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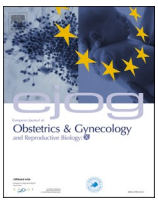

Reply to Letter to Editor from Juan-Enrique Schwarze and colleagues – Critical appraisal on "Determining the cost-effectiveness of follitropin alfa biosimilar compared to follitropin alfa originator in women undergoing fertility treatment in France"

We would like to thank Schwarze et al. for raising several issues that were considered in the development of our health economic analysis, as this provides the opportunity to further clarify our manuscript, thus we will address these points in order.

When considering the dataset to study the cost effectiveness of a follitropin alfa biosimilar (Bemfola®, Gedeon Richter Plc, Budapest, Hungary) versus the originator (Gonal-f®, Merck KGaA, Darmstadt, Germany) in France the published data set from a large French general health database in France was also considered and mentioned in our paper [1]. However, this dataset was not considered appropriate compared to the REOLA study that was based on the specialist data management systems of 17 Assisted Reproductive Technology (ART) centres throughout France [2], as the French general health database showed less granularity and lacked critical variables, the data collection period varied between originator and biosimilars, and the multiple adjustments applied to the data may have led to misleading results [3]. A dataset derived from registration trials was also considered inappropriate as patients included in such studies are not representative of those in routine clinical practice [4]. Nevertheless, a previous cost-effectiveness analysis based on the European biosimilar ART registration studies found that, from a French perspective, the cost per live birth with Gonal-f® pooled (including OHSS costs) was 2095.56 Euros vs 1718.15 Euros for biosimilars (Bemfola® and Ovaleap®, Theramex Ireland Ltd, Dublin, Ireland) [5].

Regarding the comparison of cumulative live birth (CLB) of Bemfola® versus Gonal-f®, as Schwarze comments the REOLA study had found no statistically significant difference across various starting doses [2]. There is a direct relationship between higher total dose of r-hFSH and lower chance of live birth [6] and an inverse relationship between the starting daily dose of gonadotrophins and pregnancy rates irrespective of the duration of stimulation [7]. Accordingly, it is important to ensure the groups are balanced for starting dose when comparing efficacy of two gonadotrophins, which was the approach taken in the REOLA study [2]. Similarly, when calculating the overall CLB across all starting groups it is important to balance the number of patients within each r-hFSH starting dose group as the choice of gonadotrophin is not relevant to the r-hFSH starting dose. Table 1 shows that if the groups are accordingly balanced, there is no difference in the weighted average CLB between Bemfola® (21.24 %) and Gonal-f® (20.91 %), which is consistent with the position of the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) that consider European approved biosimilars are interchangeable with their originators [8]. In contrast the large study quoted by Schwarze [1] produced results that are inconsistent with the views of these bodies and the wider literature, which may be a consequence of the methodological weaknesses previously identified [2].

As part of our base case scenario, our cost-effectiveness analysis did not include wastage and showed that even without considering drug wastage Bemfola® was more cost effective than Gonal-f®. As drug wastage is an important factor in assessment of actual drug costs, a review was performed of the published literature identifying two relevant papers, which were both included in a scenario analysis of the model suggesting an even greater cost saving with Bemfola®. Although the partial dosing feature of Gonal-f® multidose pre-filled pens allows adaptation of doses and reuse of unadministered quantities, if the residual r-hFSH amount is insufficient to administer the next full dose, a patient would have to administer two injections increasing the risk of a dosing error as well as suffering the discomfort of a double injection [9]. Even if two injections were administered, a real-world study in the UK of 4078 IVF cycles with Gonal-f® suggested FSH wastage would be less if instead the single-use Bemfola® pen was used, as typical daily wastage with Bemfola® would be lower than the terminal wastage with Gonal-f® pens [10]. In Italy, the observed wastage with Gonal-f® was even greater compared to Bemfola® than estimated in the UK [11]. In France, if the residual r-hFSH in the Gonal-f® pen is inadequate to administer that days FSH dose, usually only one injection is given and the pen with the inadequate Gonal-f® dose is discarded to reduce the risk of dosing errors [2].

Throughout the development of the model and our publication, care was taken to consider and follow relevant guidelines including those of the leading Professional Society for Health Economics and Outcomes Research (ISPOR). As explained in the paragraphs above, the REOLA study offers an exhaustive set of data specifically relevant to our research question, with an appropriate level of granularity and in case of missing data expert opinion was sought. If amendments were made especially in the context of harmonizing the patient distribution among starting doses between the two treatment arms, the intention was to reduce a bias which cannot be explained other than as an artefact of a real-world study. Whilst we agree that it is typical to use 95 % confidence intervals to display uncertainty of the result in clinical studies, it is not for cost effectiveness analysis. Instead, the impact of variance in data from each model input is assessed through one-way sensitivity analysis (OWSA). In the publication, we have used an OWSA which examines the impact of each variable in the study by varying it across a plausible range of values while holding all other variables in the analysis constant at their baseline value. This allowed the identification of the parameters which had the largest potential to impact the cost per cumulative live birth in the study. This is an especially useful technique as for many of the cost parameters taken from country databases, just one price is reported with no indication of the variance. Moreover, the probability of

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Table 1
Weighted average cumulative live birth rate of Bemfola® vs Gonal-f® balanced for equal number of patients in each r-hFSH starting dose group according to the REOLA study [2].

Starting dose	Raw number of women	Raw percentage of women (%)	Raw cumulative live-birth rate (%)	Equal weighted distribution number of women	Equal weighted distribution percentage of women (%)	Equal weighted distribution cumulative live birth-rate (%)
Bemfola®						
< 150 IU	197	8	30.46	362	16	30.46
150–224 IU	698	30	25.36	778	34	25.36
225–229 IU	527	23	21.44	441	19	21.44
≥ 300 IU	897	39	12.26	738	32	12.26
TOTAL	2319	100	19.84	2319	100	21.24
Gonal-f®						
< 150 IU	834	19	26.98	669	16	26.98
150–224 IU	1518	35	27.27	1438	34	27.27
225–229 IU	730	17	19.59	816	19	19.59
≥ 300 IU	1205	28	12.03	1364	32	12.03
TOTAL	4287	100	21.62	4287	100	20.91

Within each starting dose group, there was no statistically significant difference in cumulative live birth rates between Bemfola® and Gonal-f®.

progression through clinical stages was taken from absolute proportions of the 6606 cases in the dataset and therefore variance around the mean is not possible to calculate. Concerning the Probabilistic Sensitivity Analysis (PSA), while it is a robust method to determine the uncertainty, it is common for simple decision tree models to use the more simplistic sensitivity analysis; one-way sensitivity analysis. [5,12–15]. In addition, sufficient knowledge of the distribution for each factor may be not available to complete a robust PSA, making it of limited use.

We would like to thank again Schwarze and colleagues for their interest in our article and we are convinced that the clarifications provided in this letter, additionally to the discussion and limitations mentioned in the original article, should enable our readers to fairly interpretate the results of our analysis.

CRediT authorship contribution statement

Matthieu Lehmann: Supervision, Validation, Writing – review & editing. **Samuel George Bean:** Formal analysis, Methodology, Validation, Writing – review & editing. **Julian Jenkins:** Methodology, Validation, Writing – original draft, Writing – review & editing. **Paul Barrière:** Validation, Writing – review & editing. **Lauren Amy Boland:** Formal analysis, Methodology, Writing – review & editing. **Jean-Luc Pouly:** Validation, Writing – review & editing.

Declaration of Competing Interest

Matthieu Lehmann is an employee of Gedeon Richter Suisse, and Julian Jenkins is a scientific advisor to Gedeon Richter Suisse. Paul Barrière received fees as a consultant and/or speaker for Merck, Genevrier, Ferring, Teva, MSD and Gedeon Richter. Jean-Luc Pouly received fees as a consultant and/or speaker for Gedeon Richter. Lauren Amy Boland and Samuel George Bean are employees of Remap Consulting who was commissioned to perform the initial analysis.

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