Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Follitropin alfa (rch)

Proprietary Product Name: Bemfola, Afolia

Sponsor: Finox Biotech Australia Pty Ltd

March 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

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Common abbreviations

Abbreviation	Meaning
AE	adverse event
AMH	anti-Mullerian hormone
ART	assisted reproductive technology
AUC	area under curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMI	consumer medicine information
C_{max}	maximum concentration
DHPL	Dear Healthcare Professional Letter
EMA	European medicines agency
EU	European Union
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	good clinical practice
GIFT	gamete intra-fallopian transfer
GLP	good laboratory practice
hCG	human chorionic gonadotropin
IU	international unit
IV	intravenous
IVF	in vitro fertilisation
LH	luteinising hormone
MedDRA	Medical Dictionary for Regulatory Activity
OHSS	ovarian hyperstimulation syndrome
PCOD	polycystic ovarian disease
PD	pharmacodynamic

Abbreviation	Meaning
Ph Eur	European Pharmacopeia
PI	product information
PK	pharmacokinetic
PP	per protocol
PSUR	periodic safety update report
rhFSH	recombinant human follicle stimulating hormone
RMP	risk management plan
SAE	severe adverse effect
SAS	safety analysis set
SC	subcutaneous
SD	standard deviation
TGA	Therapeutic Goods Administration
T_{max}	time to maximum concentration
TOST	two one-sided tests
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation
ZIFT	zygote intra-fallopian transfer

I. Introduction to product submission

Submission details

Type of submission:	Biosimilar medicine and extension of indications
Decision:	Approved
Date of decision:	25 November 2015
Date of entry onto ARTG	27 November 2015
Active ingredient:	Follitropin alfa (rch)
Product names:	Bemfola, Afolia
Sponsor's name and address:	Finox Biotech Australia Pty Ltd PO Box 86 Frenchs Forest NSW 2086
Dose form:	Injection, solution
Strengths:	75 IU/0125 mL (5.5 µg), 150 IU/0.25 mL (11 µg), 225 IU/ 0.375 mL (16.5 µg) 300 IU/ 0.5 mL (22 µg) and 450 IU/0.75 mL (33 µg)
Container:	Cartridge in a pre-filled pen
Pack sizes:	1, 5 and 10 pre-filled pens
Approved therapeutic use:	*In adult women:* *Bemfola/Afolia is indicated for the treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated.* *Controlled ovarian hyperstimulation in women undergoing assisted reproductive Technologies* *Bemfola/Afolia 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 1U/L.* *In adult men:* *Bemfola/Afolia is indicated with concomitant human chorionic gonadotrophin (hCG) therapy for the stimulation of spermatogenesis in gonadotrophin-deficient men in whom hCG alone is ineffective.*
Route of administration:	Subcutaneous
Dosage:	Women: Dosing regimen commences at 75 to 150 IU (5.5 to 11 µg) follicle stimulating hormone (FSH) daily and is increased in increments of 37.5 to 75 IU (2.75 to 5.5 µg) at 7 or 14 day

	intervals to obtain an adequate, but not excessive response. Men: After treatment with hCG only, 150 IU (11 µg) FSH three times a week for a minimum of 4 months. For further details on dosage please see the Product Information (PI).
ARTG numbers:	231039, 231046, 231051, 231052, 231053, 262645, 262646, 262647, 262648, 262649.

Product background

This AusPAR describes the application by Finox Biotech Australia Pty Ltd (the sponsor) to register Bemfola and Afolia[1]; follitropin alfa (rch) as a biosimilar medicine 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 luteinizing hormone (LH) and follicle-stimulating hormone (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.*

Bemfola is a biosimilar to Gonal-f. It has an identical primary structure to the reference recombinant human FSH alpha analogue Gonal-f, and also the same primary structure as Puregon (follitropin beta (rch)).

The proposed indications for Bemfola are identical for those of Gonal-f with one additional indication. In addition, Bemfola is proposed to be used for the following indication:

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

This indication has been approved in Australia for Luveris (LH) and has been approved in the EU for recombinant human FSH (rhFSH). The physiological mechanism of efficacy in this indication is identical to the other indications, although a lower dose may be needed.

The formulation of Bemfola is comparable to that of Gonal-f solution for injection (as registered in Australia) except for the absence of m-cresol, used as a preservative in the multi-use pen presentations of Gonal-f and not required in the single dose Bemfola injector pens. The strength of the active ingredient (600 IU/mL) matches that of the reference product.

[1] In most references to the tradename in the text of this document only Bemfola will be used.

The sponsor proposed the following advantages of Bemfola which is supplied as a small single use pen over Gonal-f which is supplied as a multi-use pen.

- it is a preservative free formulation
- the device is a small single use pen with volume and injection control mechanisms
- it is possible to fine tune dosing (minimum 12.5 IU increments compared to 37.5 IU for Gonal-f).

Bemfola has the same concentration as Gonal-f (600 IU /ml).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 27 November 2015. At the time the TGA considered this application, a similar application had been approved in EU (centralised procedure), 27 March 2014.

Applications for registration have been made to Switzerland (March 2014) and Canada (October 2014). An application has been made to the USA but the FDA requires an additional efficacy and safety study in a patient population deemed more appropriate to its requirements. The FDA required an additional study which used US sourced Gonal-f, pregnancy rather than oocyte as the endpoint; and enrolled women aged 35 to 42 years. These were based on regulatory requirements in the US as opposed to concerns about efficacy or safety. This study (FIN3002) is in progress.

Product Information

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

II. Quality findings

Drug substance (active ingredient)

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 primary structure is identical to the drug substance of reference product Gonal-f. It also has the same primary structure as Puregon (follitropin beta (rch)).

The culture in serum free culture medium is in a bioreactor with a continuous harvest ultrasonic cell retention system. Clarification is performed with a depth filter followed by 0.2 µm filtration and ultra-diafiltration.

The clarified harvest is purified by a six step process with three chromatographic steps. Cell banking processes are satisfactory. All viral/prion safety issues have been addressed, including use of animal derived excipients, supplements in the fermentation process and in cell banking.

Physical and Chemical Properties

The amino acid sequence, truncations, glycosylation sites and higher order structure were verified. The disulphide bonds could not all be directly demonstrated but adequate indirect evidence was presented. Although the same glycans were found on both rhFSH products, there were some quantitative differences in glycosylation: largely less di-antennary glycans and more tri- and tetra-antennary ones (with associated differences

in sialic acid content) in Bemfola. Increased sialic acid content has been reported to increase circulatory half-life and thus potency, but the bioactivity assays did not support this, probably because the increased sialic acid is due to increased higher antennary structures which do not affect potency. These differences are also seen at site specific level but should not adversely affect the potency or immunogenicity of the product. The product has full potency by in vivo and in vitro assays. Impurity profiles were either not detectable or very similar.

Characterisation was sufficiently extensive and in depth to reveal a good quality product comparable to the reference.

Specifications

The proposed specifications are adequate to control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use. The specification for biological activity has been tightened to conform to the European Pharmacopeia (Ph Eur) monograph.

Appropriate validation data have been submitted in support of the test procedures. Batch analyses indicate a consistent product of good quality.

Drug product

The drug product is made by diluting the drug substance to form a bulk filling solution, sterilisation by filtration and filling with differing strengths determined by fill volume of the same filling solution.

Specifications

The proposed specifications are adequate to control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product. Analytical procedures used were adequately validated and batch analyses showed a consistent product of good quality.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photo stability was not tested and so the label, PI and CMI have a warning to protect from light.

The proposed shelf life is 3 years when stored at 2 to 8°C then 3 months at < 25°C. No provision for temperature excursion during shipping was made but assurance has been given that cycling studies to address this would be initiated. The pens are for single use only so the storage conditions adequately control the in use purposes.

Biopharmaceutics

Biopharmaceutic data are not required for this product because only one route of administration is used.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. There are no outstanding issues in from a quality aspect.

The quality evaluators recommend that Bemfola and Afolia (follitropin alfa (rch)) solution for injection 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 in cartridges in a pen injector should be approved.

III. Nonclinical findings

Introduction

The nonclinical dossier contained comparative studies on primary pharmacology, pharmacokinetics and single and repeat dose toxicity. The scope of the nonclinical program meets recommendations in the relevant TGA adopted guideline.[2] EU sourced Gonal-f was used as the comparator product in the studies. The sponsor proposes that there are no differences between EU sourced Gonal-f and the Australian reference product. The acceptability of the use of the EU reference product in place of Australian sourced Gonal-f (on the grounds of identity or essential similarity) needs to be confirmed by the quality evaluator.

Pharmacology

No statistically significant, consistent or biologically meaningful differences were identified between the form of follitropin alfa in Bemfola and that in Gonal-f in in vitro assays examining:

- binding affinity for the rhFSH receptor
- kinetics of association to the rhFSH receptor, and
- activation of second messenger systems following binding to the rhFSH receptor in transfected cells.

In addition, an in vivo comparative pharmacology study was included in the quality dossier: the Steelman-Pohley bioassay (measuring ovarian responsiveness in rats) (conducted according to Ph Eur). The studies are considered to have established pharmacological comparability.

Pharmacokinetics

Pharmaco/toxicokinetic data in rats showed comparable systemic exposure and kinetics following subcutaneous (SC) and intravenous (IV) administration of the Bemfola and Gonal-f forms of follitropin alfa. Bioequivalence in humans was claimed.

Toxicology

A single dose toxicity study and a repeat dose toxicity study of 4 weeks duration were conducted in rats. These were performed according to good laboratory practice (GLP) and used the clinical route of administration; SC.

The single dose study revealed no differences in the acute toxicity of the Bemfola and Gonal-f forms of follitropin alfa. This study does not offer compelling evidence of a comparable safety profile, though, given the short duration of treatment and the limited range of end points examined. The conduct of a study of this type is not recommended in the relevant guideline.

[2] Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues [EMEA/CHMP/BMWP/42832/2005]

The repeat dose toxicity study featured comprehensive histopathological examination (in control and high dose groups). Group size was appropriate, as was dose selection, with the highest dose (300 IU/kg/day) initially yielding > 15 times the serum area under curve (AUC) in humans given 225 IU SC. However, the rat is a poor model for follitropin alfa toxicity due to the extensive development of neutralising antibodies in the species, as was seen in the sponsor's study in virtually all treated animals. The dog would have been a superior choice of species, with no anti FSH antibodies following treatment with follitropin alfa found previously. Notable findings in the sponsor's study comprised increased numbers of follicles/corpora lutea, accompanied by a shift to proestrus, consistent with direct and indirect effects of FSH activity and a slight increase in granulation tissue in the subcutis of the injection site; considered not to be toxicologically significant and consistent with a response to the injection procedure rather than the drug/formulation itself. The changes in the reproductive tissues were more prominent with Bemfola compared with the Gonal-f form of follitropin alfa. This most probably reflects a highly variable confounding by anti-drug antibodies in individual animals (although no overall difference in immunogenicity was evident), but a truly different profile cannot be excluded. Accordingly, the study is considered to only be suggestive of comparability. Given that the toxicity profile for follitropin alfa is recognised to be almost entirely attributable to the drug's primary pharmacological activity and that this aspect has been addressed in other comparability studies, the deficiencies and issues noted with regard to the repeat dose toxicity program are not considered critical.

Pregnancy classification

The sponsor has proposed Pregnancy Category D[3]. This matches the existing category for Gonal-f and is considered appropriate.

Nonclinical summary and conclusions

- The nonclinical dossier contained comparative studies on primary pharmacology, pharmacokinetics and single and repeat dose toxicity. The scope of the nonclinical program meets the relevant EU guideline.
- These studies were conducted using EU sourced Gonal-f. No nonclinical comparability study against Australia sourced Gonal-f was submitted.
- Comparability between the form of follitropin alfa in Bemfola and the form of the drug in EU sourced Gonal-f was shown in terms of pharmacological activity (FSH receptor binding affinity, receptor association rate and functional activity in cell based assays; Steelman-Pohley bioassay) and pharmacokinetics (in rats). Due to limitations, the toxicity studies, conducted by the SC route in rats, can only be said to suggest (rather than establish) comparability, but this issue is not so major as to preclude registration.
- The ability of the nonclinical studies to support comparability to Australian Gonal-f depends on the conclusion of the quality evaluator regarding the identity/comparability of Gonal-f between the EU and this country. Provided that EU sourced Gonal-f is considered to be identical or highly comparable to the Australian product, there are no nonclinical objections to the registration of Bemfola. No nonclinical data relevant to the extended indications of follitropin alfa in Australia were submitted; this aspect of the application relies on clinical data alone.

[3] Australian Category D for the use of medicines in pregnancy is defined as: '*Drugs which have caused are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*'

IV. Clinical findings

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

Clinical Rationale

Follitropin alfa is the synthetic form of follicle stimulating hormone (FSH), the pituitary glycoprotein hormone which is a regulator of reproductive function in both females and males; specifically, the initiation of ovarian follicular development and spermatogenesis. The rationale for its clinical use is activation of these biological functions in patients with a variety of fertility problems, as for the comparator product Gonal-f to which biosimilarity is claimed. Additional rationale for the development of this biosimilar product and its form of presentation is to provide a preservative free injection system which is claimed to be easier, safer and more economical to use and allows greater fine tuning of dosage.

The Bemfola product differs from Gonal-f in being presented as single dose syringes, whereas Gonal-f is presented in three pack sizes of 0.5, 0.75 and 1.5 mL, all at the same concentration as for Bemfola, 600 IU/mL but designed to deliver multiple doses of variable quantity as required. The Bemfola product has been designed to deliver all of the various doses required in the therapeutic regimens for the various indications by means of the use of single dose syringes, as opposed to the patient being instructed to vary the amount given with the multiple dose syringe employed for Gonal-f.

Guidance

TGA agreed that a proposal for extrapolation to all indications in the Australian reference product was acceptable, based on the proposed clinical program. TGA also confirmed that it was acceptable for the sponsor to propose identical indications to those approved in the EU including use with LH for submission for evaluation.

The TGA follows EMA guidance on extrapolation of indications for biosimilars.[2] The current guidelines state:

> *In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. Justification will depend on e.g., clinical experience, available literature data, or whether or not the same mechanisms of action or the same receptor(s) are involved in all indications. Possible safety issues in different subpopulations should also be addressed. In any case, the company should justify the approach taken during the development of the product and might want to contact the EMA, before starting the development, for scientific and regulatory advice.*

The updated guidelines[4] are due to be adopted by the EMA in July 2015. In Australia, it is expected that these will be adopted, following industry consultation, which is due to conclude 22 May 2015. The relevant section of these guidelines is as follows:

> *'Extrapolation of efficacy and safety from one therapeutic indication to another.*
>
> *The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be*

[4] EMEA/CHMP/BMWP/42832/2005 Rev. 1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication. Additional data are required in certain situations, such as:

1. *the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications*
2. *the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications*
3. *the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, that is; is not sensitive for differences in all relevant aspects of efficacy and safety.*

Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (for example, co-medication, type of disease, immune status). Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.'

The sponsor notes having designed the clinical development program in accordance with the relevant guideline issued by the EMA[2] and advice provided by their Committee for Medicinal Products for Human Use (CHMP). In particular, this advice allowed that no PK or PD studies need be performed on Bemfola alone and that the study comparing Bemfola with the comparator product Gonal-f could be carried out on healthy subjects rather than the target population.

Contents of the clinical dossier

The submission contained the following clinical information:

- A single clinical pharmacology study, FIN1001, comparing Bemfola with the reference follitropin alfa product Gonal-f to establish bioequivalence in terms of pharmacokinetic properties
- A single pivotal efficacy/safety study, FIN3001
- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data, nor was any included in the submissions made in various international jurisdictions. The use of the product in the specified indications is not applicable to the paediatric population.

Good clinical practice

In the pivotal efficacy study FIN3001, one of the study centres (a major UK hospital) was noted to have breached some major aspects of GCP which resulted in the CHMP of the EMA requesting a reanalysis of the study data with exclusion of the data from that centre.

Details were provided; otherwise, both this and the bioequivalence study appear to have been conducted in compliance with GCP guidelines.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission contains a single PK study, FIN1001. In accordance with the relevant EU guideline[2] and advice as noted above, this was carried out on healthy subjects. For further details please see Attachment 2.

Evaluator's conclusions on pharmacokinetics

The methodology and outcomes of study FIN1001 are compliant with the requirements, for pharmacokinetic studies, of the EMEA guideline.[2] For the purpose of this evaluation the demonstration of bioequivalence, that is biosimilarity in pharmacokinetic terms, appears adequate. Additionally, it should be emphasised that the comparator product Gonal-f, to which bioequivalence has been demonstrated, is an existing registered product.

Pharmacodynamics

Studies providing pharmacodynamic data

No specific PD study is included in the application. The clinical overview does make reference to a rise in plasma oestradiol being observed in study FIN1001 following the administration of both Bemfola and Gonal-f, and to this being an acceptable market for the PD activity of both products. The study report does not however provide any between treatment comparison of the levels achieved.

Evaluator's conclusions on pharmacodynamics

Detailed comparison of PD response between the applicant and comparator products is not required for this application on the basis of biosimilarity. However the available data confirms that the PD response to Bemfola is as expected. Further confirmation of this is inferred by the bioequivalence of the test and reference products found in the pivotal efficacy study.

Dosage selection for the pivotal studies

PK study FIN1001 and efficacy study FIN3001 are each regarded as pivotal to this submission. In each of these studies, identical doses of Bemfola and Gonal-f were given as test and reference treatments respectively.

The single dose of 225 IU selected for FIN1001 is was discussed in the study report as it is a dose commonly employed in ART protocols and is in the middle of the dose range (150 to 450 IU) employed for ovarian hyperstimulation.

In study FIN3001, a fixed standard dose of 150 IU was used and continued until ultrasound criteria for follicular development were met, up to a maximum of 16 days. As described in the evaluation of this study presented below, the EMA expressed some criticism of dose adjustment not being used. This does not represent a criticism of the selection of 150 IU as the starting dose which is quite appropriate, as is the dose of 225 IU used in the PK study.

Efficacy

Studies providing efficacy data

The application is supported by a single efficacy study, FIN3001, conducted in the context of the indication '*Use in patients undergoing superovulation for assisted reproductive technologies (ART)*' which is the second of four categories of indication listed in the application.

Evaluator's conclusions on efficacy

FSH preparations in general and the comparator product Gonal-f specifically, have well established efficacy in all the claimed indications. The bioequivalence shown in study FIN3001 is adequate evidence that this efficacy can be extended to Bemfola. The marginal evidence of increased pharmacodynamic potency does not appear, on the evidence presented, to affect its level of clinical efficacy.

In Australia, the comparator product Gonal-f is registered for use in the first, second and fourth indications being claimed for Bemfola. Conclusion of efficacy of Bemfola in these three indications can readily be made on the basis of the bioequivalence demonstrated for the second indication (use in an ART protocol) and also as all three involve the same mechanism of action, namely interaction of FSH with its cell membrane bound receptor linked to activation of adenyl cyclase and generation of cyclic AMP.

In the opinion of the evaluator, the same can be concluded for the third claimed indication (use in combination with LH in cases of severe LH and FSH deficiency), as the biological setting and mechanism of action is the same as that in the basic ART setting employed for efficacy study FIN3001, with the addition that the LH deficiency is corrected by concomitant LH therapy. In the Australian regulatory setting, such use is not registered for the comparator product Gonal-f but has been evaluated in the registration of the LH formulation Luveris, lutropin alfa (rch), efficacy of which is supported by evidence of its use in combination with 150 IU daily doses of rFSH. It is not known to the evaluator whether the FSH product used in that instance was Gonal-f.

In summary, it is concluded that Bemfola has adequate evidence of efficacy for all four proposed indications.

Safety

Studies providing safety data

The majority of data evaluable for this report are provided by pivotal efficacy study FIN3001. A small amount of data was collected in PK study FIN1001.

Patient exposure

In study FIN1001, 23 patients received a single dose of 225 IU Bemfola and 24 the same dose of Gonal-f.

Duration of exposure to 150 IU daily[5] in the Bemfola and Gonal-f treatment groups for study FIN3001 is shown in Table 13 of Attachment 2. Approximately 75% of each group was exposed to 10 days of treatment and 2.2% receive the maximum 16 day exposure.

[5] Note that a small proportion of Bemfola (11.8%) and Gonal-f (7.4%) patients underwent dose reduction for OHSS at some point in the protocol. This factor is taken into account in the calculation of the mean total dose of FSH in the two treatment groups which was 1,568.4 and 1,582.6 IU respectively.

Total treatment exposure in the study at 150 IU daily was 2,943 days for Bemfola and 1,458 days for Gonal-f.

Presentation of data in the following sections is limited to that from pivotal efficacy/safety study FIN3001. There were no safety findings of significance in the single dose PK study FIN1001 conducted in healthy subjects.

Safety issues with the potential for major regulatory impact

Ovarian hyperstimulation syndrome (OHSS) was defined as an adverse event (AE) of particular interest, and was assessed as mild, moderate or severe according to the criteria recommended by the practice committee of the American society for reproductive medicine. These criteria are well accepted and are described in Table 11 of Attachment 2. The overall incidence of treatment related AE is shown in the second and fourth columns of Table 11 of Attachment 2. Apart from serious events and events causing discontinuation, which are discussed below, the incidence and qualitative pattern of these events was similar in test and reference treatment groups. There was no evidence of a pattern of events affecting body systems except for the reproductive system (OHSS related events as described below), and the category 'general disorders and administration site conditions' which was recorded in 44.0% and 37.8% of Bemfola and Gonal-f patients respectively and the majority which is accounted for by the incidence of injection site reactions which are recognised to be common with these medications and were equally distributed between the test and reference groups.

As noted above, OHSS was an AE of special interest as it is a frequent adverse effect of ovarian stimulation with FSH/ hCG treatment as part of ART protocols and some incidence of it is an inevitable accompaniment of this type of treatment. OHSS related AE terms were reported more frequently in the Bemfola group (23.3%) by comparison with the Gonal-f patients (13.3%). A large proportion of these, 17.8% and 11.9% respectively, were reported as threatened or imminent OHSS, a situation which the investigators, who were experienced in ART management, would have been anticipating and which was to act as a signal for FSH dose reduction which was implemented in 11.8% and 7.4% of Bemfola and Gonal-f patients respectively.

Deaths and other serious adverse events

No deaths occurred in the study. Serious adverse events (SAEs) were reported in 11 (4.0%) of Bemfola and in 3 (2.2%) of Gonal-f patients. 10 of these 14 were considered due to the study drug. The remaining 3 were episodes of abdominal pain, biliary colic, ovarian haemorrhage and syncope. Of the 10 events considered to be treatment related, all but one were episodes of OHSS. In the 7 Bemfola patients so affected, 2 of these episodes were classified as severe, 4 moderate and 1 mild; amongst the Gonal-f patients there was 1 moderate and 1 severe episode. All patients experiencing SAEs, whether OHSS or otherwise, recovered. Narratives of all these events were provided in the study report and are presented in Attachment 2.

Discontinuation due to adverse events

As shown in Table 14 of Attachment 2, discontinuations due to treatment emergent adverse events (TEAEs) occurred in 11 Bemfola patients by comparison with 1 Gonal-f patient. In 7 of the Bemfola patients and the single Gonal-f patient, discontinuation was due to assessment of the presence of increased risk of severe OHSS. Two of the remaining Bemfola patients were discontinued because of the presence of moderate OHSS.

Post-marketing data

No data available at this stage.

Evaluator's conclusions on safety

The single concern raised by the safety data is the increased incidence of OHSS related adverse events experienced in the Bemfola treated patients by comparison with those treated with Gonal-f. Three possible explanations are seen for this observation. The first, as acknowledged by the FIN3001 investigators in the discussion section of their report, relates to the trial design in which only the ovarian ultrasound assessors were blind to the treatment allocation. The patients were not, as the test and reference products were obviously different (single versus multi-use) and this information was readily available to the clinic staff responsible for decisions including adverse event reporting and withdrawal of treatment. Such staff would be well used to the reference treatment and which have a greater sensitivity towards reporting events with the 'experimental' treatment and protecting patients from its effects. This could readily explain the increased incidence of withdrawals due to suspicion that OHSS was 'threatened' or 'imminent' as reported above. It less readily explains the greater number of OHSS related actual, SAEs documented amongst the narratives in the FIN3001 study report, numbering 7 amongst Bemfola patients by comparison with 2 Gonal-f patients, mostly characterised by severe symptoms requiring hospitalisation.

The second possible explanation is that Bemfola is in pharmacodynamic terms slightly more potent than Gonal-f as suggested by the oestradiol response data documented above. It is also noted that, although none of the individual differences approach clinical or statistical significance, each measured parameter of follicle development or oocyte retrieval is numerically greater for Bemfola patients than for Gonal-f patients (see Table 7 and Table 9 in Attachment 2). Adverse outcomes from such slightly greater exposure to FSH could have been facilitated by another flaw in the study design, that of using a fixed 150 IU dose for the FSH stimulation phase of the treatment protocol. This is contrary to usual practice in which follicle development is observed by daily ultrasound with, if required, daily adjustment of FSH dosage. In discussing this issue, the CHMP day 180 list of outstanding issues document, included in the submission assumes 'that the applicant has misunderstood the EMA advice' on this aspect of trial design and that the protocol should have been designed to permit such dosage adjustments so as to reveal whether or not there were differences between the test products in the rate of clinically relevant dosage requirements. The CHMP document appears, however, to recognise that the applicant's proposed risk minimisation measures, including warning of the risk of OHSS, are sufficient.

A further, third confounding factor in consideration of the difference in OHSS incidence is that there was a higher proportion of Bemfola patients with anti-Mullerian hormone (AMH) level > 24 pmol/L, a recognised marker for increased risk of OHSS. The CHMP 180 day document referred to above takes the view that the small difference in proportion of patients with this level between the two groups (4.4%) is insufficient to completely explain the difference in OHSS incidence.

The conclusion of this evaluation is that all three of these factors may have contributed to the increased incidence of OHSS observed in the pivotal efficacy/safety study. Of the three, only the second (possible increased potency) is of relevance with regard to the product's acceptability for registration. If it exists at all, the difference is of small magnitude and within the limits acceptable for biosimilarity. If the product is used in accordance with usual clinical practice and with due attention to risk minimisation measures, the safety risk in relation to OHSS is acceptable.

There are no other safety concerns of significance.

First round benefit-risk assessment

In view of the nature of this submission as a biosimilar with Gonal-f, the following benefit-risk assessment is undertaken as a comparison of the benefits and risks with those of Gonal-f as used in the proposed indications, and takes the form of a critique of the benefits and risks of Bemfola as stated in the Clinical Overview of the dossier.

First round assessment of benefits

The benefits of Bemfola proposed by the sponsor are:

- Provision of a high quality rhFSH formulation for use in reproductive technology applications, near identical to Gonal-f. This benefit is seen as being equivalent to that of Gonal-f.
- Demonstrated safety and efficacy equivalent to Gonal-f. This statement is acceptable with the exception of some concern about the risk of OHSS as discussed below, but again confers no additional benefit over the comparator product.
- Reduce financial burden to healthcare system and patients. It is recognised that TGA does not consider costs, but a number of statements of this nature appear in the sponsor's benefits and risks conclusions. The preparation is stated to be 'more affordable' and to have been developed 'in direct response to this pharmaco-economic need'. No evidence is provided in support of these statements, and once again issues regarding cost are not part of the brief for this evaluation.
- Convenience, improved compliance, improved patient safety and reduce wastage of product associated with the single use injection system. It is difficult to comment upon this without having seen more adequate descriptions of the injection devices concerned. The preservative free, single use formulation has theoretical advantages but no evidence is presented of any significant problems having occurred with the alternative multi-dose syringe (Gonal-f) formulation. The claim for reduced wastage with Bemfola is difficult to support, as the procedure for administering doses in between those contained in the five presentations of 75, 150, 225, 300 and 450 IU is to adjust the dose downwards and discard the unused portion. This does not occur with a multi-dose syringe unless it contains insufficient for the last dose required.
- The smaller dosage adjustment claimed to be possible for Bemfola (12.5 IU by comparison with 37.5 IU for Gonal-f) could be advantageous in the ovarian stimulation ART protocol, although not in the other proposed indications.

First round assessment of risks

The risks of Bemfola in the proposed usage are:

- A possible increased risk of incidence of OHSS when the product is used for ovarian hyperstimulation. The multiple potential reasons for this finding in the pivotal efficacy/safety study have been discussed above (evaluators overall conclusions on clinical safety).

First round assessment of benefit-risk balance

The benefit-risk balance of Bemfola, given the proposed usage and the comparison with the existing product Gonal-f, is neutral.

First round recommendation regarding authorisation

Provided appropriate pharmacovigilance is undertaken with regard to the issue of OHSS risk, as discussed below, and pending recommended corrections to the PI, the application is suitable for approval.

Clinical questions

There were no questions raised by the clinical evaluator. However the clinical evaluator made the following comments regarding the risk management plan (RMP) and OHSS risk:

It is particularly noted that as part of the EU RMP it is proposed that a study be conducted to evaluate the risk of OHSS. This will compare incidence of OHSS with use of Bemfola compared with the same comparator product Gonal-f as used in the pivotal efficacy/safety study for this application and will also include safety data on the use of Bemfola in patients > 40 years of age. The details of the study, which is to be conducted in the USA, are given in the Australian specific annex (ASA) of the draft RMP, as follows (Table 1).

Table 1. Details of study to compare incidence of OHSS with use of Bemfola with the comparator Gonal-f[6]

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Phase-3 investigator and assessor-blinded 1:1 randomized parallel group multi-centre study. (Category 4)	Compare efficacy and safety of 2 r-hFSH formulations (AFOLIA pen vs. Gonal-f® RFF pen) in normal ovulatory women 35 to 42 years of age undergoing In Vitro Fertilization (IVF).	Gather additional data to determine whether or not a higher risk of OHSS for Bemfola exists as compared to the reference product.	Started. Approximately 1106 patients in 25 centres in the USA.	21 April 2016 (final Clinical Study Report)

It is presumed that the outcome of this important study will be communicated to TGA as part of the pharmacovigilance for this application

With regard to routine pharmacovigilance, the Australian specific annex (ASA) to the RMP included in the data package states that the criteria to be used to verify the success of proposed risk minimisation activity will be 'no increase in the incidence of drug-related adverse events of OHSS compared to historical experience' and that the proposed review period for this will be according to routine periodic safety update report (PSUR) periodicity.

[6] Note: the anticipated completion date for the Study FIN3002 is currently (at March 2016) Q2-2017, as the study is ongoing.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan Bemfola EU-RMP Version 1.3 (dated 17 November 2014 DLP 19 September 2012) with an Australian Specific Annex Version 1 (dated December 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 2.

Table 2. Summary of ongoing safety concerns

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

Pharmacovigilance plan

Routine pharmacovigilance is proposed for all safety concerns. An additional pharmacovigilance activity is proposed as follows in Table 3.

Table 3. Additional proposed pharmacovigilance activity

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Phase-3 investigator and assessor blinded 1:1 randomized parallel group multi-centre study. (Category 4)	OHSS (important identified risk)	Compare efficacy and safety of 2 rhFSH Formulations (AFOLIA pen versus Gonal-f RFF pen) in normal Ovulatory women 35 to 42 years of age undergoing in vitro fertilization (IVF).	21 April 2016 (final Clinical Study Report)

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities are sufficient to mitigate the risks associated with Bemfola. No additional risk minimisation measures are proposed (as described in the EU-RMP).

Reconciliation of issues outlined in the RMP report

Table 4 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 4. Reconciliation of issues outlined in the RMP evaluation report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated questions and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these, include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	Noted	The evaluator has no further comment regarding this recommendation.
2. It is noted that the approved indications for	The company has revised the wording of the indications to	This is acceptable from an RMP perspective.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
the reference product, whilst similar in intent, differ between the EU and Australia. The indications proposed for this biosimilar application actually align to the approved indications in the EU, not Australia. It is also noted that the proposed indication in association with a LH preparation for the stimulation of follicular development in women with severe LH and FSH deficiency is an additional indication to those approved for the reference product in Australia. The sponsor discussed their intention to apply for this additional indication at a pre-submission meeting with the TGA. From a risk minimisation perspective, for a biosimilar it is unusual that the indications do not exactly align with those of the approved Australian reference product. This disparity has the potential to create confusion regarding the appropriate use of Bemfola as a biosimilar product in Australia.	match the Australian reference product to address the evaluator's concerns. The company however, as discussed and agreed with TGA during pre-submission, will retain the additional LH indication as proposed. The company does not believe the additional indication should cause any confusion relating to the biosimilar nature of the product. Copies of revised and clean versions of updated PI are provided.	The sponsor is advised that any PI changes made in response to the RMP evaluation are subject to final consideration by the Delegate.
3. Should the proposed EU indications remain acceptable to the Delegate the following amendments to improve clarity of the proposed indications are suggested: • The anovulatory indication should refer to 'the treatment of anovulatory infertility' rather than just 'anovulation'. • The male indication be amended to: Bemfola is indicated with	As noted in response to point 2 the sponsor has updated the proposed indications to align with the Australian reference product with respect to these indications and therefore this point is no longer applicable.	See above.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
concomitant hCG therapy for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.		
4. To avoid confusion and minimise the risk of medication error, dosage and administration advice should be appropriately categorised according to indication. Alternatively the indications could be reworded to more closely align with the Australian reference product.	As noted in response to point 2 the company has updated the proposed indications to align with the Australian reference product. Copies of revised and clean versions of updated PI are provided.	The Delegate is advised that the Dosage and Administration section of the revised draft PI does not appear to include separate advice for the additional LH/FSH deficiency indication.
5. Medication errors (including device failure) should be added as an important potential risk.	'Medication errors' is included in the RMP, in which they have not been assessed as important potential risk. No issue has been identified to warrant a change to the RMP and this is confirmed by post marketing data. A respective 'Medication errors Listing' report [of 27 May 2015] is provided.	The information provided has been considered and is acceptable from an RMP perspective. The sponsor should consider Australian post-market medication error reports when considering future inclusion of 'medication errors' as an RMP safety concern.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
6. The perceived imbalance of OHSS in the pivotal study is noted and therefore the proposed activity to compare efficacy and safety with a focus on OHSS is welcomed. It is noted that this study is being conducted with Afolia (which is presumed to be the US branded product) as the comparator to Gonal-f. The sponsor should confirm that Afolia is identical in dose, form and delivery device to that proposed for Bemfola in Australia to ensure that results of this study will be directly relatable to the Australian context. Results of this study should be appropriately communicated to the TGA when available.	The company confirms that AFOLIA is identical in dose, form and delivery device to that proposed for Bemfola in Australia. Results of this study can be directly related to the Australian context and they will be communicated to the TGA when available. The company notes the clinical evaluator's perception of imbalance of OHSS in the pivotal efficacy/safety study FIN3001 as pointed out in the clinical evaluation report that is, the apparent increased incidence of OHSS related adverse events in patients treated with Bemfola versus those treated with Gonal-f. Three aspects have been identified by the clinical evaluator as possible factors contributing to the increased incidence of OHSS with Bemfola and the company wishes to address these within this response for the TGA's review.	The sponsor's assurance regarding the pharmacovigilance activity is accepted. The acceptability of the sponsor's justification regarding the perceived imbalance of OHSS is a matter for the clinical evaluator.
7. Given the DLP for this RMP was in 2012 the sponsor is requested to update the TGA with any reports relating to medication error in clinical trials or post-marketing experience.	A copy of medication error listing report is provided as requested.	This is acceptable from an RMP perspective.
8. Section 4.1 of the ASA states 'For all eleven important identified risks, routine risk minimization measures are considered sufficient' however this would appear to refer to identified and potential risks. Also this would appear to be factually inconsistent with no routine risk minimisation activities being proposed for several safety concerns. This should be considered	The company has reviewed the ASA noting the RMP evaluator's comments and has revised to address same. Updated copy of ASA is provided.	The revised Section 4.1 Routine Risk Minimisation contains the following statement: 'Based on the safety specifications of Bemfola and the experience with the reference product Gonal-f, it is proposed to manage all safety concerns (identified risks, potential risks and important missing information) by routine

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
by the sponsor and amended accordingly.		pharmacovigilance activities'. The sponsor has erroneously referred in this section to routine pharmacovigilance instead of routine risk minimisation. Also as previously stated, not all safety concerns are managed by routine risk minimisation including the potential risk 'immunogenicity' for which no risk minimisation is proposed in Australia. The aforementioned statement should be amended to reflect the above. In addition section 4.3 of the ASA is titled 'Additional risk minimisation activities' however it would appear that a more appropriate title is 'Evaluation of risk minimisation activities'. The sponsor is advised that the ASA does not follow the current ASA format guidance, as this guidance was not available at the time of submission. However, any ASA updates should be provided in the current ASA format (guidance available at: https://www.tga.gov.au/sites/default/files/risk-management-plans-australian-specific-annex-template.docx)
9. Section 4.1 of the ASA does not contain information on the risk minimisation proposed for the items of missing information and should be amended. If no risk	The company has reviewed the ASA noting the RMP evaluator's comments and has revised to address same. Updated copy of ASA is provided.	The sponsor's amendment is noted however the evaluator is not convinced that the PI text 'Treatment with Bemfola should be initiated under the

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
minimisation is proposed for a particular item of missing information then this should be stated.		supervision of a physician experienced with the treatment of fertility disorders' can be considered specific routine risk minimisation for missing information item 'Use in female patients > 40 years of age'.
10. The ASA makes brief reference to an 'Instructions for Use' (IFU) leaflet for the safe use of Bemfola. This was unable to be located in the dossier. The IFU leaflet should be provided for review and assigned in the ASA as risk minimisation to the proposed risk of 'medication error' (see section 7).	The patient instructions for use have been included in the proposed Consumer Medicine Information. Copies of revised and clean versions are provided to allow review. The ASA has been updated to include the instructions for use as risk minimisation to the proposed risk of medication error. Updated ASA is provided.	The evaluator has no specific objection to the content of the instructions for use leaflet.
11. The sponsor should add a 'Dear Healthcare Professional Letter' (DHPL) as an additional risk minimisation activity. This letter should at least contain the following information: A statement that although Bemfola is considered biosimilar it is not interchangeable with other follitropin alfa products on an individual patient basis. • The contraindications of Bemfola • The approved indications of Bemfola • A statement that Bemfola must be administered by a health professional experienced in the use of this product. • A reference to the approved PI document for further safety information.	A draft DHPL has been prepared as outlined above and is provided as Annex 8 of this response. The DHPL activity has been included in the ASA as an additional risk minimisation activity. Updated ASA is provided.	The evaluator has considered the draft provided and has determined that a DHPL is no longer required from a risk minimisation perspective. Reference to the DHPL in the ASA can be removed.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
The DHPL activity should be assigned to the relevant safety concerns including the proposed risk of 'medication error'.		
12. In the 'Name of the medicine' section, or in another prominent place at the beginning of the PI document, the PI should include a statement that Bemfola is a biosimilar medicine and therefore should not be used interchangeably with other follitropin alfa products on an individual patient basis (or a statement to that effect subject to approval by the Delegate).	The product information has been updated as requested by the Quality delegate and the following statement has been included on the proposed PI: 'Bemfola is an approved biosimilar to the reference product Gonal-f. Comparability in safety, efficacy and quality between Bemfola and Gonal-f has been established.' As statement regarding interchangeability is included as required in the Biosimilar guidelines under the precautions section as follows: 'The comparability of Bemfola with Gonal-f has been demonstrated, with regard to particular physicochemical characteristics and efficacy and safety outcomes (see pharmacology and clinical trials). The level of comparability that has been shown supports the use of Bemfola for the listed indications. The level of comparability that has been shown is not sufficient to designate this product as a generic version of Gonal-f. Replacement of Gonal-f with Bemfola, or vice versa, should take place only under the supervision of the prescribing medical practitioner.' Copies of revised and clean versions are provided.	The evaluator has noted that the proposed PI statement regarding interchangeability has been removed in a subsequent revision of the PI. The acceptability of the PI remains subject to the determination of the Delegate.
13. Risk minimisation statements in the draft PI are generally consistent with the approved PI for the reference product.	The proposed PI has been prepared in line with the current Australian innovator PI which is as required for biosimilar products. The	The sponsor has indicated that the proposed PI is in line with the current

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
However, the indications sought in this application align with the EU indications. Therefore the draft PI has also been compared with the EU SmPC for the purposes of this evaluation. The following differences are noted to the Delegate: • The EU SmPC contains a precaution for the potential risk 'ectopic pregnancy' however this does not appear in the draft Australian PI. The sponsor should provide a justificationfor this disparity. • The EU SmPC contains a precaution regarding the potential risks 'breast cancer' and 'other reproductive cancers' however this does not appear in the draft Australian PI. The sponsor should provide a justification for this disparity.	disparity noted above between the EU SPC and proposed Australian PI is due to the fact that the current AU innovator PI does not include these precautions. The sponsor notes that these precautions are both included in the innovator products approved EU SPC. Could the TGA please comment on why the Australian Gonal-f PI does not include these important identified risks as we seek TGAs input before determining whether the proposed Bemfola PI should include precautions which are not included in the Australian reference product.	Australian innovator PI. The Delegate is advised that the EU SmPC for Bemfola contains additional precautions for the potential risk 'ectopic pregnancy', 'breast cancer' and 'other reproductive cancers' however this does not appear in the proposed PI for this product or the approved PI for the innovator product.
14. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised as appropriate in response to changes made to the PI as a result of the evaluation process.	The company notes the RMP evaluator's comments and will amend the CMI as appropriate prior to finalisation of evaluation in line with agreed amendments to the PI.	The sponsor's response is noted.

Summary of recommendations

Outstanding issues

Several minor revisions to the ASA are recommended.

The evaluator has considered the draft provided and has determined that a DHPL is no longer required from a risk minimisation perspective. Therefore reference to the DHPL in the ASA can be removed.

The ASA does not follow the current ASA format guidance, as this guidance was not available at the time of submission. However, any ASA updates should be provided in the current ASA format.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

Implement EU-RMP Version 1.3 (dated 17 November 2014 DLP 19 September 2012) and Australian Specific Annex Version 2 (dated June 2015) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

The Delegate provided the following information to the sponsor regarding the extrapolation of indications.

Background on extrapolation of indications in EU

- Bemfola has been registered in Europe via the EMA's biosimilar pathway. This involved a typical abridged application to establish biosimilarity to EU-sourced Gonal-F (the reference biological medicine).
- Gonal-f in EU has four registered indications, briefly
  - Anovulation
  - Stimulation of multifollicular development among infertile women undergoing ART
  - Stimulation of follicular development in women with severe LH/FSH deficiency
  - Stimulation of spermatogenesis (men)
- A Phase III study was conducted among infertile women undergoing ART (second indication, above).
- Because all the claimed effects (that is requested indications) for Bemfola are mediated through the same well-characterised receptor system, the EMA considered it acceptable to approve all four indications for Bemfola, in line with the registered indications for the reference biological medicine (Gonal-f).

Australian application

- The Australian dossier is based on the European dossier and contains the same studies.
- The sponsor has requested the same four indications; but, in Australia, the registered indications for Gonal-f do not include stimulation of follicular development in women with severe LH/FSH deficiency. That is, in Australia, the reference biological medicine (Gonal-f) is only registered for three of the four indications requested by the biosimilar (Bemfola).

Regulatory reasoning

- For biosimilars, Australia has adopted EMA guidelines, which state that indications of the biosimilar can be extrapolated to the indications of the reference product, given valid scientific reasoning.
- The TGA has received expert clinical advice, via the Clinical Evaluation Report, that it is scientifically justified to approve all four indications.
- Unlike some overseas jurisdictions (for example, US, EU), Australia does not have specific legislation for biosimilars. Therefore, the regulatory reasoning for the indication of 'severe LH/FSH deficiency' is no different from that of any new biological medicine. That is, the regulatory question is whether efficacy and safety have been satisfactorily established.
- Given the current expert scientific and clinical advice, the TGA is of the view that, at this point in time and pending any further advice during the remainder of the evaluation process, efficacy and safety have been satisfactorily established for the indication of 'severe LH/FSH deficiency'.

Quality

The substance is manufactured by thawing one ampoule of the working cell bank (from Hamster Ovary Cells) into serum free growth medium. The cell banking processes were thought to be satisfactory. All viral/prion safety issues, including the use of animal based excipients, have been addressed.

The amino acid sequence, truncations, glycosylations and higher order structures were identified. The disulphide bonds could not all be directly demonstrated but adequate indirect evidence was provided. Although the same glycans as Gonal-f were identified, there were some quantitative differences in glycosylation (less di-antennary glycans but more tri- and tetra-antennary glycans) and associated changes in sialic acid content. These differences were considered unlikely to affect the potency or immunogenicity of the product. Characterisation was sufficiently extensive to reveal a good quality product comparable to the reference.

The quality evaluator was satisfied the proposed specifications were adequate to control the identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product. There was adequate batch to batch consistency.

The quality evaluator recommended approval.

Nonclinical

Comparative studies on primary pharmacology, pharmacokinetics, single and repeat dose toxicity were conducted using European sourced Gonal-f[7].

Comparability between Bemfola and Gonal-f were shown in terms of:

- pharmacological activity (FSH binding affinity, receptor association rate and functional activity in cell based assays; Steelman Pohley bioassay)
- pharmacokinetics in rats

The toxicology studies can only suggest rather than establish comparability. The repeat dose toxicology study in rats featured extensive histopathological examination. The high dose group received 300 IU /kg/day, initially yielding > 15 times the serum AUC in

[7] –European sourced Gonal-f is an appropriate comparator for Bemfola in the Australian context.

humans given 225 IU. However the rat is considered to be a suboptimal model for rhFSH toxicity due to the extensive development of neutralising antibodies. Notable findings included increased number of follicles/corpora lutea, accompanied by a shift to proestrus consistent with direct and indirect effects of FSH activity. The changes in the reproductive tissues were more prominent with Bemfola than with Gonal-f.

No nonclinical data relevant to the extrapolation of indications was submitted

The nonclinical evaluator recommended approval.

Clinical

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	410
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

Pharmacokinetics

Bioequivalence Study FIN1001.

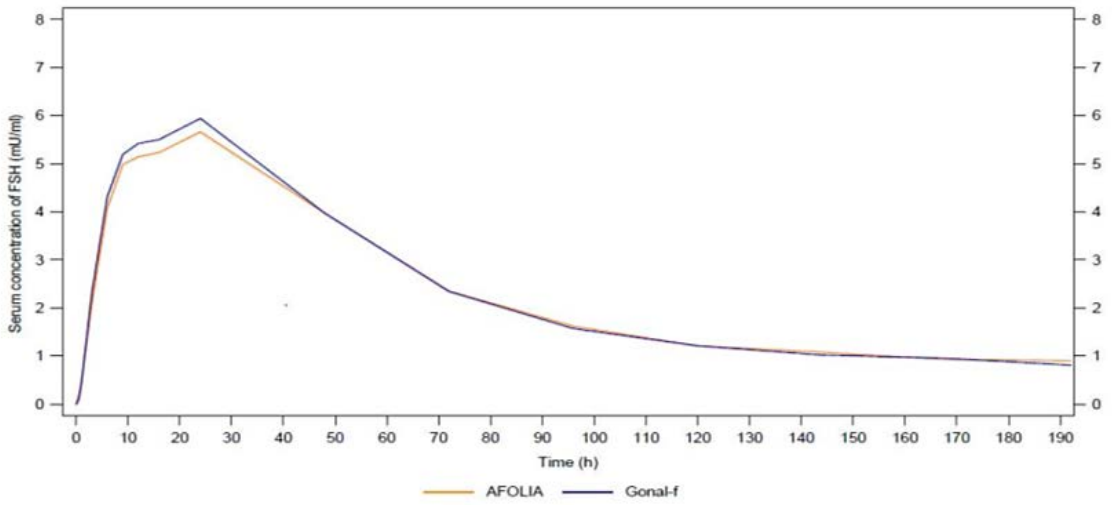
Bioequivalence of 225 IU Bemfola and 225 IU of Gonal-f were assessed in a randomised, open label two way cross over trial. Participants were 24 healthy females aged 18 to 38 years. Treatments were given 2 weeks apart. Leuprorelin was given prior to each injection to down regulate endogenous FSH. FSH was measured at 1, 3, 6, 9, 12, 16 and 24 hours then every 24 hours until 192 hours. The pre dose FSH was subtracted from subsequent measurements for correction.

The median value for T_{max} was 24 hours (range 6 to 24 hours) for each treatment, T½, 43.6 hours for Bemfola and 42.6 hours for Gonal-f. The C_{max} and AUC, falls both fell within the within the 80 to 125% CI (see Table 6 and Figure 1). FSH antibodies were measured but not identified. The EU and Swiss evaluator had some concern over the bioequivalence study as there was an 8 hour gap between testing at the time of T_{max}, which may indicate missed true C_{max}. This raises questions on the accuracy of the bioequivalence study.

Table 6. Summary of bioequivalence parameters for Bemfola versus Gonal-f

Pharmacokinetic parameter	90% Confidence Interval of parametric means		
	Point estimate (%)	Lower limit (%)	Upper limit (%)
$AUC_{(0-192)}$	98.2	84.7	113.9
C_{max}	94.7	89.2	100.6

Figure 1. 124 hour concentration time profile for Bemfola and Gonal-f



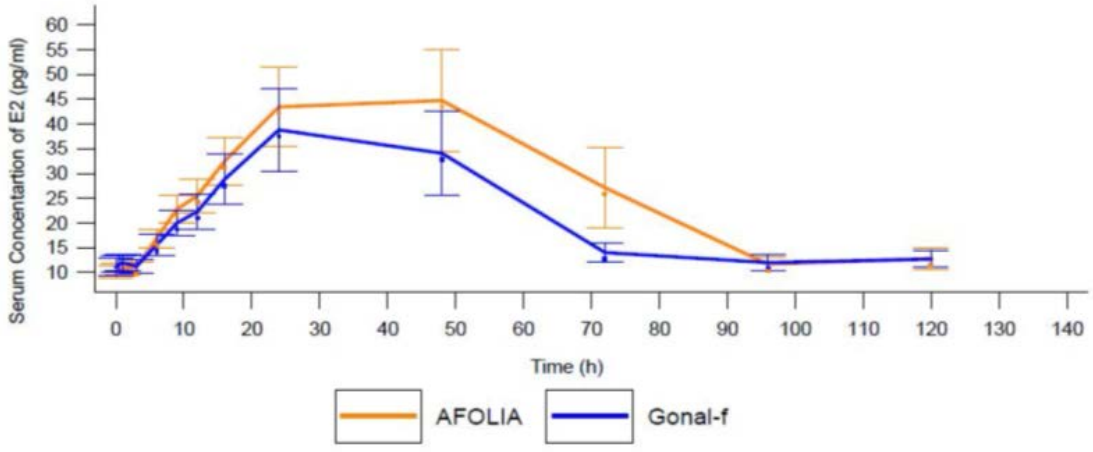
Pharmacodynamics

Limited pharmacodynamic data was available from study FIN1001 and FIN3001.

In study FIN3001, plasma oestradiol levels 8 days after FSH were similar for Bemfola and Gonal-f. However, on the day of hCG administrations, the levels were higher for Bemfola than Gonal-f (see Figure 2).

The EU evaluator considered the higher oestradiol doses after bHCG prior to HCG to be due to variability in oestradiol and FSH and not of concern.

Figure 1. Mean 120 hour profile of serum concentration of E2 in FIN3001



Efficacy

Study FIN3001; Use in patients undergoing superovulation for assisted reproductive technologies.

This was an assessor blinded, randomised, parallel group, multicentre study comparing efficacy and safety of Bemfola with Gonal-f in women undergoing assisted reproductive treatment. The primary objective was to show bioequivalence between the test and reference product in the number of oocytes retrieved in the ART protocol. Secondary objectives were to compare therapy related outcomes and safety. Blinding of patients was not possible due to the different injection devices.

Some 502 patients enrolled, 410 randomised. The duration of infertility was similar in the two groups, (3.1 years). The causes of infertility differed, a greater proportion of subjects patients randomised to Bemfola were infertile due a tubal factor or endometriosis, a greater proportion of patients randomised to Gonal-f were infertile due to a male factor. A similar proportion of subjects were considered to have 'idiopathic' infertility. More patients in the Bemfola arm withdrew due to adverse events and failure to become pregnant.

Table 7. Description of study design Study FIN3001

Patients	Women undergoing superovulation (stimulation of multi-follicular development) for assisted reproductive technologies.
Inclusion/Exclusion criteria	Inclusion – Infertile women: 20 to 38 years – Infertile due to tubal factor, mild endometriosis (ASRM—Am Soc Reproductive Medicine; stage 1 to 2), male factor, unexplained infertility – BMI: 18 to 30 kg/m^2 – Regular length of menstrual cycle: 25 to 35 days – Presumed ovulatory – Basal FSH < 10 IU/L (cycle day 2 to 5) – E2 levels < 50 pg/mL (< 0.18 nmol/L) at the day of FSH administration – Antral follicle count 10 to 25 (sum of both ovaries) Exclusion – Severe OHSS – polycystic ovaries – severe endometriosis – 2 + ART cycles without clinical pregnancy – Poor previous response to gonadotropin treatment (< 5 oocytes retrieved in a previous attempt) (These are similar to other ART studies)
Pituitary down regulation	GnRH-agonist, according to the centre's protocol (for example, triptorelin 0.1 mg/day)
Dose	Fixed dose of 150 IU was used for 6 days. This fixed dose of 150 IU was continued through day 16 unless there was a risk of imminent OHSS, as judged by the study investigator.

Patients	Women undergoing superovulation (stimulation of multi-follicular development) for assisted reproductive technologies.
hCG	Ovitelle (250 µg) if at least one follicle reach > 18 mm and 2 others reached > 16 mm
Luteal support	Micronised progesterone (Utrogestan), vaginally
Primary endpoint	Number of oocytes retrieved.
Equivalence margin	+/- 2.9 oocytes Reasoning: 3 oocytes usually results in one good quality embryo for transfer or freezing. A difference of < 3 oocytes was not considered clinically important.

Outcomes:

Primary end point:

The number of oocytes retrieved was comparable in both treatment groups, in the per protocol evaluation 11.28 in the Bemfola group versus 10.77 in the Gonal-f group. Using the Mann-Whitney U test, difference was 0.52, 95% CI -0.81 to +1.79. In the full analysis set, the number of oocytes retrieved were 11.03 in the Bemfola group compared to 10.56 in the Gonal-f group , the difference being 0.046, 95% CI -0.90 to 1.67.

These results establish equivalence of Bemfola to Gonal-f for this primary endpoint because the limits of the 95% confidence interval do not include +/- 2.9 oocytes (the pre-specified equivalence margin). The equivalence margin was justified as follows: 3 oocytes usually results in one good quality embryo for transfer or freezing, therefore, a difference of < 3 oocytes was not considered clinically important.

Secondary endpoints:

Table 8. Secondary endpoints in FIN3001; FAS population n = 369

Endpoint	Bemfola N=246	Gonal-f N=123	P value
Implantation rate	110/346 (32.6%)	66/180 (36.7%)	0.26
Clinical pregnancy rate	90 (40.2%)	55 (48.2%)	0.16
Ongoing pregnancy rate	84 (37.5%)	51 (44.7%)	0.2
Live birth rate	80 (35.7%)	50 (43.9%)	0.15
Follicles at day of hCG 12mm > 15mm > 17mm	 11.8 ± 4.73 8.3 ± 3.8 4.9 ± 3.29	 11.1 ± 4.23 7.7 ± 3.6 4.5 ± 0.4	 0.24 0.14 0.4
E2 day 8 E2 day of hCG	3958.9 ± 3669.4 8982.3 ± 4951.8	3234.0 ± 2428.1 7704.2 ± 5345.8	0.23 0.09

The EU considered the following secondary endpoints most important:

- mean number of days of rhFSH stimulation (comparable)
- number and size of follicles on stimulation Day 8 and on the day of hCG (comparable)
- % of subjects with dose reduction due to imminent OHSS (greater with Bemfola 10.6% versus 7.3%, p = 0.1737)
- Number of patients with cycle cancellation (comparable)
- Serum estradiol levels of Day 8 (comparable) and on the day of hCG (greater for Bemfola)

Safety

In study FIN3001, adverse events were more common in the Bemfola than the Gonal-f group.

Table 9. Table of adverse events from study FIN3001

Percent of Patients	AFOLIA (N = 275)				Gonal-f (N = 135)			
Experiencing	All AEs		Related		All AEs		Related	
Any TEAE	203	(73.8%)	180	(65.5%)	92	(68.1%)	75	(55.6%)
Any SAE	11	(4.0%)	8	(2.9%)	3	(2.2%)	2	(1.5%)
Any severe TEAE	17	(6.2%)	13	(4.7%)	7	(5.2%)	5	(3.7%)
Any TEAE causing discontinuation	11	(4.0%)	10	(3.6%)	1	(0.7%)	1	(0.7%)
Deaths	0	–	0	--	0	--	0	--

Rate of OHSS in this study was unusually high, generally only around 4 to 6% of a population of women undergoing IVF develop OHSS.

More OHSS events occurred in the Bemfola (23.3%) than the Gonal-f (13.3%) group. Most of these, 17.8% versus 11.9%, were threatened or imminent, initiating a dose reduction. Most cases of OHSS were mild or moderate (see Table 10).

Table 10. Severity of OHSS in FIN3001

	BEMFOLA (275)	GONAL-f (135)
Mild	40 (14.5%	12 (8.9%)
Moderate	22 (8%)	5 (3.7%)
Severe	2 (0.7%)	1 (0.7%)

Serious adverse events occurred in 4% of the Bemfola group and 2.2% of the Gonal-f patients. Of the 14 events, 10 were related to the study drug and 9 were due to OHSS. No patients had antibodies detected in the Bemfola or Gonal-f groups.

There are a number of reasons due to the design of the clinical trial that may explain the increased rate of OHSS in the Bemfola group, these include the study being open label and prone to reporting bias, differences not only in the drug but also the device, slightly higher (4.4%) levels of AMH in the Bemfola arm (a known risk factor for OHSS), difficulties in classifying OHSS, unclear definitions of severity and what is meant by the terms 'threatened' or 'imminent'. The investigators were also unable to titrate the dose of rhFSH analogue in the trial, however the effect of this would be equal in both treatment arms. It is also possible that the difference may be due to the Bemfola being more potent than Gonal-f.

OHSS was equally distributed between groups after the second treatment cycle, 6.9% versus 5.3%. The European evaluator concluded that 'overall the AE profile of Bemfola is comparable to Gonal-f'.

Clinical evaluator's recommendation

The clinical evaluator recommended approval.

Risk management plan

The sponsor identified the safety concerns described in Table 2 (above). The RMP evaluator suggested that 'medication errors' (including device failures) should be added as an important potential risk.

Routine pharmacovigilance is proposed for all safety concerns. In addition, the sponsor has initiated a Phase III investigator and assessor blinded 1:1 randomized parallel group multi-centre study comparing the efficacy and safety of Gonal-f versus Bemfola in normal ovulatory women aged 35 to 42 years undergoing IVF. One of the aims of this study is to evaluate the risk of OHSS in an older population of women.

More active surveillance may be required depending upon the results of the PBAC committee regarding substitutability. This may be possible if IVF clinics keep data in relation to outcomes.

Conditions of registration

The RMP evaluator recommended the following conditions of registration:

- Implementation of the EU-RMP Version 1.3 (dated 17 November 2014 DLP 19 September 2012) and Australian Specific Annex Version 2 (dated June 2015)
- That the sponsor provide a sample of the first 5 batch releases to the Laboratories Branch of the TGA to monitor quality
- That the sponsor advises the TGA of the results of any relevant studies as soon as they are available.

Risk-benefit analysis

Discussion

There are some concerns as to the conduct of the bioequivalence study due to inadequate number of collections around the time of T_{max}. However the study satisfactorily demonstrated bioequivalence and the clinical study satisfactorily demonstrated equivalence for the primary and most of the secondary endpoints in an appropriate and sensitive population. The chemistry, manufacturing and bioequivalence of Bemfola are adequate.

The increased oestradiol levels and increased rate of OHSS in the clinical study FIN3001 is noted. This may represent increased potency of Bemfola. The Delegate considers this unlikely to have a clinical impact on patients as treatment with rhFSH is very closely monitored with a reduction in doses if signs of impending OHSS arise. OHSS is a known risk factor of rhFSH and there are sufficient warnings in the PI and RMP.

The primary efficacy outcomes in this study were the number of oocytes achieved. The FDA has requested another study examining the live pregnancy rate as the primary outcome factor. It was noted that in study FIN3001, there was a trend to decreased clinical

pregnancy and live birth rate that was non-significant. An expert opinion of the most relevant outcome factor for this product will be requested at the ACPM meeting.

Delegate's considerations

1. Application of biosimilar, with usual issues around if it is 'bioequivalent'. The C_{max} and AUC in the bioequivalence study fell within the acceptable limits, however there was a large gap in measurements of the drugs at the time or T_{max}.
2. Extrapolation of indications: the Delegate has been advised by the clinical evaluator that extrapolation to all four indications is scientifically justified.
3. Is Bemfola more significantly potent than Gonal-f? The quality and nonclinical evaluators were satisfied that the two products were bio equivalent. However, it was also noted that there was a higher rate of ovarian follicles in the rat toxicology study with Bemfola, that in the efficacy study, at the time of hCG there were higher oestrogen levels, and overall there were more adverse events and OHSS in the Bemfola arm. Although these results may be artefactual due to small study numbers and other potential biases in the clinical trial, it raises the possibility that Bemfola may be more potent or that the device delivers a higher dose than Gonal-f.
4. A higher rate of OHSS was noted in the Bemfola arm of clinical trials. However in clinical practice, women are closely monitored for and strategies to prevent this outcome are available.
5. How does the proposed dose form match the prescribing patterns of IVF in Australia? One of the postulated advantages of this product is the single dose syringes which said to deliver doses more accurately. However, with a change in dose the patients will presumably need to go to the pharmacy to pick up new supply. Is this practical for patients? What will happen if patients have unused syringes?

Proposed action

The Delegate has no reason to say, at this time, that the application for Bemfola should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Is oocyte count an appropriate primary outcome measure for the clinical trials? This outcome factor was approved by the EU but questioned by the FDA.
2. Is the higher rate of OHSS in the efficacy study a clinical concern?
3. How often are dose adjustments made in an IVF cycle? Are single dose syringes practical in the context of Australian practice?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor agrees with the Delegate's assessment that there is no reason that the application for Bemfola should not be approved for registration.

The sponsor respectfully requests the ACPM members to consider the discussions and the materials presented. The sponsor firmly believes that this information will assist the ACPM considering the summary of issues raised by the Delegate and provides information

regarding the advice sought from the committee and will permit the committee to recommend approval for Bemfola.

Clinical

The sponsor acknowledges the clinical evaluator's first round evaluation comments that application is suitable for approval. The sponsor highlights the following clinical evaluation comments and conclusions:

- the methodology and outcomes of the pharmacokinetic study (FIN1001) were compliant with the requirements, for pharmacokinetic studies, of the EMEA guideline on biosimilarity of products containing biotechnology derived proteins
- the conclusion that bioequivalence has been demonstrated between Bemfola and Gonal-f
- the available data confirms that the pharmacodynamic response to Bemfola is as expected. Further confirmation of this is inferred by the bioequivalence of the test and reference products found in the pivotal efficacy study
- conclusion that Bemfola has demonstrated adequate evidence of efficacy for all four proposed indications
- no safety findings of significance were identified in the single dose PK study FIN1001 conducted in healthy subjects
- no evidence of immunogenicity that is no antibodies were found in either test or reference groups
- The sponsor agrees with the clinical evaluator's conclusion that all of the three identified factors may have contributed to the increased incidence of OHSS observed in the pivotal efficacy/safety study. Along with the conclusion that 'If the product is used in accordance with usual clinical practice and with due attention to risk minimisation measures, the safety risk in relation to OHSS is acceptable'. The sponsor refers ACPM to an expert opinion (provided) and also the response provided to Question 4 (sponsor's comments to Summary of Issues).

The clinical evaluator concluded that there were no other safety concerns of significance.

The sponsor disputes the clinical evaluator's comments regarding potency based on the oestradiol levels and refers the ACPM to the document 'Company's response to Delegate's summary of issues number 3' in relation to this matter.

Non-clinical

The sponsor acknowledges and agrees with the nonclinical evaluator's conclusion and recommendation that there are no nonclinical objections to the registration of Bemfola.

Quality

The sponsor acknowledges the quality evaluator's recommendation that Bemfola should be approved. Stating that the characterisation was sufficiently extensive and in depth to reveal a good quality product comparable to the reference product. The quality evaluator noted that the comparability data evaluated indicates that although there are differences in glycosylation, these are unlikely to have any significant effect on the safety or efficacy of Bemfola. The comparability package concluded that Bemfola could be considered to be biosimilar (with respect to quality aspects) to the reference product Gonal-f.

Delegate's overviews

Sponsor's comments to summary of issues

1. *Application of biosimilar, with usual issues around if it is 'bioequivalent'. The C_{max} and AUC in the bioequivalence study fell within the acceptable limits, however, there was a large gap in measurements of the drugs at the time of T_{max}.*

Sponsor's response:

In the FIN1001 study, C_{max} was defined as secondary PK parameter. The sampling scheme was optimized for determination of AUC, which was the primary PK parameter and was kept as practical as possible. The sampling scheme was also in close correlation to previously published PK studies of Gonal-f (Table 11).

Table 11. Comparison of blood collection schemes used in FIN1001 and published studies investigating the pharmacokinetics of FSH, comparison of T_{max} and C_{max}

Study	r-hFSH	Sampling scheme	T_{max} median (range)	T_{max} mean	C_{max}
Picard 2008	Pergoveris 300 IU	1,2,4,6,9,12,15,24,36,48, 60,72,96,120,144,168 h	12 h (6-24)	16.2 h	10.3 IU/L
Lugan 2005	Gonal-f freeze dried 300 IU	1,2,4,6,8,10,12,15,24, 48,72,96,120,144 h	12 h (4-48)	15.8 h	9.5 IU/L
	Liquid 300 IU	1,2,4,6,8,10,12,15,24, 48,72,96,120,144 h	15 h (6-48)	18.8 h	9.0 IU/L
Le Cotonnec 1998a	Gonal –f 150 IU	0.5,1,2,4,6,9,12,24,36, 48, 72,96,120,144 h		16 h	3.0 IU/L
Le Cotonnec 1998b	Gonal –f 150 IU	0.5,1,2,3,4,5,6,9,12, 24, 48,72,96,120,144 h	24 h (6-24)		2.7 IU/L
SmPC	Gonal –f 300 IU			15.5 h	9.8 IU/L
FIN1001	Bemfola 225 IU	0.5, 1, 3, 6, 9, 12, 16 , 24, 48, 72, 96, 120, 144, 168, 192 h	24 h (6-24)	19 h	5.7 IU/L
	Gonal-f 225 IU	0.5, 1, 3, 6, 9, 12, 16 , 24, 48, 72, 96, 120, 144, 168, 192 h	24 h (9-24)	18.8 h	6.0 IU/L

The sponsor agrees that more blood samples taken around T_{max} would allow better characterization. However, Finox believes that the comparability of C_{max} between Bemfola and Gonal-f was sufficiently demonstrated. Mean plasma concentration curves obtained for Bemfola and Gonal-f are superimposable in all 15 measured time points, there is therefore no reason to assume that a difference would have been observed with additional time points close to C_{max}.

Finally, in the performed equivalence testing the 90% confidence interval for C_{max} ranged from 0.89 to 1.01 (FIN1001 study report). The confidence intervals are well within the acceptance criteria: 0.80 to 1.25, indicating that the Bemfola and Gonal-f formulations are bioequivalent. The bioequivalence results are tabulated below (Table 12).

Table 12. Results of bioequivalence testing for AUC_{0-192} and AUC_{0-120}

	FSH AUC (0-192h)	FSH AUC (0-120h)
AUC Bemfola	424.09 mIU. h/ml	361.8 mIU. h/ml
AUC Gonal f	432.7 mIU. h/ml	369.7 mIU. h/ml
GM Ratio Bemfola/Gonal f	0.98	0.98
90% Confidence Interval	0.85 – 1.14	0.88 - 1.09
CV (%)	29.6 %	20.8 %
Source	Clinical study report	Additional analysis (in response to day 120 questions)

2. *Extrapolation of indications: the Delegate has been advised by the clinical evaluator that extrapolation to all four indications is scientifically justified.*

Sponsor's response:

The sponsor agrees with the Delegate and the Clinical Evaluator. We also refer the ACPM to the Delegates summary regarding extrapolation of indications.

3. *Is Bemfola more significantly potent than Gonal-f? The quality and nonclinical evaluators were satisfied that the two products were bio-equivalent. However, it was also noted that there was a higher rate of ovarian follicles in the rat toxicology study with Bemfola, that in the efficacy study, at the time of hCG there were higher oestrogen levels, and overall there were more adverse events and OHSS in the Bemfola arm. Although these results maybe artefactual due to small study numbers and other potential biases in the clinical trial, it raises the possibility that Bemfola may be more potent or that the device delivers a higher dose than Gonal-f.*

Sponsor's response:

Bemfola and Gonal-f were compared during the biochemical/physicochemical comparability exercise, preclinical pharmacological and toxicological evaluation and during the clinical investigation.

The extensive physicochemical comparability exercise of Bemfola and the chosen reference medicinal product Gonal-f revealed no significant differences on both, the drug substance and the drug product level. An orthogonal approach using sensitive methods were employed for this comparability exercise to enable the detection of even minor differences between the two products on all relevant protein structure levels including primary, secondary, tertiary and quaternary structures. Details were provided in the comparability exercise report submitted in course of the registration process. Minor differences in the biochemical/physicochemical comparability are expected, since the cell line and the manufacturing process including cell expansion, fermentation and downstream purification are not identical for a biosimilar product compared to its originator reference. Finally, such minor differences were detected between the biosimilar medicinal product Bemfola and Gonal-f in the overall comparability program, but they are expected to have no impact on quality, safety and efficacy.

In all preclinical and clinical studies primary endpoints to demonstrated bioequivalence were met. Results for secondary endpoints also demonstrated high similarity of the products and a statistically significant difference was not observed for any of the parameter investigated.

The three points raised by TGA that potentially could hint a higher potency of Bemfola are discussed in the response document provided.

4. *A higher rate of OHSS was noted in the Bemfola arm of clinical trials. However, in clinical practice, women are closely monitored for and strategies to prevent this outcome.*

Sponsor's response:

As the assessor states it is important to consider the situation in routine clinical practice where treatment is individualised to optimise patient care rather than in the randomised control trial where treatment is dictated by a standard study protocol to test a hypothesis such as equivalence of number of oocytes produced comparing two gonadotropins. A clear example of the relevance of this issue is the use of AMH to guide the stimulation protocol where patients with higher AMH levels are typically treated with lower doses of gonadotrophin than standard and GnRH antagonists are used rather than GnRH agonists.[8] Both of these measures reduce the occurrence of OHSS and would have been anticipated to obviate the minor difference of OHSS rates seen in the two groups of patients in the FIN3001 study.

5. *How does the proposed dose form match the prescribing patterns of IVF in Australia? One of the postulated advantages of this product is the single dose syringes which said to deliver doses more accurately. However, with a change in dose the patients presumably need to go back to the pharmacy to pick up new supply. Is this practical for patients? What will happened if patients have unused syringes?*

Sponsor's response:

Prescribing Patterns

As detailed by the expert statement (provided) the proposed Bemfola single dose pen strengths match exactly the current standard dosing practices in Australia. The single dose disposable pens readily enable incremental dosing in line with established guidelines with incremental increases of 75 IU or 150 IU being the norm. The introduction of the Bemfola single dose pens will not change the prescribing or dosing patterns of IVF physicians.

Advantages of the Single dose pens

The sponsor agrees with the TGA on potential improved accuracy and as stated by the expert in his statement '*An additional advantage with the single dose pen will be the potential reduction in dosing errors sometimes seen with multi-dose pens. It would be reasonably expected that such a reduction in patient dosing errors would translate into a reduction in reported cases of ovarian hyperstimulation or under stimulation'*.

Changes to dose/Patient practicality

The company reiterates the expert's statement that regardless of the FSH treatment prescribed to a patient, 15 to 20% in their 1st cycle will require dose adjustments, thereby requiring new prescriptions. This is not specific to Bemfola and therefore the introduction of a single dose disposable pen will not increase inconvenience or add additional requirements to further scripts in these instances of dose adjustment. The expert concludes that '*Treatment will always be tailored to individual patient needs following accurate clinical assessment and pre-treatment testing. Bemfola pens will continue to provide IVF physicians with ability to tailor an individual's dosage of rFSH, to thereby minimise product wastage and to maintain the safety of IVF for our patients*.'

Unused Syringes

Disposal of used and unused syringes and Bemfola pens is outlined within the CMI advising patients to dispose of used syringes and pens in a sharps container and/or return to your pharmacist for safe disposal. The CMI also advises patients to return any unused or

[8] La Marca A and Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. *Human Reproduction Update* 2014; 20: 124–140.

expired product to the clinic. The single dose presentation does not change the disposal method for such medicinal products.

Sponsor's comments to advice sought

1. *Is oocyte count an appropriate primary outcome measure for the clinical trials? This outcome factor was approved by the EU but questioned by the FDA.*

Sponsor response:

The primary endpoint 'number of oocytes retrieved' is in accordance with the EU guideline[9]. This endpoint has been deemed by both the EMA and sponsor as an adequate endpoint to demonstrate efficacy comparability of the biosimilar Bemfola to the reference product as it is a direct measure of the primary effect of rhFSH on the ovaries that is,. oocyte production. Pregnancy rates are not appropriate as a clinical endpoint for comparison of two rhFSH products as these are influenced by multiple confounding factors [10] hence inappropriate to compare effect of two rhFSH preparations on the ovary.

The sponsor draws the ACPM's attention to the TGAs alignment with the EU Scientific Guidelines, acknowledging that this guideline has not yet been formally adopted but noting that the TGA website states the following:

> '*The TGA closely aligns its regulatory approaches to therapeutic products with those of comparable international regulatory counterparts wherever possible.*
>
> *Technical data requirements for applications to register or vary the registration of prescription medicines in Australia are closely aligned with requirements set out in relevant European Union (EU) Guidelines and Guidelines issued by the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.'*

The company also highlights for the ACPM's information that scientific guidance meetings were conducted in 2008 with the EMA regarding the study design and it was agreed and deemed acceptable that '*number of oocytes retrieved*' was an appropriate primary endpoint of clinical comparability studies comparing efficacy between a similar and reference biological medicinal product.

The clinical evaluator concluding that the results of the pivotal efficacy study (FIN3001) showed that similarity between the test and reference group satisfied the statistical test for equivalence. Noting that bioequivalence shown within the study is adequate evidence that the well-established efficacy of the reference product can be extended to Bemfola.

2. *Is the higher rate of OHSS in the efficacy study a clinical concern?*

Sponsor response:

The sponsor refers the committee to the detailed response provided which addresses this concern along with the additional information noted by the expert within his statement regarding the overall incidence of OHSS within Australia.

3. *How often are dose adjustments made in an IVF cycle? Are single dose syringes practical in the context of Australian practice?*

Sponsor response:

As noted in the expert statement (provided) dose adjustments are made in approximately 15 to 20% of patients during their first cycle. The single dose pens strengths match the current standard dosing practices in Australia and will readily enable incremental dosing

[9] EMA/CHMP/BMWP/671292/2010 Guideline on nonclinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH).
[10] Templeton A et al. Factors that affect outcome of in-vitro fertilisation treatment *Lancet* 1996; 348: 1402–1406.

in line with established guidelines with incremental increases of 75 IU or 150 IU being the norm.

Therefore the sponsor affirms that the single dose pens are very practical in the context of the Australian fertility practice and will continue to provide the Australian IVF physicians with the ability to tailor their individual patient's dosage of rhFSH.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Bemfola solution for injection containing 75 IU / 0.125 mL, 150 IU /0.25 mL, 225 IU / 0.375 mL, 300 IU / 0.5 mL, 450 IU / 0.75 mL of follitropin alfa (rhFSh) to have an overall positive benefit–risk profile for the indications;

In adult women:

- *Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate*
- *Stimulation of multi-follicular 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 luteinizing hormone (LH) and follicle-stimulating hormone (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.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

> A statement in the Dosage and Administration section of the PI and relevant sections of the CMI to include dosage for women with severe LH and FSH deficiency which needs to be specified. This can follow the EU specifications.

Specific advice

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

1. *Is oocyte count an appropriate primary outcome measure for the clinical trials? This outcome factor was approved by the EU but questioned by the FDA.*

The ACPM advised that the use of oocyte count as a primary outcome measure is appropriate. The clinical reasoning for the equivalence margin of +/- 2.9 oocytes is that 3 oocytes usually results in one good quality embryo for transfer or freezing. A difference of < 3 oocytes was not considered clinically important.

2. Is the higher rate of OHSS in the efficacy study a clinical concern?

The ACPM advised that OHSS is clinically manageable given Australian practice. The rate of OHSS in this study was unusually high, generally only around 4 to 6% of a population of women undergoing IVF develop OHSS.

More OHSS events occurred in the Bemfola (23.3%) than the Gonal-f (13.3%) group. Most of these, 17.8% versus 11.9%, were threatened or imminent, initiating a dose reduction. Most cases of OHSS were mild or moderate. This may reflect differing reporting protocols as dose reduction solved the majority of 'threatened or imminent' cases.

3. How often are dose adjustments made in an IVF cycle? Are single dose syringes practical in the context of Australian practice?

The ACPM advised that dose adjustments are not done often and are clinically manageable. The presentation is practical for the purpose, when required.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Bemfola/ Afolia follitropin alfa (rch) solution for injection75 IU/0125 mL (5.5 µg), 150 IU/0.25 mL (11 µg), 225 IU/ 0.375 mL (16.5 µg) 300 IU/ 0.5 mL (22 µg) and 450 IU/0.75 mL (33 µg) indicated for:

In adult women:

- *Bemfola/Afolia is indicated for the treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated.*
- *Controlled ovarian hyperstimulation in women undergoing assisted reproductive Technologies*
- *Bemfola/Afolia 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 1U/L.*

In adult men:

Bemfola/Afolia is indicated with concomitant human chorionic gonadotrophin (hCG) therapy for the stimulation of spermatogenesis in gonadotrophin-deficient men in whom hCG alone is ineffective.

Specific conditions of registration applying to these goods

- The follitropin alfa (rch) EU Risk Management Plan (RMP), version 1.3, dated 17 November 2014 (data lock point (DLP) 19 September 2012) and Australian Specific Annex, version 3, dated 21August 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- Batch Release Testing; As a minimum, the first five batches (made from at least two batches of drug substance) of Bemfola/Afolia (follitropin alfa (rch)) solution for injection 75 IU/0.125 mL, 150 IU/0.25 mL, 225 IU/0375 mL, 300 IU/0.5 mL and 450 IU/0.75 mL in pre filled pen imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Attachment 1. Product Information

The PI approved for Bemfola at the time of approval is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>. The PI for Afolia is identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

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