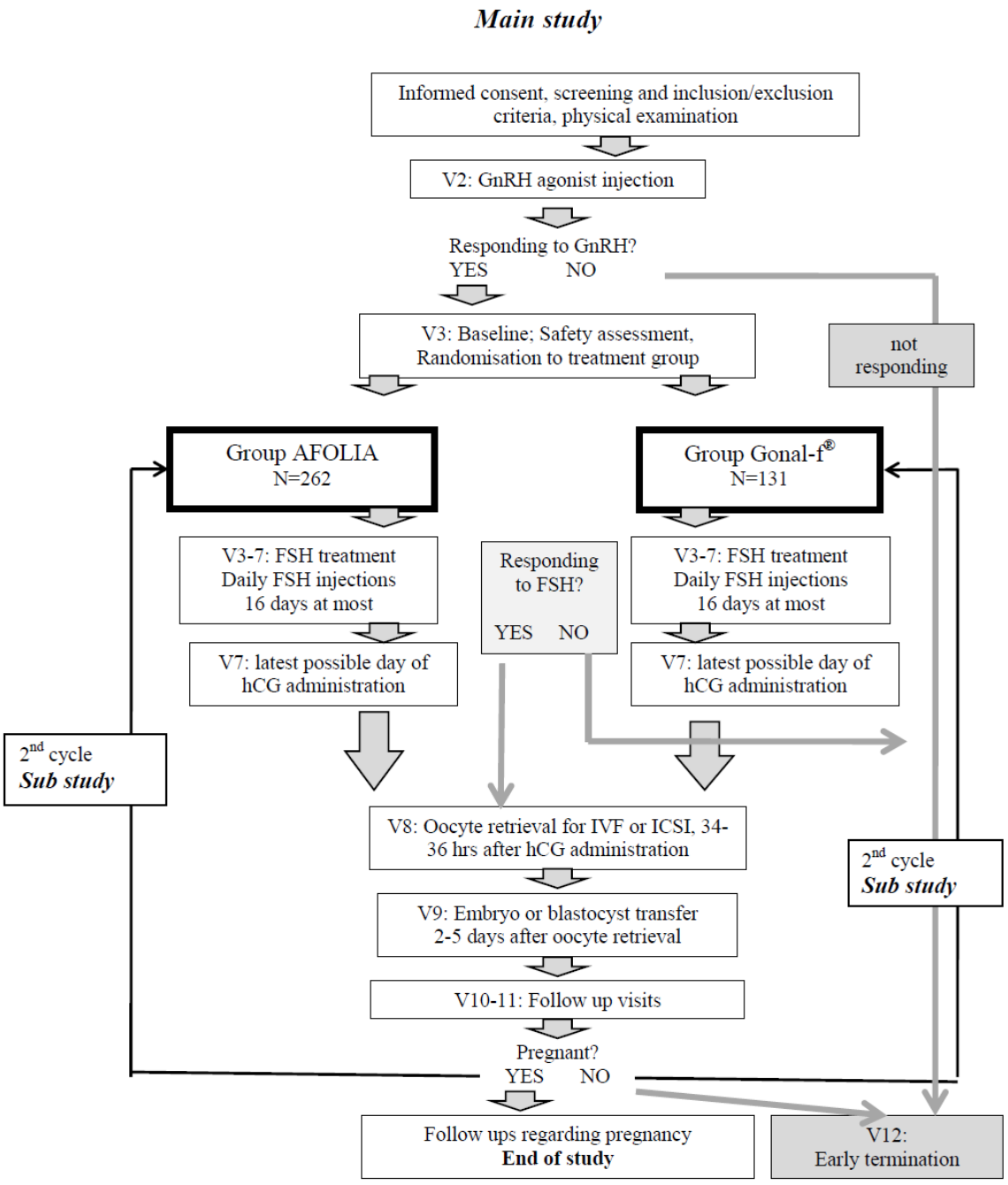
Down-regulation was performed within 14 to 21 days at the latest. Patient's treatment with the GnRH agonist was allowed to be extended until down-regulation was confirmed by E2 level or ultrasound, but not more than 35 days. GnRH-agonist administration continued until end of r-hFSH-administration. The patients were randomized in a 2:1 ratio (Bemfola:Gonal-f), and received a fixed subcutaneous dose of 150 IU of rFSH once daily for at least 6 days; afterwards ultrasonic assessment and E2 level measurements for patient's safety reasons were performed. This fixed dose of 150 IU throughout the study period was maintained unless in case of risk of imminent OHSS (as judged by the principal investigator, no definition was provided in the protocol). The maximum days of rFSH administration according to the protocol was 16 days.

Ovulation was induced by hCG (Ovitrelle, 250 µg) administration if at least 1 follicle reached a diameter of ≥ 18 mm and 2 additional follicles reached a diameter of ≥ 16 mm. If the E2 level raised concern about the safety status of the patient, the investigator was allowed to reduce the hCG dose. The administration of hCG was done the same evening or within 24 hours after the criteria for induction of ovulation had been met. Oocyte retrieval was taken place 36 to 38 hours after administration hCG.

Utrogestan (micronized progesterone) was used as luteal support at a concentration of 3 x 200 mg/day, vaginally administered. The support treatment was started at the day of oocyte retrieval or embryo/blastocyst transfer until after the confirmation of clinical pregnancy up to visit 11 after oocyte retrieval or upon a negative serum β-hCG test at visit 10.

A maximum of two embryos were transferred 2 to 5 days after oocyte retrieval. Pregnancy rate was determined biochemically (β-hCG test) and clinically (intrauterine gestational sac with heart activity).

Figure 1: Study Design



Objectives

The primary objective was to demonstrate the equivalence of Bemfola compared to Gonal-f in infertile but ovulatory women undergoing superovulation for ART.

Study endpoints

Primary efficacy endpoint

The primary endpoint is the "number of oocytes retrieved".

Secondary endpoints

- Total dose of r-hFSH required
- Number of days of r-hFSH stimulation
- Number and size of follicles at the day 8 of stimulation
- Number and size of follicles at the day of hCG administration
- E2 concentration at the day 8 and at the day of hCG administration
- Trough FSH levels after repeated administration of r-hFSH
- Time to first dose reduction due to imminent OHSS
- Percentage of patients with dose reduction due to imminent OHSS
- Quality of oocytes retrieved
- Fertilisation rate of oocytes
- Embryo quality
- Number of cryopreserved 2PN stages, embryos/blastocysts
- Number of transferred embryos
- Number of patients with cycle cancellation
- Number of non-responders
- Implantation rate
- Clinical pregnancy rate (transvaginal ultrasound showing at least one intrauterine gestational sac)

Randomisation

Randomistion was performed using a central randomisation system. Since the average number of patients per center (limited to maximally 40) was small, a dynamic stratification by country was applied.

Blinding

Due to the different visual appearance of the two pens (Gonal-f pen and the Bemfola pen), a double-blind design of the Phase III study was not feasible. All laboratory personnel was blinded as was all the other study personnel, including the ultrasonic assessor. Only the patients and study nurse were not blinded. The assessment of the local and systematic adverse events was not performed by the unblinded study nurse, but by the blinded investigator. The patients had to record their symptoms in a patient diary. The blinded investigator had to make the assessment based on the symptoms recorded by the patient.

Statistical methods

Statistical approach for the primary endpoint (number of oocytes retrieved)
Equivalence of means within the set difference was analysed using Schuirmann's TOST (two one-sided tests, p=0.025) test. The mean number of oocytes retrieved was a random variable, which is asymptomatically normally distributed, but in case of a lot of poor responders (i.e. greater

than 30%) a Mann-Whitney TOST test and Bootstrap-T for non-normal data will be performed. The 95% interval for the mean number of number of oocytes in each treatment group was computed.

Rationale equivalence margin
A difference of less than 3 retrieved oocytes between the two treatments was considered to be clinically not meaningful.

Secondary efficacy parameters
Descriptive statistics (number of observations (n), arithmetic mean (m), standard deviation (SD), minimum (min), median (Median), and maximum (max)) for continuous data and proportion for categorical data were planned. Continuous secondary outcomes will be compared using Student's t-test. In case of non-normality, t-test will be replaced by nonparametric Wilcoxon rank-sum test. Comparison between categorical secondary outcomes will be done using Chi^2 test. If expected cell frequency is lower than 5, Chi^2 test will be replaced by exact Fisher test. Time to event parameters will be analysed using Kaplan-Meier estimates and the log-rank test.

Sample size

'Number of oocytes retrieved' was the primary endpoint on which the comparison was based in order to establish *equivalence* versus Gonal-f. The mean number of oocytes was taken from a pooled analysis of Frydman et al., 2000 (Hum Reprod), Bergh et al., 1997 (Hum Reprod) and Schats et al., 2000 (Hum Reprod). The number of oocytes of poor responders, i.e. number of retrieved oocytes <5, was set to zero. The clinical equivalence would be declared if the mean difference between number of oocytes retrieved was less than 3 with a SD of 7.06. To demonstrate the equivalence between the two treatment groups using two one-sided tests (TOST approach) with regards to the number of ooctyes retrieved with a power of 90%, an alpha error of 2.5% and a poor responder rate of 5%, a sample size of 351 patients with a 2:1 ratio (234/117) was calculated under the hypothesis (± 2.9 is the considered IC for the mean difference):

$H0: \Delta < -2.9$ or $\Delta > 2.9$ null hypothesis
$H1: -2.9 \leq \Delta \leq 2.9$ alternative hypothesis

The sample size was increased by 12% for dropouts and evaluated to 393 patients.

Results

- ***Study FIN3001***

Summary of main efficacy results

The following table summarises the efficacy results from study FIN3001.

Table 9 Summary of efficacy for main trial FIN3001

Title: Efficacy, safety and tolerability of Bemfola compared to Gonal-f in women undergoing assisted reproductive technologies			
Study identifier	FIN3001		
Design	Multi-national, multi-center, randomized, controlled, assessor-blind, parallel group study including follow-up periods conducted at 15 centers in 6 countries: Austria (5 centers), Denmark (3 centers), Germany (2 centers), Spain (2 centers), Switzerland (1 center) and UK (2 centers). Centre 8200 has been excluded, because of GCP issues.		
	Date of first patient enrolled: Date of last patient completed:	1 July 2010 22 November 2011	
Hypothesis	Equivalence, margin [-2.9, +2.9] for primary endpoint		
Treatments groups	Gonal-f 123 patients randomized	Fixed subcutaneous dose of 150 IU once daily for at least 6 days. This fixed dose was maintained throughout the study period unless in case of risk of imminent OHSS. Stimulation continued until adequate follicular development (at least 1 follicle $\geqslant$ 18 mm and 2 additional follicles $\geqslant$16 mm) was reached.	
	Bemfola 249 patients randomized	The treatment and duration were similar in the Bemfola group.	
Endpoints and definitions	Primary endpoint	Number of oocytes retrieved. Equivalence of Bemfola and Gonal-f was considered to be shown if the two-sided 95% CI for the difference in the number of oocytes retrieved was within the equivalence range [-2.9 oocytes, +2.9 oocytes].	
	Selection of secondary endpoints	- Total r-hFSH dose (IU) - Percentage of patients with dose reduction due to imminent OHSS - Number of patients with cycle cancellation - Number of days of r-hFSH stimulation - Serum estradiol (Stimulation Day 8 and on the Day of hCG administration) - Number and size of follicles on Stimulation Day 8 and on the Day of hCG administration - Oocyte quality - Embryo quality - Implantation rate - Ongoing pregnancy rate per randomized patient - Take home baby rate per embryo transfer - Number of children	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per-Protocol population: all patients who completed the study according to the protocol.		
Descriptive statistics and estimate variability	Treatment group	Bemfola	Gonal-f
	Number of subject	249	123
	Primary endpoint: number of oocytes retrieved -- mean	10.85	10.58
	SD	5.11	6.06
	Secondary endpoints -total dose of r-hFSH (IU), mean (SD) median (range)	1555.7 (293.00) 1512.5 (900-2400)	1569.2 (259.20) 1500 (1050-2400)
	- percentage of patients with dose reduction due to imminent OHSS	10.6%	7.3%
	- number of patients with cycle cancellation	5.3%	4.1%
	- number of days of r-hFSH stimulation, mean (SD)	10.6 (1.91)	10.7 (1.72)
	- serum estradiol, mean (SD) pmol/L Stimulation Day 8	3958.89 (3699.41)	3233.97 (2428.09)
	Day of hCG administration	8982.29 (6535.33)	7704.17 (5345.84)
	- number and size of follicles on Stimulation Day 8 ⩾ 12 mm	7.1	6.5
	Day of hCG administration ⩾ 12 mm ⩾ 15 mm ⩾ 17 mm	11.8 8.3 4.9	11.1 7.7 4.5
	- oocyte quality M2 mature oocytes (%)	83.4%	83.3%
	- embryo quality Equally sized blastomeres on Day 2 (%)	59.8%	65.6%
	Equally sized blastomeres on Day 3 (%)	53.2%	64.8%
	- implantation rate	31.8% (110/346)	36.7% (66/180)
	- biochemical pregnancy rate per randomized patient	47.2% (116/246)	48.8% (60/123)
	- clinical pregnancy rate per randomized patient	36.6% (90/246)	44.7% (55/123)
	- ongoing pregnancy rate per randomized patient	34.1% (84/246)	41.4% (51/123)
	- Take-home baby rate per embryo transfer	32.5% (80/246)	40.7% (50/123)
	- number of children	99	60
Effect estimate per comparison	**Primary endpoint**	**Bemfola**	**Gonal-f**

		ZIP regression model	0.27
		95% confidence interval	-1.34, +1.32
Analysis description	Equivalence is established for the primary endpoint. The 95% confidence interval falls within the pre-specified equivalence margin [-2.9, +2.9].		

Participant flow

A total of 502 patients were enrolled in the study at 16 centers in 6 countries. After screening 410 patients were randomized: Austria (5 centers), Denmark (3 centers), Germany (2 centers), Spain (2 centers), Switzerland (1 center) and UK (3 centers). However, center 8200 in the UK has been excluded, because of GCP issues. When excluding center 8200, 372 patients were randomized.

Two analysis populations were identified:

- Full analysis set, which includes all patients who received at least one study drug dose according to protocol.
- Per protocol set, i.e. all patients who completed the study according to the protocol.

Recruitment

The date of first enrolment was 1 July 2010; the date of the last study visit completed was 22 November 2011.

Conduct of the study

The protocol was dated 9 March 2010 and required changes were included in amendment 01 of the protocol, dated 21 October 2010. The global amendment 01 addressed the following:

- administrative changes,
- clarifications of certain procedures (visit assessments, ultrasound parameters, laboratory parameters, clinical parameters),
- concerns raised by the competent authorities and Ethics Committees during the review process (extension of exclusion criteria, safety reporting requirements, statistical analysis).

Due to local regulatory requirements, local protocol amendments were made for Germany (21 July 2010), Switzerland (23 September 2010), Denmark (21 December 2010) and UK (15 February 2011).

- Germany: These amendments included the inclusion of additional exclusion criteria and reasons for discontinuation.
- Switzerland: the amendment was related to the text on treatment compliance.
- Denmark and United Kingdom: Utrogestan was replaced by the general term 'progesterone treatment' in the protocol.

Based on an audit performed by the sponsor at center 8200 (St. Bart's and the London Trust) two patients were found who had been ineligible to enter the trial and additional queries had to be raised. As a result of these findings, the database was reopened and queries were resolved by the principle investigator. The corresponding correction of the database set was followed by a new database lock on 19 September 2012.

Major protocol violations

Major violations occurred in 32 patients (11.6%) in the Bemfola group and 10 patients (7.4%) in the Gonal-f group. See also Table 13 below. The highest percentages were due to "No documented oocytes assessment form" and "Termination date before date of punction".

Table 13: Summary of Major Protocol Violations - SAS Population (EC01T)

Patients included in Safety Analysis Set (SAS) Population	AFOLIA 275 (100%)	Gonal-f 135 (100%)
Any major protocol violation*	32(11.6%)	10(7.4%)
No follicle measurement between visits 5 and 7	3(1.1%)	-
Age not between 20 and 38 years or no regular menstrual cycles of 25-35 days	3(1.1%)	1(0.7%)
More than two previous cycles in the present series of ART	3(1.1%)	-
BMI <18 or ≥30 kg/m)	1(0.4%)	-
Basal FSH ≥10 IU/L (cycle day 2-5)	1(0.4%)	1(0.7%)
No documented oocyte assessment form	7(2.5%)	2(1.5%)
Termination date before date of punction	7(2.5%)	3(2.2%)
Endpoint criterion not fulfilled	3(1.1%)	2(1.5%)
Punction not within 2 days after hCG administration	3(1.1%)	1(0.7%)
More than 1 hCG administration	1(0.4%)	-
Treated not as randomised	2(0.7%)	-

These patients were excluded from the PP population. A patient may have had more than one violation. Percentages are based on the safety population.

Minor protocol violations

Patients with minor protocol deviations were not excluded from the per-protocol population. An overview is lacking from these minor protocol violations.

An overview of the minor protocol violations in study FIN3001 is provided in Table 10.

Table10: Overview of FIN3001 Minor Protocol Violations

Patient	Treatment group	Violation Criterion
210001	Bemfola	EXCL19
300008	Bemfola	EXCL13
300013	Bemfola	EXCL13
500004	Gonal-f	EXCL13
500010	Bemfola	EXCL13
600015	Gonal-f	EXCL13
700024	Bemfola	EXCL13
700027	Gonal-f	EXCL21
800020	Bemfola	EXCL19
910005	Bemfola	EXCL2
910018	Bemfola	EXCL2
910034	Bemfola	EXCL7
910034	Bemfola	EXCL14
930011	Bemfola	EXCL15

- Excl 2: History of >=2 succeeding ART retrieval cycles (which includes fresh and frozen embryo transfers) before the study cycle without clinical pregnancy (applies only for the first cycle)
- Excl 7: Presence of polycystic ovaries (PCO)
- Excl 13: Endocrine abnormality such as TSH or prolactin level elevations outside the reference range if clinically relevant at screening
- Excl 14: Any hormonal treatment within 1 month before the start of the FSH treatment (with the exception of levothyroxin)
- Excl 15: History of drug, nicotine or alcohol abuse within the last 12 months (>10 cigarettes/day)
- Excl 19: Concomitant participation in another study protocol
- Excl 21: Known allergy of hypersensibility to progesterone or to any of the excipients (including peanut oil) of the additional study medication (GnRH-agoinist used, Ovitrelle and Utrogestan)

Baseline data

No clinically relevant differences were observed in the antral follicle count (15.1 for Bemfola vs. 15.3 for Gonal-f), mean age (31.8 years vs. 32.1 years), and mean body weight (62.5 kg for Bemfola vs. 62.7 kg for Gonal-f. Ethnic origin was Caucasian in the majority of the patients. The baseline characteristics on infertility were not part of the approved protocol, though the Applicant has made efforts to collect the data after study closure. Information could be collected from 56% patients in the Bemfola and Gonal-f arms. The baseline characteristics of these patients (137 patients in the Bemfola group and 69 patients in the Gonal-f group) did not show clinically relevant differences between both groups. The duration of infertility was in both groups 3.1 years. The causes of infertility were male factor (45.3% for Bemfola vs. 50.7% for Gonal-f), idiopathic (34.3% for Bemfola vs. 33.3% for Gonal-f), tubal factor (12.4% for Bemfola vs. 4.3% for Gonal-f) and endometriosis (2.2% for Bemfola vs. 0% for Gonal-f).

Numbers analysed

All randomised patients received active drug and were included in the Safety Analysis Set (SAS) population. Two patients were randomised to Gonal-f, but received Bemfola. These patients were randomised in the Bemfola group.

Table 5: Demographic Data Excluding Centre 8200 – Safety Analysis Set

	Cycle 1 (SAS)		Cycle 2 (SAS)	
	AFOLIA N=249	Gonal-f N=123	AFOLIA N=72	Gonal-f N=38
Age (years)				
Mean (SD)	31.8 (4.02)	32.1 (3.76)	32.2 (3.66)	31.6 (3.49)
Median	32.0	32.0	33.0	31.0
Range	21 to 39	22 to 38	24 to 38	24 to 38
Age group (n, %)				
≤ 35	195 (78.3)	95 (77.2)	55 (76.4)	32 (84.2)
> 35	54 (21.7)	28 (22.8)	17 (23.6)	6 (15.8)
Race (n, %)				
Caucasian	229 (92.0)	117 (95.1)	64 (88.9)	35 (92.1)
Asian	12 (4.8)	3 (2.4)	4 (5.6)	2 (5.3)
Other	6 (2.4)	2 (1.6)	2 (2.8)	0
Black	2 (0.8)	1 (0.8)	2 (2.8)	1 (2.6)
Country (n, %)				
Austria	88 (35.8)	43 (35.0)	20 (27.8)	7 (18.4)
Denmark	73 (29.7)	37 (30.1)	32 (44.4)	16 (42.1)
Spain	32 (13.0)	19 (15.4)	2 (2.8)	3 (7.9)
Germany	24 (9.8)	11 (8.9)	9 (12.5)	7 (18.4)
United Kingdom	21 (8.5)	10 (8.1)	8 (11.1)	4 (10.5)
Switzerland	8 (3.3)	3 (2.4)	1 (1.4)	1 (2.6)
Height (cm)				
Mean (SD)	166 (6.27)	167 (6.58)	167 (6.16)	168 (7.08)
Median	165	167	167	169
Range	148 to 186	162 to 172	152 to 186	151 to 180
Weight (kg)				
Mean (SD)	62.5 (9.10)	62.7 (8.30)	65.2 (9.36)	63.8 (7.93)
Median	60.9	61.3	64.4	62.0
Range	45.0 to 94.8	44.4 to 85.0	45.7 to 98.5	50.2 to 86.4
BMI				
Mean (SD)	22.7 (2.90)	22.4 (2.56)	23.5 (2.90)	22.6 (2.74)
Median	22.1	21.9	23.3	22.0
Range	18.0 to 30.3	18.2 to 28.7	18.5 to 30.4	18.7 to 29.0

Discontinuation

The most common reasons for premature termination of treatment were: Failure to become pregnant and increased risk of severe OHSS (2.8% for Bemfola vs. 0.8% for Gonal-f).

Table 17: Demographic Data (DM01T)

	SAS	
	AFOLIA [N=275]	**Gonal-f [N=135]**
Age [years]: Mean (SD)	31.9 (4.01)	32.1(3.94)
Age Group		
<=35	213 (77.5%)	104 (77.0%)
>35	62 (22.5%)	31 (23.0%)
Race		
Caucasian	246 (89.5%)	127 (94.1%)
Hispanic	1 (0.4%)	0 (0.0%)
Black	4 (1.5%)	1 (0.7%)
Asian	18 (6.5%)	5 (3.7%)
Other	6 (2.2%)	2 (1.5%)
Country		
Austria	88 (32%)	43 (31.9%)
Denmark	75 (27.3%)	37 (27.4%)
Germany	24 (8.7%)	11 (8.1%)
Spain	33 (12%)	19 (14.1%)
Switzerland	8 (2.9%)	3 (2.2%)
UK	47 (17.1%)	22 (16.3%)
Height [cm]: Mean (SD)	166 (6.28)	167(6.96)
Weight [kg]: Mean (SD)	62.7 (9.08)	62.7 (8.64)
BMI: Mean (SD)	22.8 (2.89)	22.5 (2.69)
FSH Baseline Concentration [IU/L]: Mean (SD)	6.9 (1.51)	6.8 (1.54)
Antral Follicle Count: Mean (SD)	15.1 (3.71)	15.2 (3.72)
GnRH Duration [days]: Mean (SD)	22.8 (7.89)	22.1 (7.42)

Outcomes and estimation

Primary efficacy analysis

The mean (SD) number of oocytes retrieved in the PP group was 10.8 (5.11) for the Bemfola group and 10.6 (6.06) for the Gonal-f group.

The estimated treatment difference was 0.27 oocytes in favour of Bemfola, while the 95% confidence interval was [-1.34; 1.32] for analysis for non-normal data. This indicates that the two treatment groups were equivalent based on the pre-defined equivalence range of (-2.9, +2.9) oocytes. Results for the FAS population were comparable (0.29, 95% CI -129; 1.34).

The treatment effect was analysed in the PP population adjusting for age in years at randomization and FSH concentration at baseline. No treatment effect was demonstrated for the number of oocytes retrieved.

Secondary efficacy analysis

- The mean (median) total dose of r-FSH was 1555.7 (1512.5) IU in the Bemfola group and 1569.2 (1500) IU in the Gonal-f group.

- The mean number of days of r-FSH stimulation was 10.6 for Bemfola and 10.7 for Gonal-f At least 70% of patients in both treatment groups had 10 days of treatment.

- The proportion of patients requiring dose reductions was higher in the Bemfola group (10.6%) than in the Gonal-f group (7.3%).

- The range of the time to dose reduction due to OHSS was in the Bemfola group (7.0 – 16.0 days) and in the Gonal-f group (8.0 to 12.0 days).

- The mean (SD) number of follicles ≥ 12 mm on Stimulation Day 8 (Visit 5) was slightly higher for Bemfola 7.1 (5.11) compared to Gonal-f 6.5 (4.65).

- The mean (SD) number of follicles (≥ 12 mm, ≥ 15 mm and ≥ 17 mm) on the Day of hCG administration was slightly higher for Bemfola compared to Gonal-f in all three size categories.

- Median estradiol levels on Stimulation Day 8 were 2818 pmol/L for Bemfola vs. 2870 pmol/L for Gonal-f.

- Median estradiol levels on the Day of hCG administration (7090 pmol/L for Bemfola vs. 6606 pmol/L for Gonal-f).

- Patients with cycle cancellations were 13 patients (5.3%) for Bemfola and 5 patients (4.1%) for Gonal-f. Cycle cancellations were mostly due to OHSS.

- The proportion of good responders was 91.4% for Bemfola and 89.4% for Gonal-f. The proportion of poor responders, defined as oocyte retrieval <5 oocytes, was 8.6% for Bemfola and 10.6% for Gonal-f.

  The ICSI method was more applied for the oocytes retrieved in the Gonal-f group (59.3% versus 55.31%) and the IVF method was more applied in the Bemfola group (44.7% versus 40.7%).

- The profiles of cumulus oophorus maturity were similar for the three classifications (very mature, mature, immature). Also, the oocyte nuclear maturity was similar in all three classifications (G, M1 and M2) for both treatment groups. The highest count was observed for metaphase II oocytes, which are preferably used: 83.4% in the Bemfola group and 83.3% in the Gonal-f group.

- Quality of Embryos (Day 2 and Day 3)

On Day 2 and Day 3 small differences were found in the Quality of the Embryos retrieved in "Blastomere uniformity" and "Degree of Fragmentation".

The "Blastomere uniformity" had a higher percentage of equally sized blastomeres in the Gonal-f group compared to Bemfola: on Day 2 59.8% for Bemfola vs. 65.6% for Gonal-f, and on Day 3 53.2% for Bemfola vs. 64.8% for Gonal-f.

Staessen et al. (Hum Reprod 1005;10:3305-12) reported a threshold of 20% fragmentation to demonstrate a difference in implantation rates. A small difference is observed in the percentage of embryos with "0-20% fragmentation": on Day 2 83.0% for Bemfola and 88.3% for Gonal-f, and 73.3% for Bemfola and 87.4% for Gonal-f.
It is however reassuring that the implantation rates are comparable between both treatment groups: for Bemfola 110/346 (31.8%) and for Gonal-f 66/180 (36.7%).

- Quality of Embryos (Day 5)

On Day 5 blastocysts were assessed in both groups on blastocoel cavity, inner cell mass (ICM) and trophectoderm. Only at the inner cell mass a small difference was observed between Bemfola and Gonal-f, which was in favour of Bemfola as more blastocysts were graded B in comparison to Gonal-f. Gardner et al. 2000 (Fertil Steril 73:1155-1158) has shown that an expanded blastocyst with a tightly packed highly cellular ICM has a higher implantation rate compared with a blastocyst with a scarce ICM with very few cells.

- The fertilization rate of oocytes per patient was similar between the treatment groups (66.0% for Bemfola versus 66.79% for Gonal-f).

- The mean number of embryos transferred was comparable: 1.5 for Bemfola and 1.6 for Gonal-f. Also, the proportion of patents with 1, 2 or 3 embryos transferred was similar.

- The implantation rate in the Bemfola and Gonal-f treatment group on day 1 (31.8% vs. 36.7%), 2 (28.3% vs. 26.7%), 3 (33.7% vs. 38.3%) and 5 (36.4% vs. 48.4%) were similar.

Second treatment cycle

The objective of the second treatment cycle was to assess the immunogenicity and safety of Bemfola. Patients who did not become pregnant after a completed first study cycle could undergo a second cycle of FSH treatment at least 4 weeks after termination of the first treatment cycle. Patients remained allocated to the study group arm Bemfola or Gonal-f, respectively. The design of the study was similar to the design of the first treatment cycle.

Study center 8200 was also excluded from the analysis of the second treatment cycle. Out of the 129 patients who gave informed consent, 19 patients were screening failures and 110 patients were included in cycle 2 of this study and treated with Bemfola (n=72) or Gonal-f (n=38). The reasons for screening failure differed, such as too high FSH level, failed downregulation, spontaneously pregnancy or withdrawal of the informed consent. The results of the second treatment cycle were analysed descriptively only, which is acceptable, as the primary aim was to assess immunogenicity and the number of patients included was small.

	Bemfola (n=72)	**Gonal-f (n=38)**
Mean (SD) number of oocytes retrieved	10.4 (4.2)	10.1 (5.3)
Mean (SD) total dose r-FSH (IU)	1612.3 (217.67)	1604.9 (216.61)
Mean (SD) treatment durations (days)	10.9 (1.33)	10.9 (1.31)
Mean (SD) number of follicles on Stimulation Day 8 ≥ 12 mm	5.8 (3.79)	5.9 (4.08)
Mean (SD) number of follicles on Day of hCG administration ≥ 12 mm ≥ 15 mm ≥ 17 mm	 11.4 (3.96) 8.0 (3.20) 4.5 (2.97)	 11.3 (4.11) 7.7 (3.52) 4.2 (3.41)
Patients requiring dose reductions	3 (4.2%)	2 (5.3%)
Patients with cycle cancellation	0 (0.0%)	1 (2.6%)
Median (range) Estradiol on Stimulation Day 8 (pmol/L)	2824.8 (307.5 – 19120.7)	2632.5 (182.8 – 18159.2)
Median (range) Estradiol on Day of hCG administration (pmol/L)	7195.1 (1308.4 – 23260.5)	6396.8 (2483.9 – 32413.4)
Biochemical pregnancy rate per embryo transfer	30 (46.2%)	18 (50%)
Clinical pregnancy rate per embryo transfer	25 (38.5%)	10 (27.8%)
Clinical pregnancy rate per started IVF cycle	25 (34.7%)	10 (26.3%)
Number of patients with liveborn children per embryo transfer	22 (33.8%)	9 (25%)

- The mean total dose of r-hFSH was similar for both treatment groups (1612 IU for Bemfola and 1605 IU for Gonal-f), though higher than used in the Main study (1556 IU for Bemfola and 1569 for Gonal-f).

Differences were noted between treatment cycles 1 and 2:

- The OHSS incidence were comparable for Bemfola and Gonal-f in treatment cycle 2, whereas in treatment cycle 1 the OHSS incidence were higher for Bemfola compared to Gonal-f. These differences could be due to the fact that patients who experienced OHSS in the first treatment cycle or did not complete the first treatment cycle were not included in the second treatment cycle. The patient population is therefore likely less sensitive to FSH compared to the patient population in the first treatment cycle. This is also apparent from the patients who had dose reductions; in treatment cycle 1 (10.6% for Bemfola vs. 7.3% for Gonal-f) this percentage was higher than in treatment cycle 2 (4.2% for Bemfola vs. 5.3% for Gonal-f).

- The percentage of M2 mature oocytes was similar in treatment cycle 1 (83.4% for Bemfola vs. 83.3% for Gonal-f), whereas in treatment cycle 2 it was slightly lower in the Bemfola group (81.3% vs. 85.4% for Gonal-f). More patients received ICSI procedures in the Gonal-f group in treatment cycle 2, which may have resulted in a disbalance between both treatment groups in the percentage of M2 mature oocytes.

No differences were observed between the treatment groups in the secondary endpoints in the second treatment cycle, except for the clinical pregnancy rate per started IVF cycle, which was higher in the Bemfola group (34.7%) compared to the Gonal-f group (26.3%). However, it should be noted that the number of patients in the second treatment cycle was very small (72 in Bemfola vs. 38 in Gonal-f) compared to the first treatment cycle (246 in Bemfola vs. 123 in Gonal-f), and this difference could therefore be the result of chance. The results of the second treatment cycle are in support of biosimilarity.

2.5.2. Discussion on clinical efficacy

One pivotal Phase III study (FIN3001) was conducted in 410 patients to document the equivalent efficacy of Bemfola compared to Gonal-f in the stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART), which is acceptable, as it is in accordance with the 'Draft guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-FSH, EMA/CHMP/BMWP/671292/2010)'. Due to GCP issues identified at the UK site 8200, it was decided to exclude the subjects from this site from all analyses. Without site 8200, 372 patients were randomized.

The study was designed as a randomized, assessor-blind, multi-national, multi-center, controlled, parallel group equivalence trial involving centers in Europe. Gonal-f is appropriate as the reference product. The number of patients included is acceptable. Infertile women aged 20-38 years and having a BMI between 18-30 kg/m2 were included. The women needed to have a regular menstrual cycle length (25- 35 days and presumed to be ovulatory). Patients with a history of severe OHSS, or polycystic ovaries were excluded for safety reasons. The applied inclusion and exclusion criteria are adequate and in line with other ART studies. The design of the study had several flaws (e.g. dose adjustment was only possible in case of risk of imminent OHSS, in which imminent OHSS was not further specified in the study protocol) and infertility characteristics of the patient population were collected post-hoc.

The primary endpoint 'number of oocytes retrieved' for establishing equivalence is in accordance with the draft guideline EMA/CHMP/BMWP/671292/2010. This endpoint is an adequate endpoint, as it is strongly influenced by the effect of FSH on the ovaries.

The equivalence margin for the primary endpoint 'number of oocytes retrieved' was -2.9 and +2.9 oocytes and is adequately justified, as 3 oocytes usually result in one good quality embryo for transfer or freezing. The equivalence margin for Bemfola [-2.9, +2.9] is tighter than has been used in the registered Elonva (modified r-hFSH with a longer half-life) equivalence trial comparing Elonva with r-hFSH (Puregon [-3, +5]). The sample size has a 90% power for rejecting the null hypothesis that Bemfola is different to Gonal-f with an equivalence margin of -2.9, +2.9, which is appropriate. The statistical approach for the primary analysis, using Schuirmann's TOST in the PP population supported by the FAS population or, in case of a lot of poor responders, a Mann-Whitney TOST with bootstrap-T simulation for determining the 95% CI, is considered appropriate. The statistical analyses of secondary outcomes is also appropriate, using t-tests and chi^2-tests, or in case of

non-normality or expected cell frequencies below 5 respectively, Wilcoxon rank-sum tests or Fisher tests.
No clinically relevant differences were observed in the baseline characteristics between both groups. Further to the GCP inspection, the applicant has submitted an updated Study Report of FIN3001 without centre 8200. After exclusion of centre 8200 also equivalence for the primary endpoint was achieved. Furthermore, exclusion of centre 8200 did not result in clinically relevant differences in the secondary endpoints compared to the analyses when study centre 8200 was included.

2.5.3. Conclusions on the clinical efficacy

Therapeutic equivalence for the primary efficacy endpoint 'number of oocytes retrieved' has been established for Bemfola and the reference product Gonal-f. The secondary endpoints 'total r-hFSH dose', 'number of days of r-hFSH stimulation', 'mean number of follicles on Stimulation Day 8 and Day of hCG administration', 'median estradiol levels on Stimulation Day 8', and 'number of patients with cycle cancellation' were comparable between both treatment groups.

Differences were noted in the first treatment cycle in the 'proportion of patients requiring dose reductions due to risk of imminent OHSS' and 'median estradiol levels on the Day of hCG administration'. However, these differences are considered small, i.e. 3.3% difference between Bemfola and Gonal-f in proportion of patients with dose reductions. Further, the difference in median estradiol levels is also considered small considering the range in estradiol concentrations. Thus, the results of the primary endpoint and the secondary endpoints are in accordance with the concept of biosimilarity (Article 10(4) of directive 2001/83/EC).

2.6. Clinical safety

The safety data presented summarized adverse events for all subjects who were included in the Phase I trial and the active-controlled Phase III trial (FIN3001). As it concerns a biosimilar, the submission of two studies, from which one efficacy/safety study for a r-hFSH biosimilar is sufficient provided that Bemfola fulfils all requirements for a biosimilar, including quality and non-clinical requirements.

Patient exposure

A total of 273 subjects received at least one dose of Bemfola. A total of 24 healthy subjects were treated with a single dose in the Phase I trial (FIN1001). In the Phase III trial FIN3001, 249 patients were randomised to Bemfola. In the second treatment cycle 72 patients received Bemfola. Medical history was collected from 56% patients in the Bemfola and Gonal-f arms. No clinically relevant differences were present between both treatment groups.

Adverse events

In the first treatment cycle the incidence of possibly, probably or definitely drug-related treatment-emergent adverse events (TEAEs) was higher for the Bemfola treatment group (64.3%) compared to the Gonal-f treatment group (53.7%).

Table 11 TEAEs with Bemfola and Gonal-f

	Bemfola (N=249)				Gonal-f (N=123)			
	All AEs		Related		All AEs		Related	
Any TEAE	182	73.1%	160	64.3%	83	67.5%	66	53.7%

Drug-related TEAEs that were most frequently reported were injection site erythema (23.7% Bemfola vs. 28.5% Gonal-f), injection site haematoma (20.9% Bemfola vs. 10.6% Gonal-f), OHSS (22.1% Bemfola vs. 13.0% Gonal-f), and headache (20.9% Bemfola vs. 17.9% Gonal-f). Treatment differences in the incidence of individual events were reported for OHSS (9% more frequent in the Bemfola group) and injection site haematoma (10% more frequent in the Bemfola group).

Serious adverse event/deaths/other significant events

No deaths were reported in the completed studies. The frequency of SAEs was higher in the Bemfola group (11 patients, 4.4%) than in the Gonal-f group (3 patients, 2.4%). This difference is largely attributable to the higher incidence of OHSS in the Bemfola group compared to the Gonal-f group (2.8% vs. 1.6%).

Validation of the antibody assay

ADA (antidrug-antibodies) was measured using SPR (surface plasmon resonance). The method was thoroughly and properly validated using commercially available mAbs. Purified mAbs can be expected to be different qualitatively from polyclonal antibodies as a result of immunogenicity. Normally polyclonal antibody preparations (mostly from rabbit or rat immunisation) were also used as positive control. The FSH used as an antigen is the Bemfola FSH in both the Gonal-f and the Bemfola treated patients. The assay range was considered adequate.

Immunogenicity testing in clinical trials

No anti-FSH antibodies were detected in the phase III study in both treatment cycles nor in the Phase I study, which is in line with the statement in the draft Guideline (EMEA/CHMP/BWMP/671292/2010) that immunogenicity of r-FSH is generally low and that neutralizing antibodies were not reported after administration of r-hFSH.

Laboratory findings

No clinically relevant effects were observed between the treatment groups in the completed Phase III study in biochemistry variables, haematology variables and urinalysis variables.

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to AEs

The frequencies of drug-related AEs leading to permanent discontinuation of study drug were not balanced between the two treatments: 10 patients (4.0%) in the Bemfola group and 1 (0.8%) in the Gonal-f group. This difference was mainly due to the higher incidence of OHSS (3.6% vs. 0.8%). All cases of OHSS were classified as moderate in severity, except for one case in the Bemfola group, which was classified as mild in severity.

AE of special interest – Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is an iatrogenic complication of controlled ovarian stimulation with potentially serious outcomes. Independent risk factors for developing OHSS include polycystic ovarian syndrome, previous history of OHSS, high absolute or rapidly rising serum estradiol levels (>11,000 pmol/l in ART) and large number of developing ovarian follicles (≥20 follicles of ≥12 mm in diameter in ART; Gonal-f SmPC).

Two forms of OHSS have been described.

1) The early-onset pattern (early OHSS) occurs within 9 days after oocyte retrieved after hCG administration and appears to be associated with an excessive ovarian response to gonadotropin stimulation.
2) On the contrary, the late-onset pattern (late OHSS) occurs after the initial 10-day period, as a consequence of the endogenously produced hCG from an implanting pregnancy[6,7,8].

Methods to prevent OHSS
To minimise the risk of OHSS, ultrasonographic assessments of follicular development and/or determination of serum estradiol level should be performed prior to ART treatment and at regular intervals during treatment, with the dose adjusted according to the patient's response.

Depending on the ovarian response, the following measurements can be used to prevent OHSS:

1) Coasting, i.e. withholding FSH administration at the end of ovarian stimulation before hCG administration, for a maximum of 3 days;
2) Delay triggering final oocyte maturation with hCG administration until estradiol levels stabilize or decrease;
3) Administer a lower hCG dose;
4) Withhold hCG and cancel the treatment cycle.

[6] *Dahl Lyons CA, Wheeler CA, Frishman GN et al. Early and late presentation of the ovarian hyperstimulation syndrome: two distinct entities with different risk factors. Hum Reprod 1994;9:792-9.*
[7] *Mathur RS, Akande VA, Keay SD et al. Distinction between early and late ovarian hyperstimulation styndrome. Fertil Steril 2000;73:901-7.*
[8] *Papanikolaou EG, Tournaye H, Verpoest W et al. Early and late ovarian hyperstimulation syndrome: early pregnancy outcome and profile. Hum Reprod 2005;20:636-41.*

Measurements taken in the Phase III FIN3001 study

The following exclusion criteria were included in the pivotal study to exclude patients at risk for OHSS, which is acceptable: 1) Antral follicle count (AFC) $\geqslant$ 10 to $\leqslant$ 25 follicles; 2) presence of polycystic ovaries; 3) previous history or presence of severe OHSS.

The FSH dose in the FIN 3001 study was fixed during the entire treatment period and could only be decreased when there was a risk of imminent OHSS (definition not provided in the protocol, to be decided by the investigator). The FSH dose was not adjusted based on the individual patient's ovarian response (as measured by monitoring of serum oestrogen concentrations and/or ultrasound examination). This study design could have resulted in a higher overall incidence of OHSS.

1) Coasting: Coasting (withholding FSH treatment) was allowed for more than 1 day. Coasting between last FSH and hCG for 2 days or more was performed in 7 (2.8%) patients in the Bemfola group and 3 (2.4%) patients in the Gonal-f group.
2) Delay oocyte maturation: Final oocyte maturation could not be delayed. The administration of hCG had to be done the same evening or within 24 hours after the criteria for induction of ovulation had been met.
3) Reduce hCG dose: The investigator was not allowed to reduce the hCG dose if E2 levels raised concern. Nevertheless, one patient received 200 µg rather than 250 µg.
4) Withhold hCG and cancel treatment cycle: The protocol did not specify when to withhold hCG. For safety reasons, i.e. risk of OHSS, it would have been advisable to indicate in the protocol that no hCG should be given if the estradiol level was above a certain serum level and/or if there were more than a certain number of follicles in total.

Classification of OHSS

The OHSS cases were classified according to severity by the investigator (mild, moderate, severe). In addition, study discontinuation due to the adverse event OHSS was reported. Further, OHSS was additionally classified according to the recommendations of "The Practice Committee of the American Society for Reproductive Medicine".

First treatment cycle

OHSS was reported in the first treatment cycle in 55 patients (22.1%) in the Bemfola group and with a lower frequency in the Gonal-f group (16 patients (13.0%). This is due to an imbalance between study arms in the first treatment cycle in the incidence of mild and moderate OHSS, and OHSS leading to study discontinuation: mild OHSS 12.4% vs. 8.1%, moderate OHSS 8.8% vs. 2.4%, OHSS leading to study discontinuation 3.6% vs. 0.8%.

There was a discrepancy between the patients with threatened OHSS (40 for Bemfola vs. 14 for Gonal-f) and the patients with dose reductions (38 for Bemfola vs. 16 for Gonal-f), because there were 9 patients in the Bemfola group and 2 patients in the Gonal-f group who did not receive a dose reduction according to protocol despite the fact that they experienced threatened OHSS. On the other hand, there were 7 patients in the Bemfola group and 4 patients in the Gonal-f group who received a dose reduction although they did not experience a threatened OHSS.

Also differences were noted in:

- Average day of onset of dose reduction in patients with dose reductions was later (8.8 days) in the Bemfola group vs. 6.8 days in the Gonal-f group.
- Average duration of dose reduction in patients with dose reductions was 2.7 days in the Bemfola group vs. 4.1 days in the Gonal-f group.

Table 11 OHSS with Bemfola and Gonal-f

Treatment Cycle 1	**Bemfola (n=249)**	**Gonal-f (n=123)**
Total TEAE OHSS	**55 (22.1%)**	**16 (13.0%)**
Threatened OHSS	40 (16.1%)	14 (11.4%)
OHSS	22 (8.8%)	3 (2.4%)
OHSS classified by the investigator		
mild	31 (12.4%)	10 (8.1%)
moderate	22 (8.8%)	5 (4.1%)
severe	2 (0.8%)	1 (0.8%)
OHSS leading to study discontinuation	9 (3.6%)	1 (0.8%)

In the study protocol of the FIN3001 study no definition had been provided 'a priori' from "threatened OHSS" and "real OHSS". Moreover, the difference between "threatened OHSS" and "real OHSS" has not been used previously in registration studies for ART, nor are these terms used in public literature. It could therefore easily be that OHSS cases have been misclassified by the investigators – i.e. "threatened OHSS" should be "real OHSS" or the other way around, which was also indicated by the Applicant in their response. Therefore, both groups were combined, and looked at the adverse event classified as OHSS as a whole without making a subsequent distinction in "real" and "threatened".

The OHSS incidence in both treatment arms reported in the first treatment cycle in the pivotal phase III study FIN3001 is much higher than the incidence that is reported in the SmPC of Gonal-f (mild or moderate OHSS classified as common, i.e. between 1% and below 10%; severe OHSS classified as uncommon, i.e. 0.1% and below 1%), and for the other r-FSH formulation Puregon (approximately 4% overall OHSS incidence). This could be due to the study design of FIN3001, which did not allow dose decrease based on the individual response unless there was a risk of imminent OHSS (no definition provided, to be decided by the investigator). Further, the fact that the adverse event OHSS also includes "threatened OHSS", which is according to the Applicant the expectation of the investigator that OHSS can develop, but not yet OHSS, could have led to the higher incidence rates of OHSS observed in both treatment groups in study FIN3001 when compared to other registration studies, e.g. for Elonva or Ovaleap.

The Applicant provided a possible explanation for the difference in OHSS incidence between both arms. The Applicant explained that the Phase III trial was not powered to detect differences in

OHSS, which was agreed with. Further, the Applicant discussed several differences between both treatment groups that could have led to the difference in OHSS between both treatment groups. These are:

1. Imbalance in AMH level of ≥24 pmol/L
2. Inconsistent reporting of mild/moderate OHSS incidence
3. Inaccurate reporting of real OHSS
4. Imbalance in dose reductions

In the Phase III trial the primary endpoint was equivalent compared to Gonal-f, and no differences were present in the other secondary endpoints that could explain this higher OHSS incidence. The higher proportion of AMH levels ⩾ 24 pmol/L in the baseline characteristics of the Bemfola group could have contributed to this higher OHSS incidence in the Bemfola group. However, as the difference in proportion of patients with an AMH level of ⩾24 pmol/L between Bemfola and Gonal-f is only 4.4%, the imbalance cannot completely explain the difference of 22.1% for Bemfola vs. 13.0% for Gonal-f in OHSS incidence. Further, dissimilarities in dose reduction were observed between the Bemfola and Gonal-f arms, which also could have resulted in a higher incidence of OHSS for Bemfola.

Second treatment cycle

Patients who experienced OHSS in the first treatment cycle or did not complete the first treatment cycle were not included in the second treatment cycle. The patient population is therefore likely less sensitive to FSH compared to the patient population in the first treatment cycle. This is in correspondence with the lower OHSS incidences observed in the second treatment cycle compared to the first treatment cycle: i.e. Bemfola and Gonal-f, 6.9% and 5.3%, respectively.

2.6.1. Discussion on clinical safety

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

The OHSS incidence in both treatment arms reported in the first treatment cycle in the pivotal phase III study FIN3001 is higher than the incidence reported in the SmPC of Gonal-f (mild or moderate OHSS classified as common i.e. between 1% and below 10%; severe OHSS classified as uncommon i.e. 0.1% and below 1%) and for the other r-FSH formulation Puregon (4% overall OHSS incidence). These higher incidences might be due to the strict fixed dose regimen, in which dose reduction was only possible in case of risk of imminent OHSS. Further, the fact that the adverse event OHSS also includes "threatened OHSS", which is according to the Applicant the expectation of the investigator that OHSS can develop, but not yet OHSS, could have also contributed to the higher incidence of OHSS in FIN3001.

A higher incidence of OHSS was noted for Bemfola: Bemfola (22.1%) vs. Gonal-f (13.0%). Also, the discontinuation due to OHSS was higher in the Bemfola group versus the Gonal-f group, 9 (3.6%) vs. 1 (0.8%). The Applicant was requested to discuss these differences between treatment arms. The higher proportion of AMH levels ⩾ 24 pmol/L in the baseline characteristics of the Bemfola group could have contributed to this higher OHSS incidence in the Bemfola group. Further, dissimilarities in dose reduction were observed between the Bemfola and Gonal-f arms, which also

could have resulted in a higher incidence of OHSS for Bemfola.

2.6.2. Conclusions on the clinical safety

OHSS incidence, withdrawal due to OHSS, and proportion of patients requiring dose reductions due to risk of imminent OHSS were ample explain by the applicant. In their response, the Applicant has adequately discussed the observed differences in the Phase I and Phase III trial. The small differences in FSH and estradiol concentrations are in accordance with the concept of biosimilarity considering the wide range in FSH and estradiol concentrations, and the pulsatile release of endogenous FSH. To explain the difference in OHSS incidence, the Applicant evaluated several parameters. The higher proportion of AMH levels ≥ 24 pmol/L in the baseline characteristics of the Bemfola group could have contributed to this higher OHSS incidence in the Bemfola arm. Further, dissimilarities in dose reduction were observed between the Bemfola and Gonal-f arms, which also could have resulted in a higher incidence of OHSS for Bemfola.

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

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The following table provides an overall summary of the risk management plan.

Summary of safety concerns	
Important identified risks	• Ovarian hyperstimulation syndrome (OHSS) • Hypersensitivity reactions including • anaphylactic reactions • Thromboembolic events usually with OHSS • Asthma aggravated / exacerbation • Multiple pregnancies • Gynecomastia in males
Important potential risks	• Immunogenicity which may manifest as lack of effect • Breast cancer • Other reproductive system cancers • Ectopic pregnancy • Congenital abnormalities
Missing information	• Use in female patients >40 years of age

Updated "Summary of risk minimisation measures"

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation
Important identified risks		
Ovarian hyperstimulation syndrome (OHSS)	Warning in Section 4.4 describing OHSS, symptomatology, risk factors, how to minimise these risks and subsequent treatment recommendations. Mild to moderate OHSS is listed as a common ADR and severe OHSS as an uncommon ADR in Section 4.8 of the BEMFOLA SPC. Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	None
Hypersensitivity reactions including anaphylactic reactions	Listed in Section 4.3 Contraindications: Hypersensitivity to the active substance follitropin alfa, FSH or any of the excipients. In Section 4.8 Undesirable effects: Very rare: Mild to severe hypersensitivity reactions including anaphylactic reactions and shock.	None

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation
	Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	
Thromboembolic events usually with OHSS	Warning in Section 4.4 that, "Very rarely, severe OHSS may be complicated by ovarian torsion or thrombolic events such as pulmonary embolism, ischaemic stroke or myocardial infarction". Furthermore, a separate paragraph in Section 4.4 entitled "Thrombolic events" describes risk factors for thrombolic events. Listed in Section 4.8 under vascular disorders, "Very rare: Thromboembolism, usually associated with severe OHSS (see Section 4.4)." Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	None
Asthma aggravated /exacerbation	Listed in Section 4.8, "Very rare: Exacerbation or aggravation of asthma." Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	None
Multiple pregnancies	Warning in Section 4.4 alerting prescribers to the increased risk of multiple pregnancy and that multiple pregnancy carries an increased risk of adverse maternal and perinatal outcomes. The warning advises prescribers to carefully monitor ovarian response and advise patients of the potential risks of multiple births before starting treatment. Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	None
Gynecomastia in males	Listed in Section 4.8 as a common adverse event. "Common: Gynaecomastia." Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	None
Important potential risks		
Immunogenicity which may manifest as lack of effect	Use of BEMFOLA is restricted to physicians experienced in the treatment of fertility disorders. It is not considered necessary to include specific text in the SPC regarding the potential for immunogenicity which may manifest as a lack of effect.	None

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation
	Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	
Breast cancer	Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	None
Other reproductive system cancers	Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	None
missing information		
Use in female patients >40 years of age	Prescription only medicine. Use restricted to physicians experienced in the treatment of fertility disorders.	None

The applicant has aligned the Bemfola RMP with the RMP for Gonal-f as requested. The proposed risk minimisation measures (routine only) are sufficient to minimise the risks of the product in the proposed indication.

PRAC Advice

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

Risk management Plan (RMP)

Additional risk minimisation measures

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

Obligation to conduct post-authorisation measures

Not applicable

The CHMP endorsed this advice without changes.

3. Benefit-Risk Balance

Benefits

Bemfola (also referred to as Bemfola) contains the active substance follitropin alfa. Follitropin alfa is a recombinant human follicle-stimulating hormone (r-hFSH) that is produced in Chinese Hamster Ovary Cells (CHO DHFR-) by recombinant DNA technology.

This application is a centralised procedure made according to Article 10(4), Directive 2001/83/EC, biosimilar application. Bemfola has been developed as a similar biological medicinal product (biosimilar) with Gonal-f as the reference product.

The claimed indications are similar to the indications of Gonal-f:

"In adult women

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

In adult men

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

The dose recommendations are also identical to those of Gonal-f.

Bemfola is provided in 5 different single-use pre-filled pens of 75 IU, 150 IU, 225 IU, 300 IU and 450 IU. In contrast, for Gonal-f 3 pre-filled multidose preparations are available of 300 IU, 450 IU and 900 IU.

Beneficial effects

Quality
In the analytical comparability exercises no qualitative differences in rh-FSH were observed between Bemfola and Gonal-f and evidence for a similar quality profile was obtained. However, as can be expected for complex molecules, some minor differences were observed in glycosylation between Bemfola and Gonal-f, and the percentage of truncated alpha chain between Bemfola batches. These differences are only small, and can be expected for products derived from a biological production process.

Non-clinical
Non-clinical studies showed similar activity of Bemfola and Gonal-f in a functional cell assay in which the human FSH receptor was expressed. Both products also showed similar potency in rat bioassay were increase in ovary weight was assessed (Steelman-Pohley assay).

Clinical pharmacokinetics
The pharmacokinetic properties of Bemfola and Gonal- were determined in a single dose cross-over study FIN1001. Based on study FIN1001 bioequivalence may be concluded.

Efficacy data and additional analyses
One pivotal Phase III study (FIN3001) was conducted in 410 patients to document the efficacy of Bemfola in the stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART). Due to GCP issues at center 8200, this site was excluded. With the exclusion of site 8200, 372 patients were randomized. Treatment ratio was 2:1. Performing a study for the ART indication is appropriate, as it is the most sensitive indication with regard to detection of product-specific differences. The study was designed as a randomized, multi-national, parallel group trial. The study had an assessor-blind design. Due to the different visual appearance of the two pens (Gonal-f pen and Bemfola pen), a double-blind design was not feasible. All laboratory personnel and other study personnel, including the ultrasonic assessor, were blinded. Only the patients and study nurse were not blinded. The reference product was the registered r-hFSH Gonal-f, which is appropriate. The dose of 150 IU r-hFSH was fixed throughout treatment, and could only be lowered in case of risk of imminent OHSS. Six European countries participated. The women included were aged 20-38 years, with a BMI between 18-30 kg/m2 and having a regular menstrual cycle length (25- 35 days).

The results for the primary efficacy endpoint '*number of oocytes retrieved'* were 10.9 in the Bemfola group compared to 10.6 oocytes retrieved in the Gonal-f group. Equivalence was shown by the Mann-Whitney U test. The 95% confidence intervals for the difference between Bemfola and Gonal-f (0.52, 95% CI -1.34, +1.32) were well within the pre-defined equivalence margin of [-2.9, +2.9] that is adequately justified.

The following key secondary endpoints were considered comparable:

- Median total dose of r-hFSH (15132 IU for Bemfola vs. 1500 for Gonal-f)
- Number of days of r-hFSH stimulation (10.6 for Bemfola vs. 10.7 for Gonal-f)
- Median estradiol levels on Stimulation Day 8 (2818 pmol/L for Bemfola vs. 2870 pmol/L for Gonal-f)
- Mean number of follicles on Stimulation Day 8 ≥ 12 mm for Bemfola (7.1) and Gonal-f (6.5)
- Mean number of follicles on the Day of hCG administration for Bemfola vs. Gonal-f in all three size categories was: ≥ 12 mm (11.8 vs. 11.1), ≥ 15 mm (8.3 vs. 7.7) and ≥ 17 mm (4.9 vs. 4.5)
- Number of patients with cycle cancellation was 13 patients (5.3%) for Bemfola and 5 patients (4.1%) for Gonal-f. Cycle cancellations were mostly due to OHSS

- The percentages of women with ≥ 12 mm, ≥ 15 mm and ≥ 17 mm with 0 follicles, 1 to 5 follicles, 6 to 10 follicles and > 10 follicles on Stimulation Day 8 and on the day of hCG administration.

- Pregnancy follow-up. Birth weight was similar between treatment groups. Also the adverse events in the group 'Congenital, familial and genetic disorders' were similar in both arms.

In the other key secondary endpoints slight differences were noted:

- Proportion of patients requiring dose reductions due to risk of imminent OHSS was higher in the Bemfola group (10.6%) than in the Gonal-f group (7.3%)
- Median estradiol levels were higher on the Day of hCG administration for Bemfola (7090 pmol/L; range 107.9 to 39669.0 pmol/L) compared to Gonal-f (6606 pmol/L; range 566.6 to 29855.5 pmol/L).
- Ongoing pregnancy rate per randomized patient was 34.1% (84/246) for Bemfola vs. 41.4% (51/123) for Gonal-f.

Uncertainty in the knowledge about the beneficial effects

Usability

Dose increase is inconvenient compared to the reference product. For instance, when a woman uses the 150 IU pen and she needs to increase the dose, she will need to use a different pen, i.e. 225 IU, 300 IU or 450 IU. In contrast, with the 900 IU/1.5 ml Gonal-f pen this is not necessary, as multiple different doses can be administered with the same pen within 28 days after opening. Consequently, with the single-use system more unused medicinal product will be discarded.

Clinical pharmacokinetics

The relative pharmacokinetic properties of Bemfola and Gonal-f were determined in a single dose cross-over bioequivalence study (study FIN1001). In the original documentation only the method validation report and the analytical results were provided, not a full analytical report. In the responses to the D180 CHMP LoOI, the applicant submitted the requested analytical report in which the most relevant details on the methodology and the study results were presented. In this regards, the applicant was asked to provide the KIMCL proficiency testing data that were obtained for the intra-laboratory test program in 2009 and to compare these data with the results of study FIN1001. The submitted KIMCL Proficiency Testing Data and the results of routine intra-laboratory test program show that it can be concluded that the accuracy of the analytical method used in Study FIN1001 is appropriate. Therefore the analytical method used in study FIN1001 is considered acceptable.

Routine GCP inspection

The Applicant has filed two GCP serious breach reports to the MHRA about one of the UK sites (8200) in the FIN3001 study. The MHRA was notified on 31 October 2012. Protocol violations that were identified were inclusion of non-eligible patients, and the blind of the ultrasound scans was potentially compromised. Site 8200 included 42 patients. Based on these findings, the Applicant indicated that there is a potential impact to scientific value/data credibility.

A routine GCP inspection was agreed on by the EMA, investigating three sites, including Site 8200. As a result of the GCP inspection of site 8200, the applicant was requested to provide a re-analysis of the Efficacy and Safety data of the Phase III study without the inclusion of site 8200 data (of 42 patients). The applicant submitted these data together with the responses to the D120 LoQ.
A GMP certificate for Vela Labs has been provided.

Dosing
The FSH dose in the pivotal clinical study has not been adjusted based on the patient's ovarian response (as measured by monitoring of serum oestrogen concentrations and/or ultrasound examination) by increasing or decreasing the dose, which is not in line with clinical practice in Europe and the rest of the world, and is not in accordance with the draft guideline EMA/CHMP/BMWP/671292/2010, and the draft European Scientific Advice (EMEA/CHMP/SAWP/ 593346/2008).

Risks

Unfavourable effects
In the first treatment cycle the incidence of possibly, probably or definitely drug-related treatment-emergent adverse events (TEAEs) was higher for the Bemfola treatment group (64.3%) compared to the Gonal-f treatment group (53.7%). Drug-related TEAEs that were most frequently reported were injection site erythema (23.7% Bemfola vs. 28.5% Gonal-f), injection site haematoma (20.9 Bemfola vs. 10.6% Gonal-f), OHSS (22.1% Bemfola vs. 13.0% Gonal-f), and headache (20.9% Bemfola vs. 17.9% Gonal-f).

No deaths were reported. SAEs were reported in 11 (4.4%) patients in the Bemfola group and 3 (2.4%) in the Gonal-f group.

OHSS
Both the patient and study nurse were aware of the treatment. The assessment of the local and systematic adverse events was not performed by the unblinded study nurse, but by the blinded investigator. The patients had to record their symptoms in a patient diary. The blinded investigator had to make the assessment based on the symptoms recorded by the patient. OHSS was classified by the investigator in mild, moderate and severe, which is acceptable. In addition, study discontinuation due to the adverse event OHSS was reported.

In the first treatment cycle, OHSS was reported in 55 patients (22.1%) in the Bemfola group, and with a lower frequency in the Gonal-f group (16 patients; 13.0%). This is due to an imbalance between study arms in the first treatment cycle in the percentage of mild and moderate OHSS, and OHSS leading to study discontinuation: mild OHSS 12.4% vs. 8.1%, moderate OHSS 8.8% vs. 2.4%, OHSS leading to study discontinuation 3.6% vs. 0.8%. No differences were noted in percentage of patients with severe OHSS (0.8% in each group).

In the second treatment cycle, the incidence of OHSS was comparable for Bemfola and Gonal-f, 6.9% and 5.3%, respectively, but lower than in the first treatment cycle. As patients who experienced OHSS in the first treatment cycle or did not complete the first treatment cycle were not included in the second treatment cycle, the patient population was therefore less sensitive to FSH compared to the patient population in the first treatment cycle.

Immunology
The ADA (anti-drug antibody) assay was thoroughly and properly validated. No anti-FSH antibodies were detected in the confirmatory assay in the main phase III study in both treatment cycles and phase I study.

Uncertainty in the knowledge about the unfavourable effects
OHSS
The patient needed to report local and systemic adverse events. The blinded investigator had to make the assessment based on the symptoms recorded by the patient in the Patient Diary. It is agreed that the diagnosis between mild or moderate OHSS is heavily influenced by the Patient Diary assessment done by the patient. As the patient was aware whether they received Gonal-f or Bemfola it cannot be excluded that this has impacted their reporting of symptoms, especially the mild OHSS. However, it remains unknown whether the unblinding of the patient impacted the reporting of OHSS, and if so, what the impact has been.

The Applicant discussed the possible role of the strict dosing regimen on the overall higher incidence of OHSS found in the study. In the protocol of the Phase III study the following was indicated: "Only dose reduction allowed in case of imminent OHSS." This may have led to too late dose adaptations, and an overall high OHSS incidence in the Phase III study.

Benefit-risk balance

Importance of favourable and unfavourable effects
Quality
In the analytical comparability exercises sufficient evidence for a highly similar quality profile for Bemfola and Gonal-f was obtained. Bemfola is not claimed to be fully identical to Gonal-f and, as can be expected for complex molecules manufactured by two processes, some minor differences were observed with regard to the glycosylation profile:

- the ratio of tetra-antennary to di-antennary structures is for BEMFOLA slightly higher compared to Gonal-f.

- for the most complex glycosylation site 3 (beta subunit), slight differences in distribution of fucosyl residues in relation to antennarity were observed between Bemfola and Gonal-f.

- a small amount of the sialic acid residues of the alpha –subunit of Gonal-f samples contain an O-acetyl group, whereas the level in Bemfola was below detection.

These minor differences are in line with the similarity principle. A major impact on the efficacy and safety profile is not expected. In summary, it is concluded that Bemfola and Gonal-f show a highly similar physico-chemical and biological quality profile.

Non-Clinical
The non-clinical data support the view that the active substance of Bemfola is the same or highly similar compared to the active substance of Gonal-f.

Clinical pharmacokinetics

The pharmacokinetic properties of of Bemfola and Gonal- were determined in a single dose cross-over study FIN1001. Based on study FIN1001 bioequivalence may be concluded.

Clinical efficacy and safety

Therapeutic equivalence for the primary efficacy endpoint 'number of oocytes retrieved' has been established between Bemfola and the reference product Gonal-f in the pivotal study FIN3001. Several secondary endpoints were taken into account that investigated possible differences between the Bemfola and the reference product Gonal-f. The secondary endpoints 'total r-hFSH dose', 'number of days of r-hFSH stimulation', 'mean number of follicles on Stimulation Day 8 and Day of hCG administration', 'number of patients with cycle cancellation' and ' ongoing pregnancy rate' were comparable between both treatment groups. However, slight differences were seen between the following secondary endpoints between Bemfola and the reference product Gonal-f: E2 levels (both Phase I and Phase III, FSH levels in Phase III, OHSS incidence, withdrawal due to OHSS, and proportion of patients requiring dose reductions due to risk of imminent OHSS. The Applicant was therefore asked to discuss these differences.

In their response, the Applicant has adequately discussed the observed differences in the Phase I and Phase III trial. The small differences in FSH and estradiol concentrations are in accordance with the concept of biosimilarity considering the wide range in FSH and estradiol concentrations, and the pulsatile release of endogenous FSH. To explain the difference in OHSS incidence, the Applicant evaluated several parameters. The higher proportion of AMH levels $\geqslant$ 24 pmol/L in the baseline characteristics of the Bemfola group could have contributed to this higher OHSS incidence in the Bemfola arm. Further, dissimilarities in dose reduction were observed between the Bemfola and Gonal-f arms, which also could have resulted in a higher incidence of OHSS for Bemfola.

Benefit-risk balance

A similar quality profile was obtained for Bemfola and Gonal-f. In addition, non-clinical data and clinical pharmacokinetics are in support of biosimilarity with Gonal-f. In the Phase III study equivalence was obtained for the primary endpoint, and for the secondary endpoints only a higher OHSS incidence was observed to which the imbalance in AMH levels and dissimilarities in dose reductions could have contributed. Taken all data into account, including the quality and non-clinical package, Bemfola can be considered biosimilar to Gonal-f.

Discussion on the benefit-risk balance

The CHMP requested a routine GCP inspection of the one pivotal study FIN3001. Based on the reporting inspector there have been persistent departures from GCP and the protocol at site 8200, having impact on the majority of aspects of the conduct of the trial. For that reason, the Applicant submitted a revised analysis of the Phase III trial excluding center 8200 and the data presented in this overview AR exclude this center.

3.1.1.1. Recommendations

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

In adult women

- Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate.

- Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT).

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

In adult men

- Bemfola is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotrophin (hCG) therapy.

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

- **Periodic Safety Update Reports**

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

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

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