21 February 2013
EMA/92876/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments on 'Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH)' (EMA/CHMP/BMWP/671292/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1)	Ferring Pharmaceuticals A/S
2)	EGA

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1. General comments

Stakeholder number *(See cover page)*	General comment (if any)	Outcome (if applicable)

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 153 - 165	1	Comment: primary endpoint. The endpoint “ongoing pregnancy rate at least 10 weeks after embryo transfer” should be included as co-primary endpoint along with “number of oocytes retrieved”. This will accomplish to document for the major indication of rFSH the pharmacological effect on a surrogate endpoint (“number of oocytes retrieved”) and demonstrate efficacy on a truly clinically relevant endpoint (“ongoing pregnancy rate”). Demonstration of equivalence on oocytes retrieved and non-inferiority on ongoing pregnancy rate between the test product and the reference product should be required. Given that the clinical data obtained with the test product in one indication will be extrapolated to all other indications of the reference product, the primary endpoint of the single adequately powered, randomised, parallel group clinical trial requested should adequately demonstrate both pharmacological equivalence and clinical treatment outcome non-inferiority. Proposed change (if any): <u>Lines 153-162</u> “Number of oocytes retrieved” and “ongoing pregnancy rate at least 10 weeks after embryo transfer” are the recommended primary endpoints. They serve to document both the pharmacological effect and the efficacy of the test product. With regard to the co-primary endpoint “number of oocytes retrieved”, demonstration of equivalence between the test	Not agreed. The purpose of the biosimilar development is to demonstrate similarity with the reference product, not to demonstrate patient benefit *per se*. For this purpose a sensitive ‘test model’ should be employed, which is able to detect potential product-related (not patient- or disease-related) differences between the biosimilar and the reference product. Efficacy endpoints should ideally reflect the unconfounded pharmacological action of the active ingredient. The primary function of FSH is to stimulate recruitment and growth of ovarian follicles. Therefore, “number of oocytes retrieved” is considered the most appropriate endpoint for evaluation of efficacy of a biosimilar FSH. “Ongoing pregnancy rate” is mentioned as alternative endpoint in the guideline but is usually more confounded by factors unrelated to FSH action. Due to the expected increased variability in this endpoint, the sample size is likely to be larger for demonstration of equivalent efficacy without increasing the certainty about the comparability of efficacy.

Line number(s) of the relevant text	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product and the reference product is required. The equivalence margin should be prospectively defined. It should be taken into account that over-stimulation as well as understimulation can result in cycle cancellation and a number of zero oocytes retrieved (co-primary endpoint). Thus, the data should be presented in such a way that a detailed comparison of the reasons for cancellation of ART cycles is possible. With regard to the co-primary endpoint “ongoing pregnancy rate at least 10 weeks after embryo transfer”, demonstration of non-inferiority between the test product and the reference product is required. The non-inferiority margin should be prospectively defined. <u>Lines 164-165</u> To be deleted	
	2	The EGA welcomes the opportunity to comment. The planned new guideline for the non-clinical and clinical development of r-hFSH CHMP/BMWP/671292/2010 provides a good foundation for the development of a biosimilar follicle stimulating hormone. It is refreshing to see the approach taken to avoid unnecessary pre-clinical studies in animals based on experience with similar products.	Acknowledged
Line 117	2	**Comment:** We very much welcome the reduction in additional animal investigation by removing the need for repeat dose toxicity studies and safety pharmacology studies provided that the pharmacopoeial in-vivo bioactivity assay is performed in a	Acknowledged

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		comparative way.	
190-192	2	**Comment:** Immunogenicity studies have been requested on all women included in the efficacy trial but there is no guidance on the time required after treatment both to allow immune responses to develop and for FSH to be eliminated. We kindly ask for guidance on an appropriate time range after treatment for immunogenicity studies to commence. **Proposed change**:	Agreed. Data to determine the ideal time points for measuring anti FSH antibodies are scarce. In the study by Normal RJ et al. (Human Reprod 2011) sampling was performed before treatment and 2-3 weeks after embryo transfer or cycle cancellation and up to 3 treatment cycles. We believe that antibody measurements at 3 months after the last FSH administration is appropriate and, in case of a positive result, a follow-up measurement 3 to 6 months later. Pre-treatment samples should be drawn and kept to be able to determine the baseline antibody status of patients with positive antibody results.
190-192	2	**Comment:** Immunogenicity studies have been requested also on women exposed to “more than one ART cycle, pre-approval”. It should be appropriate for the pivotal Safety and Efficacy study to comprise only one ART cycle per patient as reflective of clinical practice (daily dosing during the cycle and potential for dose titration after the first five days) and since extrapolation to other indications such as OI, which may require multiple treatment cycles, is considered appropriate	Since rFSH may be given during more than one ART cycle and intermittent exposure is known to be more immunogenic than e.g. continuous exposure, the requirement of immunogenicity data for more than one ART cycle is considered appropriate.

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		only one pivotal Safety and Efficacy study in ART may be required for registration. **Proposed change:** 1) We kindly ask to remove the requirement for pre-approval immunogenicity testing in women exposed to more than one ART cycle.	
203	2	**Comment:** The extension of indication after demonstration of efficacy and safety of the similar product is welcomed.	