## *RECOMBINANT (R-HFSH) BIOSIMILAR PREPARATIONS*

Biosimilars of FSH (follitropin alfa) are highly similar versions of the original drug used to stimulate the the ovaries. Regulatory bodies such as the EMA, FDA, MHRA and TGA* base the authorisation of the biosimilars on demonstrated comparability at the level of pharmaco-chemical, pharmaco-kinetic, pharmaco-dynamic, drug safety and immunogenicity data. According to the regulatory bodies, clinical equivalence is inferred from these comparability data (EMA Biosimilar Medicines Overview), especially if the mechanism of action the drug is well-known (Bielsky et al., 2020).

### Evidence

A systematic review and meta-analysis, including 8 RCTs, compared recombinant follitropin alfa biosimilar preparations to the reference product (Kiose et al., 2025). No difference was observed in the number of oocytes retrieved at the oocyte retrieval. A significantly lower live birth rate after a fresh embryo transfer was noted using the biosimilars of follitropin alfa compared to the originator in women undergoing ovarian stimulation (RR 0.83, 95% CI 0.72-0.96; 6 RCTs, n=2335). Sensitivity analysis, excluding two RCTs due to high risk of bias, did not alter the effect direction or effect size (RR 0.83, 95% CI 0.71–0.97; 4 RCTs, n=1881), neither did limiting the analysis to only EMA approved biosimilar products (RR 0.82, 95% CI 0.70-0.96, 3 RCTs, n=1771). Similarly, ongoing pregnancy rates (RR 0.81, 95% CI 0.70-0.94, 7 RCTs, n=1886) were lower in the biosimilars group. No significant difference was observed in OHSS rates (RR 1.17, 95% CI 0.90-1.52; 8 RCTs, n=2986) between the two groups. Data on cumulative outcomes from fresh and frozen embryo transfers are currently not present, nor a clear mechanism of action leading to the differences.

### Conclusion

In spite of the findings described, uncertainty with regards to relevant differences between r-hFSH alpha biosimilar preparations and the reference product has been noted by the GDG. On the basis of this, the GDG has decided to refrain from formulating a formal recommendation.

### Justification

The GDG acknowledges that biosimilars of recombinant follicle-stimulating hormone (rFSH) have received regulatory approval from the EMA based on demonstration of equivalence in key pharmacodynamic endpoints, such as the number of oocytes retrieved, and are therefore authorized for use under the same conditions as the originator product. However, the most clinically relevant outcomes in assisted reproduction—live birth and clinical pregnancy rates—have not been consistently demonstrated to be equivalent. Recent meta-analyses of randomized controlled trials indicate that biosimilars may be associated with lower live birth and pregnancy rates compared to the originator, although the certainty of this evidence is moderate to low and methodological concerns persist (de Mora and Howles, 2022, de Mora and Howles, 2023, de Mora et al., 2025, Santulli et al., 2025, Venetis et al., 2025, Venetis and Mol, 2023) .

### Research recommendation

Further well-powered, high-quality RCTs and real-world-evidence studies using rigorous adjustment for confounding factors are needed to further demonstrate the comparative effectiveness and safety of r-hFSH biosimilars, as well as the mechanism explaining the differences, across diverse patient subgroups, and using strong outcome measures such as cumulative live birth rate.

Draft for review

* EMA: European Medicines Agency, FDA: Food and Drug Administration (USA); MHRA: Medicines and Healthcare products Regulatory Agency (UK); TGA: Therapeutic Goods Administration (Australia)

*References*

de Mora F, Howles CM. Overlapping biosimilar and originator follitropin alfa preparations: How much closer can they get? *Drug Discov Today* 2022;27: 2071-2075.
de Mora F, Howles CM. Randomized controlled trials do not always fit the purpose: A science-based response to Venetis and Mol's editorial on biosimilars of follitropin alfa. *Drug Discov Today* 2023;28: 103524.
de Mora F, Howles CM, Trew G. Follitropin alfa biosimilars: unfounded doubts on the road to reproductive care. *Human reproduction (Oxford, England)* 2025;40: 1789-1790.
Kiose KI, Storr A, Kolibianakis EM, Mol BW, Venetis CA. Biosimilars versus the originator of follitropin alfa for ovarian stimulation in ART: a systematic review and meta-analysis. *Human reproduction (Oxford, England)* 2025;40: 343-359.
Santulli P, Brandão P, D'Amato G, Grynberg M, Hamamah S, Luco MI, Marci R, Salle B, Freour T. Methodological concerns and clinical relevance: a critical appraisal of the meta-analysis on biosimilars versus originator follitropin alfa in ART. *Human reproduction (Oxford, England)* 2025;40: 1791-1792.
Venetis CA, Kiose KI, Storr A, Mol BW, Kolibianakis EM. Reply: Biosimilars versus the originator of follitropin alfa in ART: eyes wide shut? *Human reproduction (Oxford, England)* 2025;40: 1793-1796.
Venetis CA, Mol BW. Biosimilars versus the originator of follitropin alfa: Randomized controlled trials are still the best way to evaluate their comparative effectiveness in assisted reproduction. *Drug Discov Today* 2023;28: 103425.

Draft for review