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ORIGINAL RESEARCH

A cost-effectiveness evaluation of the originator follitropin alpha compared to the biosimilars for assisted reproduction in Germany

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Background and objectives: Demand for assisted reproduction technology (ART) in Germany is high, with 100,844 treatment cycles during 2016. Many ART procedures involve ovarian stimulation with follicle stimulating hormone (FSH). Recently, biosimilar FSH products have become available. The objective of this study was to evaluate the cost-effectiveness of the recombinant FSH Gonal-f® (Originator) in comparison to biosimilar follitropin alfa, Bemfola® (Biosimilar 1) and Ovaleap® (Biosimilar 2), from a German payer perspective in terms of cost per live birth.

Methods: A decision tree model was developed, based on one cycle of assisted reproduction, to compare the original product to biosimilars. Clinical inputs, including live birth rates and adverse event rates were obtained from published randomized trials. Cost inputs were obtained from publicly available German sources. Clinical inputs, model structure and methodology were based on previous publications and validated by a clinical expert.

Results: Results indicated that the live birth rate is higher for the Originator compared to Biosimilar 1 (40.7% vs 32.1% respectively), and Biosimilar 2 (32.2% vs 26.8%). The average cost per live birth for women treated with the Originator was estimated to be lower than those who were treated with biosimilars: Originator vs Biosimilar 1 (€10,510 vs €12,192), Originator vs Biosimilar 2 (€12,590 vs €13,606). The analysis also found that the Originator is associated with an incremental cost-effectiveness of €4,168 and €7,540 per additional live birth versus Biosimilar 1 and Biosimilar 2 respectively. Sensitivity analysis indicated probabilities of pregnancy, embryo transfer and live birth, were key drivers of model costs. Scenario analysis confirmed the robustness of the model outcomes.

Conclusion: This study suggests that treatment with the Originator could result in a lower cost per live birth in comparison to biosimilars. Further analysis using real-world data, when available, is recommended to validate the results of the present study.

Keywords: reproductive techniques, follitropin alfa, cost per live birth

Introduction

Demand for assisted reproductive technology (ART) in Germany is high, with a reported 100,844 treatment cycles during 2016.[1] This included 15,476 in-vitro fertilization (IVF) cycles, 50,111 intracytoplasmic sperm injection (ICSI) cycles and 24,842 cryo-transfer cycles.[1] With restrictive public financing and a high cost burden, there is pressure to limit the costs of fertility treatments, whilst maximizing success rates.[2,3]

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IVF and ICSI procedures both involve controlled ovarian stimulation (COS) with follicle stimulating hormone (FSH) injections.[4] This strategy of stimulating ovaries, with gonadotropins is well established with the first generation of gonadotropins, produced from the urine of menopausal women, on the market since the 1970's.[5] Gonal-f®, (Merck , Darmstadt, Germany; the Originator) is a fourth-generation gonadotropin, a recombinant FSH (rFSH), which first entered the market in 1995, that has a well-established portfolio of published efficacy, safety and clinical real-world post-marketing evidence and experience.[6–13]

Follitropin alfa biosimilars (Bemfola®, Gedeon Richter UK Ltd, London, UK [Biosimilar 1]; and Ovaleap®; CVC Capital Partners, Luxembourg [Biosimilar 2]) have recently entered the market, with the sole purpose of producing cost savings over the originator product. Each biosimilar is supported by a single study powered to test non-inferiority in the number of oocytes collected compared with the originator product.[14,15] Although gonadotropins are prescribed to stimulate the ovaries to increase egg production, the primary goal of administration is to achieve a live birth.[16] By definition, a biosimilar medicine should be biologically similar to the reference medicine, with comparable safety and efficacy.[17] However, differences in the batch-to-batch consistency between the products could lead to differences in effectiveness during stimulation cycles. For the Originator product, there is very low batch-to-batch variability (<2%),[18] which enables precise dosing.[19] Indeed, the batch-to-batch variability for glycosylation profile and specific activity was assessed for >200 batches before the filled by mass and relative specific activity parameters were considered by the European Medicines Agency (EMA). However, the filled-by-mass calibration for biosimilars was assessed on only two pivotal clinical batches. Furthermore, a recent study comparing in-vivo biological activity and glycosylation between the Originator and Biosimilar 1 found differences in the glycan profile of the biosimilar, which may be associated with differences in receptor activation and biological activity (Biosimilar 1 potency was 14,522 IU/mg and the mean specific activity was 105.6% of the nominal value; the Originator potency was 13,159 IU/mg and the mean specific activity was 97.3% of the nominal value [p=0.0048]).[20] Although this was within the range stated in the product label, it clearly shows a difference between the two products.

Furthermore, while authorization of a biosimilar is based on similarity to the originator product, this does not necessarily imply that biosimilars are interchangeable, rather their use is regulated according to individual countries and the treating physician.[21] Consequently, there is a pressing need to ensure that the choice of a biosimilar is fully informed, including any comparisons of cost-effectiveness. As there are insufficient real-world data on which to base a suitably powered cost-effectiveness analysis on follitropin alfa biosimilars, the currently available multicenter randomized controlled trials that were conducted in broadly similar populations provide the most reliable data on pregnancy and live birth outcomes to date.[14,15] As these trials were designed to enable marketing approval, we can assume that they reflect clinical use and, consequently, the data reported are robust enough to be used as the basis of the cost-effectiveness analysis. While this may not be standard methodology, there are precedents for this approach published in the literature.[22–24]

As the impact of biosimilars on costs per assisted reproduction treatment course and clinically meaningful outcomes has yet to be investigated in Germany, the objective of this study was to develop a cost-effectiveness model to investigate the cost and clinical outcomes of the Originator in comparison to rFSH biosimilars from a German payer perspective, in terms of the cost per live birth.

Methods

Studies by Rettenbacher et al and Strowitzki et al, the two randomised controlled trials used to demonstrate similar efficacy and safety to the originator follitropin-alpha as part of the marketing authorization application of the biosimilar to the EMA, were chosen to inform clinical inputs for the comparison versus the Originator.[14,15] These trials were chosen as no other studies for the Originator versus Biosimilar 1 or Biosimilar 2 where available at time of the analysis. These studies and the model we have employed have been used in several other estimates of the cost-effectiveness of follitropin alfa.[22–24]

Model structure

A decision tree model was developed in Microsoft Excel 2013. The model was based on one cycle of assisted reproduction for the comparison of the Originator to both biosimilars (Figure 1). Key stages of one fresh cycle of assisted reproduction were defined in terms of eight discrete states (oocyte retrieval, no oocyte retrieval, embryo transfer, no embryo transfer, pregnancy, no pregnancy, live birth, and miscarriage). During the cycle, patients may also experience an adverse event from ovarian stimulation: ovarian hyper-stimulation syndrome

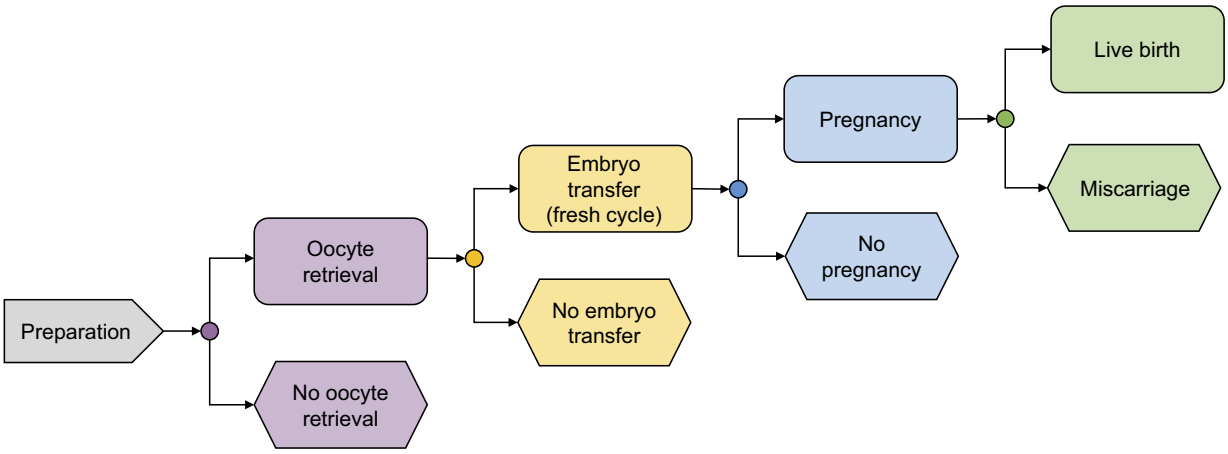

Figure 1 Cost-effectiveness model decision-tree structure.

(OHSS). The model was composed of four different pathway endpoints (no oocyte retrieval, no embryo transfer, live birth, no live birth).

Each of the model states was associated with a separate cost. The proportion of patients at the end of each treatment pathway, multiplied by the relevant cost and resource use, and the total sum of all pathways was used to generate overall costs for each intervention.

Model outputs included live birth rates, total costs, cost per live birth, and incremental cost-effectiveness ratio (ICER), estimated as the difference in costs divided by the difference in live birth rates of two comparators.

Clinical inputs

The probability of moving from one model state to another was based on the biosimilar clinical trial data (Rettenbacher et al[14] and Strowitzki et al[15]). The primary objective of both Rettenbacher et al[14] and Strowitzki et al[15] was to demonstrate non-inferiority to the Originator, in terms of the number of oocytes retrieved. The rate of live birth was a secondary outcome in both trials.

The proportion of patients moving from oocyte retrieval to embryo transfer, etc were conditional on the success of the previous stage and, as such, the final birth rate, was conditional upon those who achieved an "ongoing pregnancy" (Table 1). "Ongoing pregnancy" rates[14,15] were extracted from trial data preferentially over "clinical pregnancy" rates.

Mild–moderate and severe OHSS rates were obtained from Rettenbacher et al[14] and Strowitzki et al[15] (Table 2). It was assumed that cycle discontinuation/interruption due to OHSS was captured in the "no oocyte retrieval" or "no embryo transfer" states.

A comparison between the Originator and both biosimilars together ("pooled biosimilars") was also conducted. A simple methodology was employed to estimate the pooled efficacy data, whereby the numbers of patients in the Originator, Biosimilar 1 and Biosimilar 2 arms of the Rettenbacher et al[14] and Strowitzki et al[15] trials, were combined to create a "pooled biosimilars" arm and pooled Originator arm. This enabled a combined analysis of clinical outcomes for the Originator versus both Biosimilar 1 and Biosimilar 2 (Table 1).

Dosing

Dosing was determined according to three levels of response to ovarian stimulation; normal, hyper and poor responders (Table 3). It was assumed that women who were "normal responders", defined as >9 and ≤15 oocytes, received the mean dose of each intervention; "hyper-responders", defined as >15 oocytes, received the lower standard deviation of the mean dose; and "poor responders", defined as <4 oocytes received the upper standard deviation of the mean dose, as reported in each publication.[25,26] For the pooled biosimilars analysis, dosing for Biosimilar 2, as reported in Strowitzki et al, was used as a proxy for "pooled biosimilars".[15] It was also assumed that the duration of stimulation (number of days) was equal to the mean duration of stimulation, for response type. The proportions for normal, hyper- and poor responders (73%, 6% and 21%, respectively) were used to estimate a weighted mean dose for each treatment.[27]

Cost inputs

Cost inputs were categorized into assisted reproduction and birth costs, adverse event costs and drug costs.

Table 1 Transition probabilities

Transition probability of oocyte retrieval					
Analysis	**Intervention**	**Total number of women in each arm**	**Number of women with oocyte retrieval**	**Probability of oocyte retrieval**	**Reference**
Originator vs Biosimilar 1	Originator	123	123	100%	Rettenbacher et al 2015[14]
	Biosimilar 1	249	249	100%	
Originator vs Biosimilar 2	Originator	146	143	97.9%	Strowitzki et al 2016[15]
	Biosimilar 2	153	152	99.3%	
Originator vs pooled biosimilars	Originator	269	266	98.9%	Rettenbacher et al and Strowitzki et al[14,15]
	Pooled biosimilars	402	401	99.8%	
Transition probability of embryo transfer					
Analysis	**Intervention**	**Number of women with successful oocyte retrieval**	**Number of women that had embryo transfer**	**Probability of embryo transfer conditional upon oocyte retrieval**	**Reference**
Originator vs Biosimilar 1	Originator	123	114	92.7%	Rettenbacher et al 2015[14]
	Biosimilar 1	249	224	90.0%	
Originator vs Biosimilar 2	Originator	143	134	93.7%	Strowitzki et al 2016[15]
	Biosimilar 2	152	141	92.8%	
Originator vs pooled biosimilars	Originator	266	248	93.2%	Rettenbacher et al and Strowitzki et al[14,15]
	Pooled biosimilars	401	365	91.0%	
Transition probability of pregnancy					
Analysis	**Intervention**	**Number of women with embryo transfer**	**Number of pregnant women**	**Probability of pregnancy conditional upon embryo transfer**	**Reference**
Originator vs Biosimilar 1	Originator	114	51	44.7%	Rettenbacher et al 2015[14]
	Biosimilar 1	224	84	37.5%	
Originator vs Biosimilar 2	Originator	134	49	36.6%	Strowitzki et al 2016[15]
	Biosimilar 2	141	42	29.8%	
Originator vs pooled biosimilars	Originator	248	100	40.3%	Rettenbacher et al and Strowitzki et al[14,15]
	Pooled biosimilars	365	126	34.5%	
Transition probability of live birth					
Analysis	**Intervention**	**Number of pregnant women**	**Number of women with a live birth**	**Probability of live birth conditional upon pregnancy**	**Reference**
Originator vs Biosimilar 1	Originator	51	50	98.0%	Rettenbacher et al 2015[14]
	Biosimilar 1	84	80	95.2%	

(*Continued*)

Table 1 (Continued).

Analysis	Intervention	Number of pregnant women	Number of women with a live birth	Probability of live birth conditional upon pregnancy	Reference
Originator vs Biosimilar 2	Originator	49	47	95.9%	Strowitzki et al 2016[15]
	Biosimilar 2	42	41	97.6%	
Originator vs pooled biosimilars	Originator	100	97	97.0%	Rettenbacher et al and Strowitzki et al[14,15]
	Pooled biosimilars	126	121	96.0%	

Notes: Biosimilar 1: Bemfola®, Gedeon Richter UK Ltd, London, UK. Biosimilar 2: Ovaleap®; CVC Capital Partners, Luxembourg.

Table 2 Mild–moderate and severe OHSS event rates

Analysis	Intervention	Mild–moderate OHSS			Severe OHSS			Reference
		n	N	%	n	N	%	
Originator vs Biosimilar 1	Originator	15	123	12.2	1	123	0.8	Rettenbacher et al 2015[14]
	Biosimilar 1	53	249	21.3	2	249	0.8	
Originator vs Biosimilar 2	Originator	3	146	2.1	1	146	0.7	Strowitzki et al 2016[15]
	Biosimilar 2	6	153	3.9	1	153	0.7	
Originator vs pooled biosimilars	Originator	18	269	6.7	2	269	0.7	Rettenbacher et al and Strowitzki et al[14,15]
	Pooled biosimilars	59	402	14.7	3	402	0.7	

Notes: Biosimilar 1: Bemfola®, Gedeon Richter UK Ltd, London, UK. Biosimilar 2: Ovaleap®; CVC Capital Partners, Luxembourg.

Table 3 Daily dosing inputs for normal, hyper- and poor responders

Analysis	Intervention	Mean normal responder dose	Mean hyper-responder dose	Mean poor-responder dose	Duration (days)	Reference
Originator vs Biosimilar 1	Originator	147 IU	122 IU	171 IU	11	Rettenbacher et al 2015[14]
	Biosimilar 1	147 IU	119 IU	174 IU	11	
Originator vs Biosimilar 2	Originator	166 IU	116 IU	216 IU	10	Strowitzki et al 2016[15,a]
	Biosimilar 2	165 IU	112 IU	218 IU	9	

Notes: Biosimilar 1: Bemfola®, Gedeon Richter UK Ltd, London, UK. Biosimilar 2: Ovaleap®; CVC Capital Partners, Luxembourg. [a]For the pooled biosimilars analysis, dosing for each arm was assumed to equal that from Strowitzki et al 2016.

Assisted reproduction and birth costs

Individual components and total costs estimated for each stage of the treatment cycle (preparation, oocyte retrieval, no oocyte retrieval, embryo transfer etc) are outlined in Table 4. In some instances, where the cost was dependent on the type of ART carried out (IVF or ICSI), the cost was weighted by the proportion of IVF (24%) and ICSI (76%) procedures carried out, according to the German IVF register 2016.[1]

It was assumed that the cost of "preparation" for an ART cycle was comprised of the cost of general treatment, the treatment plan and serological tests, as outlined in the Kassenärztliche Bundesvereinigung (KBV) (Table 4).[28] Whilst patients also receive medications during preparation for ART, prior to the administration of gonadotropins for COS, it was assumed that there would be no differences in treatment between the

Table 4 Unit cost: assisted reproduction and birth

Cost component	Cost (EUR €)	Reference
Preparation		
General treatment, treatment plan	22.59	Kassenärztliche Bundesvereinigung (KBV)[13]
Serological tests (HIV, Hb_c, HCV, Hb_s)	50.60	
Total	73.19	Calculated
Oocyte retrieval		
ICSI consultation for couples	8.63	Kassenärztliche Bundesvereinigung (KBV)[13]
Outpatient surgery visit, including post-procedure surveillance	101.10	Kassenärztliche Bundesvereinigung (KBV)[13]
Preparation of sperm and processing medium	42.40	Kassenärztliche Bundesvereinigung (KBV), Federal Association of Centres for Reproductive Medicine[11,13]
Ovum pick-up and biopsy needle	114.72	Kassenärztliche Bundesvereinigung (KBV), Federal Association of Centres for Reproductive Medicine[13,28]
Anesthesia, including monitoring	119.17	Kassenärztliche Bundesvereinigung (KBV)[13]
Total	463.95	Calculated
No oocyte retrieval		
Discontinuation before ovum pickup	212.13	Kassenärztliche Bundesvereinigung (KBV)[13]
ICSI consultation for couples	8.63	Kassenärztliche Bundesvereinigung (KBV)[13]
Anesthesia, including monitoring	119.17	Kassenärztliche Bundesvereinigung (KBV)[13]
Total	417.86	Calculated
Embryo transfer		
ICSI and embryo transfer	1,316.66	Kassenärztliche Bundesvereinigung (KBV)[13]
IVF and embryo transfer	932.60	
Total (weighted)	1,224.33	Calculated (based on proportion of IVF [24%]/ICSI [76%])
No embryo transfer		
ICSI, no embryo transfer	1,179.11	Kassenärztliche Bundesvereinigung (KBV)[13]
IVF, no embryo transfer	932.60	
Total (weighted)	1,119.85	Calculated (based on proportion of IVF [24%]/ICSI [76%])
Pregnancy/no pregnancy		
Blood test for beta human chorionic gonadotropin (pregnancy test)	6.10	Kassenärztliche Bundesvereinigung (KBV)[13]
Live birth		
Live birth	3,686.12	Fallpauschalen-Katalog: Weighted average of vaginal and C-section births,[14] Statistisches Bundesamt[30]
Miscarriage		
Miscarriage	302.90	Kassenärztliche Bundesvereinigung (KBV)[13]

Abbreviations: HIV, human immunodeficiency virus; Hb_c, hepatitis B_c antigens; HCV, hepatitis C virus; Hb_s, hepatitis B surface antigen; ICER, incremental cost-effectiveness ratio; ICSI, intracytoplasmic sperm injection; IVF, in-vitro fertilization.

Originator and biosimilars and, therefore, these costs were excluded from the analysis.

The cost of a live birth was assumed to be composed of the weighted average of vaginal and C-section births from the Fallpauschalen-Katalog, based on a reported proportion of 30.5% C-section births in Germany in 2016 (Table 4).[29,30]

Table 5 Unit cost: mild to moderate and severe OHSS

Cost component	Cost (EUR €)	Reference
Mild–moderate OHSS		
Hematology test (x2)	0.25	Kassenärztliche Bundesvereinigung (KBV)[13]
Hematocrit test (x2)	0.25	
Creatinine test (x2)	8.45	
Electrolyte test (x2)	1.00	
Hepatic test (x2)	10.25	
Total	20.20	Calculated
Severe OHSS		
Poisoning/toxic effects of drugs	1,900.75	GKV- Spitzenverband, DRG X62Z[36]

Abbreviation: OHSS, ovarian hyper-stimulation syndrome.

The cost of a miscarriage was assumed to equal the cost for dilation and curettage, including anesthesia (Table 4).[13]

Adverse event costs

The cost components of mild–moderate and severe OHSS are outlined in Table 5. To mirror real-world practice in Germany, the base case analysis did not include the cost of vitrification or cryopreservation (egg-freezing) as part of the cost of severe OHSS, which can lead to cycle interruption. This is due to complexities in reimbursement of this procedure in Germany, which is normally self-funded.[31]

Drug costs

The German cost of each strength of each intervention were obtained from Lauer-Fischer GmbH WEBAPO® InfoSystem, using the ATC-group G03GA class.[6] In Germany, the cost of the Originator preparations is higher compared to the biosimilar preparations. The pharmacy-selling price (including value added tax) was used for all gonadotropins (Table 6). The final cost of each treatment was calculated as a weighted cost of the proportion of normal, hyper- and poor responders and the cost of the combination of vials required to achieve the normal, poor- or hyper responder dose (Table 7). The final total weighted

Table 6 Unit cost: gonadotropin vial

Vial strength (FSH IU)	Originator (EUR €)	Biosimilar 1 (EUR €)	Biosimilar 2 (EUR €)	Reference
FSH 900 IU	537.26[a]	-	430.01[a]	® InfoSystem[29] Lauer-Fischer GmbH WEBAPO
FSH 450 IU	274.13[a]	227.64	220.00[a]	
FSH 300 IU	186.41[a]	151.78	150.00[a]	
FSH 225 IU	-	116.50	-	
FSH 150 IU	-	78.83	-	
FSH 75 IU	53.69	42.95	-	

Notes: [a]Multi-dose vial. Biosimilar 1: Bemfola®, Gedeon Richter UK Ltd, London, UK. Biosimilar 2: Ovaleap®; CVC Capital Partners, Luxembourg.
Abbreviation: FSH, follicle stimulating hormone.

Table 7 Gonadotropin costs for normal, poor and hyper-responders for one fresh cycle based on daily dosing

Comparison	Normal responder cost (EUR €)	Poor responder cost (EUR €)	Hyper-responder cost (EUR €)	Weighted cost (EUR €)[a]	Δ Cost Originator vs biosimilar (EUR €)
Originator vs Biosimilar 1[14]					
Originator	972.46	1,128.21	811.39	994.19	42.12
Biosimilar 1	867.13	1,281.50	867.13	952.08	
Originator vs Biosimilar 2[15,b]					
Originator	1,074.52	1,348.65	811.39	1,114.06	222.23
Biosimilar 2	860.02	1,080.02	650.01	891.83	

Notes: Biosimilar 1: Bemfola®, Gedeon Richter UK Ltd, London, UK. Biosimilar 2: Ovaleap®; CVC Capital Partners, Luxembourg. [a]Weighted by the proportion of different responder types; [b]For the pooled biosimilar comparison, dosing for each arm and costs were assumed to equal those reported in the Biosimilar 2 trial.[15]

cost for the Originator and Biosimilar 1 was €994.19 and €952.08 respectively. The final average total weighted cost for Originator and Biosimilar 2 was €1,114.06 and €891.83 respectively. For the pooled biosimilars analysis, dosing and unit costs were conservatively assumed to equal dosing and costs for Biosimilar 2, as this was the lowest cost biosimilar.

Sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted for all clinical and cost parameters by investigating the plausible upper and lower values from the reported outcomes. OWSA of cost input parameters was conducted by investigating outcomes around the upper and lower 25% variance of input parameters. Scenario analyses on model outcomes were also conducted by changing the proportions of responder-types to 100% normal responders, 100% hyper-responders and 100% poor responders.

Clinical expert validation

Clinical and cost inputs, model structure and methodology were validated by a German clinical expert with extensive experience in assisted reproduction in Germany.

Results

The results of each analysis are outlined in Figure 2 and Tables 8–10. Results indicate that the Originator is associated with a higher rate of live birth and a lower cost per live birth compared to Biosimilar 1, Biosimilar 2 and pooled biosimilars.

Clinical outcomes

Following stimulation and one fresh embryo (non-frozen) transfer, the estimated live birth rate for the Originator was higher, compared to Biosimilar 1 (40.7% vs 32.1% respectively), Biosimilar 2 (32.2% vs 26.8% respectively) and the pooled biosimilars (36.0% vs 30.1% respectively).

Cost outcomes

The average total costs for women treated with the Originator were estimated to be higher than those treated with biosimilars: the Originator versus Biosimilar 1 (€4,272 vs €3,917), the Originator versus Biosimilar 2 (€4,053 vs €3,646), and the Originator versus pooled biosimilars (€4,207 vs €3,777). For each comparison, cost breakdown (gonadotropin costs, adverse event costs, assisted reproduction costs and birth costs) were reported as the average cost for patients treated with the Originator, Biosimilar 1 and Biosimilar 2. The estimated gonadotropin costs account for a small proportion of total costs in all treatment arms (23.3–27.5% for the Originator and 24.3%, 24.5% and 23.6% for the Biosimilar 1, Biosimilar 2 and pooled biosimilars respectively), compared to the sum of assisted reproduction and live birth costs.

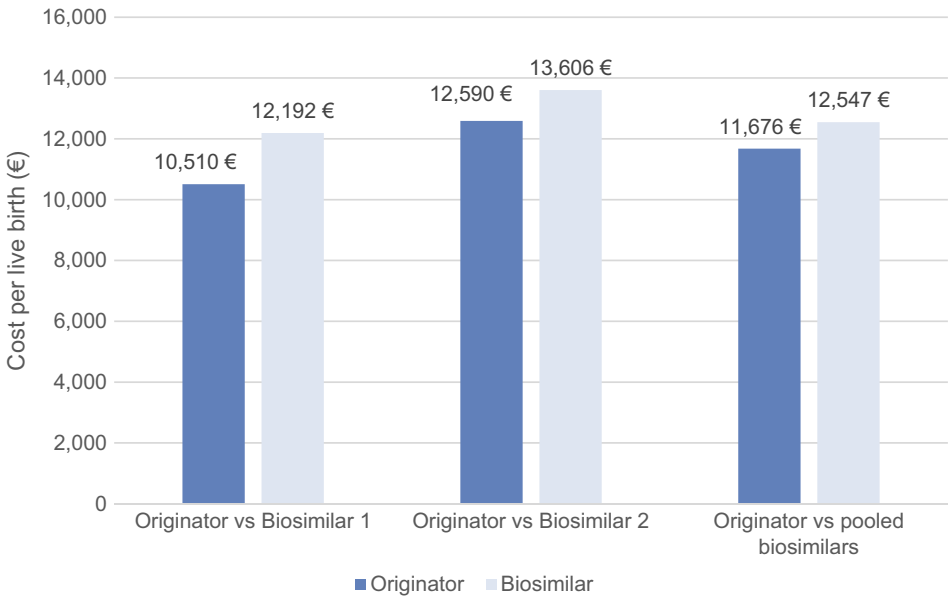

Figure 2 Cost per live birth for Originator versus Biosimilar 1, Biosimilar 2 and pooled biosimilars.
Notes: Biosimilar 1: Bemfola®, Gedeon Richter UK Ltd, London, UK. Biosimilar 2: Ovaleap®; CVC Capital Partners, Luxembourg.

Table 8 Key clinical and cost-effectiveness results for Originator versus Biosimilar 1

	Originator	Biosimilar 1	Difference
Live birth rate	40.7%	32.1%	8.5%
Total costs (€)[a]	4,272	3,917	355
Gonadotropin costs (€)	994	952	42
Adverse event costs (€)	18	20	−2
Assisted reproduction costs (€)	1,759	1,756	3
Birth costs (€)	1,501	1,189	312
Cost per live birth (€)	**10,510**	**12,192**	
ICER (€)	**4,168**		

Notes: Biosimilar 1: Bemfola®, Gedeon Richter UK Ltd, London, UK. [a]Cost breakdowns were estimated as the average cost for women within each treatment arm.
Abbreviation: ICER, incremental cost-effectiveness ratio.

Table 9 Key clinical and cost-effectiveness results for Originator versus Biosimilar 2

	Originator	Biosimilar 2	Difference
Live birth rate	32.2%	26.8%	5.4%
Total costs (€)[a]	4,053	3,646	407
Gonadotropin costs (€)	1,114	892	222
Adverse event costs (€)	13	13	0
Assisted reproduction costs (€)	1,735	1,751	−17
Birth costs (€)	1,191	990	201
Cost per live birth (€)	**12,590**	**13,606**	
ICER (€)	**7,540**		

Notes: Biosimilar 2: Ovaleap®; CVC Capital Partners, Luxembourg. [a]Cost breakdowns were estimated as the average cost for women within each treatment arm.
Abbreviation: ICER, incremental cost-effectiveness ratio.

Table 10 Key clinical and cost-effectiveness results for Originator versus pooled biosimilars

	Originator	Pooled biosimilars	Difference
Live birth rate	36.0%	30.1%	5.9%
Total costs (€)[a]	4,207	3,777	430
Gonadotropin costs (€)	1,114	892	222
Adverse event costs (€)	15	17	−2
Assisted reproduction costs (€)	1,746	1,754	−8
Birth costs (€)	1,332	1,113	218
Cost per live birth (€)	**11,676**	**12,547**	
ICER (€)	**7,256**		

Note: [a]Cost breakdowns were estimated as the average cost for women within each treatment arm.
Abbreviation: ICER, incremental cost-effectiveness ratio.

Cost-effectiveness

Results suggested that the estimated average cost per live birth for women treated with the Originator are lower than those treated with biosimilars: Originator versus Biosimilar 1 (€10,510 vs €12,192); Originator versus Biosimilar 2 (€12,590 vs €13,606), and Originator versus pooled biosimilars (€11,676 vs €12,547). The Originator was associated with an ICER of €4,168, €7,540 and €7,256 versus Biosimilar 1, Biosimilar 2 and pooled biosimilars respectively.

Sensitivity analysis

OWSA for incremental live births of the Originator versus the biosimilar products, indicated that model results were most sensitive to the probability of pregnancy for all interventions. Other key drivers included the probability of embryo transfer and the probability of live birth for all interventions. Scenario analyses varying the proportions of responder-types had minimal impact on the overall results, suggesting the robustness of the model outcomes.

Discussion

This study investigated the cost and clinical outcomes of the Originator in comparison to Biosimilar 1, Biosimilar 2 and pooled biosimilars, from a German payer perspective. Biosimilar follitropin alfa preparations have demonstrated non-inferiority to their reference medicinal product, the Originator, in terms of oocyte retrieval.[14,15] However, the impact on live birth rates and costs associated with the entire treatment have not yet been established. The results of this study indicated that in Germany the Originator is associated with a higher live birth rate and a lower cost per live birth compared to Biosimilar 1 and Biosimilar 2 (Figure 2).

Previous publications comparing the Originator to Biosimilar 1 and Biosimilar 2 have concluded comparability based on the number of oocytes retrieved, the primary end-point recommended by the EMA).[14,15,21] While there is no meaningful difference in the number of oocytes retrieved between originator and biosimilar products, no assessment of the qualitative difference and how this affects other outcomes, such as live birth, has been undertaken. The clinical end-point of this analysis was the rate of live birth, which, as stipulated by the participants at the Harbin Consensus Conference, is the preferred primary outcome for all clinical trials of treatment for infertility.[32] Whilst comparing the number of oocytes may be an effective measure of in-vivo efficacy, the live birth rate is a more clinically meaningful measure to payers, patients and IVF specialists.[2,16] In the biosimilars trials, live birth was not shown to be similar, although neither study was adequately powered to detect this outcome. However, in a post-hoc analysis of the Rettenbacher[14] and Strowitzki[15] trials, the data reported in the EMA public assessment were pooled and analysed using an additive logistic regression model and maximum likelihood estimate, showing live birth rates of 35.8% for Gonal-f versus 30.3% for the pooled biosimilars (p=0.034).[33] The incremental live birth rate for the Originator compared to Biosimilar 1, Biosimilar 2 and pooled biosimilars based on clinical trial results is 8.5%, 5.4% and 5.9%, respectively. When translated into a potential real-world setting, where a cohort of 1,000 women undergo COS as a part of ART, treatment with the Originator may result in 59–85 more live births compared to biosimilars. The difference in the live birth rate may be explained by variations in the structural profiles and manufacturing processes of the biosimilar and reference product, potentially leading to variations in FSH receptor activation and thus biological activity, as investigated by Mastrangeli et al[20].

Total costs, including gonadotropins but excluding other ART medications, for one fresh cycle of assisted reproduction (IVF/ICSI) were estimated to range between €4,053–€4,272 for the Originator and €3,777–€3,646 for biosimilars. These estimates are similar to a previous estimate by Rauprich et al, which estimated the cost of a standard IVF cycle in Germany, including medication, to be about €3,000 and an ICSI to be about €3,600 in 2008.[3] Our findings suggested that gonadotropin costs may account for a smaller proportion of total costs compared to the combined cost of assisted reproduction and birth. In our model, total costs were largely driven by the average birth costs, which accounted for 29–35% of total costs.

It was found that the estimated average cost per live birth is lower for the Originator versus Biosimilar 1 (€10,510 versus €12,192) and Biosimilar 2 (€12,590 versus €13,606). An additional analysis using the pooled data from both biosimilar trials confirmed the individual analysis for the Originator versus Biosimilar 1 and Biosimilar 2 (€11,676 versus €12,547). In our analysis, the ICER for the Originator was estimated to be €4,168, €7,540 and €7,256 versus Biosimilar 1, Biosimilar 2 and the pooled biosimilars respectively.

The results from this study are in line with previous cost-effectiveness analyses of follitropin alfa products. Silverio et al (2015) estimated the cost-effectiveness of the Originator versus Biosimilar 1 over one treatment

cycle in Portugal. The cost per live birth was estimated to be lower for the Originator in comparison with Biosimilar 1, at €7,534.49 versus €9,205.31, respectively.[34] Gizzo et al (2016) estimated the cost-effectiveness of the Originator compared to Biosimilar 1 over two treatment cycles in Italy and Spain. The cost per live birth was also estimated to be lower for Originator in Italy and Spain, €7,044 and €12,283 respectively, compared to €7,411 and €13,494 for Biosimilar 1.[23] Like the analysis presented in the current study, the analyses by Silverio et al (2015) and Gizzo et al (2016) were based on clinical evidence reported by Rettenbacher et al[14]. Gizzo et al (2016) acknowledged that Rettenbacher et al[14] was not powered to demonstrate the live-birth rate, in addition to other study limitations, such as the use of data reported in the literature.

In another study, Gizzo et al (2018) estimated the cost-effectiveness of the Originator compared to Biosimilar 2, based on live birth rates reported in Strowitzki et al[15]. Gizzo et al (2018) also reported a lower cost per live birth for the Originator versus the Biosimilar 2 in three countries (Germany €8,135.04 versus €9,185.34; Italy €8,545.22 versus €9,733.37; Spain €14,859.53 versus €17,767.19).[22] Similarly, Silverio et al (2016) estimated the cost-effectiveness of the Originator versus the Biosimilar 2 in Portugal, based on data from Strowitzki et al[15]. The authors found that in Portugal, the Originator was also associated with a lower cost per live birth (€9,391.67), compared to Biosimilar 2 (€10,977.42).[35]

A German study in 2008, estimated the cost per live birth to be approximately €15,000.[3] These costs are in line with the current study estimates for the cost per live birth, which were estimated to range between €10,510 - €12,590 for the Originator and €12,192, €13,606 and €12,547 for Biosimilar 1, Biosimilar 2 and pooled biosimilars respectively.

The authors of the current study acknowledge that the results obtained in this study are subject to some limitations, primarily related to a lack of clinical trial data or real-world evidence. This analysis compared the Originator to each biosimilar over one ART cycle rather than over multiple cycles, as often occurs in real-world practice. However, given that live birth rates decline for repeated cycles of ART,[1] it was thought that in the absence of data to inform the probability of subsequent live birth rates, extrapolating the available evidence over successive cycles would be misleading. Related to this, due to a lack of data reported in the trials for Biosimilar 1[14] and Biosimilar 2,[15] it was not possible to account for the patients who discontinued or interrupted a cycle due to OHSS. To overcome this limitation, the authors assumed that these patients would be accounted for in the "no oocyte retrieval" of "no oocyte embryo transfer" states. Another limitation relates to the studies by Rettenbacher et al[14] and Strowitzki et al,[15] which were not designed or powered to assess live birth rates. Several of these limitations could be overcome by utilizing real-world evidence, mirroring efficacy in populations in countries of interest. As previously discussed, our current analysis is an exploratory one that is based on live-birth rates because this is a more valid endpoint for ART than the number of oocytes retrieved and is the only outcome that can be measured in terms of cost-effectiveness. In order for live birth rates to be considered as a primary outcome, a much larger sample size would be required, to achieve sufficient statistical power. However, in the absence of such publicly available data, implementing data as reported in the literature provides a measure of clinical efficacy and cost-effectiveness.

Conclusion

Within the limitations of this study, our results suggest that in comparison to Biosimilar 1 and Biosimilar 2, the Originator is associated with a higher live birth rate and a lower cost per live birth in Germany. This analysis therefore could carry implications on the perception of "value for money" with lower-cost biosimilar follitropin alfa preparations. This study was based on the only efficacy and safety data currently available for the biosimilars. We acknowledge that further research is required to validate our results, with studies using real-world data and adequate power to detect the significance of these findings.

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Author contributions

WX, AL and EF were responsible for the creation of study documents, data analysis, data interpretation, and writing of the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

WX, AL and EF are employees of IQVIA, London, UK and CR and RP are employees of Merck KGaA. KB has received honoraria from Merck. WX reports personal fees from MSD, Teva, and Ferring, during the conduct of the study; AL reports grants from Merck KGaA, during the conduct of the study; grants from Merck Inc, Ferring, and Teva, outside the submitted work; EF reports personal fees from Merck KGaA, during the conduct of this study; CR is a consultant for Merck. The authors report no other conflicts of interest in this work.

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