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17

Originator recombinant human follitropin alfa versus recombinant human follitropin alfa biosimilars in Spain: A cost-effectiveness analysis of assisted reproductive technology related to fresh embryo transfers

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A B S T R A C T

This study compared the cost per live birth and cost-effectiveness of the originator recombinant human follicle-stimulating hormone follitropin alfa (r-hFSH-alfa) and r-hFSH-alfa biosimilars for ovarian stimulation prior to assisted reproductive technology treatment in Spain. A decision tree model was developed, comprising pregnancy and live birth for one treatment cycle with fresh embryo transfer. Clinical inputs were based on a recent meta-analysis by Chua et al. [4]. Cost inputs were extracted from publicly available Spanish sources. The costs per live birth were lower with originator r-hFSH-alfa (€18,138) versus r-hFSH-alfa biosimilars (€20,377). The incremental cost-effectiveness ratio was €7208 for originator r-hFSH-alfa versus biosimilars. Drug acquisition costs for originator r-hFSH-alfa represented 10.5% of total costs in the base case analysis, and 6.2% in a treatment cycle resulting in live birth with one fresh embryo transfer. Results from the sensitivity analyses confirmed the robustness of the findings.

Introduction

Exogenous gonadotropins are used to treat infertility by inducing ovulation or by stimulating multifollicular development in women undergoing assisted reproductive technology (ART) treatment [1]. Recombinant human follicle-stimulating hormone follitropin alfa (originator r-hFSH-alfa, GONAL-f®, Merck Healthcare KGaA, Darmstadt, Germany), hereafter referred to as originator r-hFSH-alfa, was first approved in Europe in 1995 (GONAL-f®) [2] and in the USA in 1997 (GONAL-f® RFF) [3], with more than 4 million babies estimated to have been born following treatment with originator r-hFSH-alfa [4].

Biosimilar preparations, defined as a biological medicinal product that contains an often reverse-engineered version of the active substance of an already authorized original biological medicinal product (reference [originator] medicinal product) [5], are also available for follitropin alfa. Biosimilar preparations are required to be biologically and clinically 'non-inferior' to the originator product [6]. A number of biosimilar preparations of follitropin alfa have been approved and are currently available in different countries. For example, Ovaleap®, which was launched in 2013 [7,8], and Bemfola® (also known as Afolia), which was launched in 2014 [9,10], were approved in the EU based on Phase III clinical trials that showed they were not inferior to the originator product based on a predefined threshold for the number of oocytes retrieved and safety. In addition, Primapur® was approved in the Russian Federation in 2020 based on the number of retrieved oocytes [11], and Follitrope®, which is only available in Asian countries, has been on the market since 2006, but it is not clear which primary endpoint/clinical outcome was considered for the marketing authorization approval [4,12].

In order to obtain regulatory approval, biosimilars must show equivalent pharmacological, pharmacokinetic, toxicological, efficacy and safety profiles to originator r-hFSH-alfa, which are generally assessed using non-inferiority studies [5]. Owing to the shorter regulatory pathway compared with originator products, biosimilars are usually marketed at a lower purchase price compared with the originator product [13]. As treatment costs can restrict patient access to high-quality medicines, biosimilars may seem economically attractive as they provide potentially lower-cost alternatives for doctors, payers and patients. However, despite biosimilars offering a lower purchase price in many countries, cost-effectiveness studies comparing originator r-hFSH-alfa with biosimilars have shown conflicting findings, with some studies favouring biosimilars [14,15], while several studies favoured originator r-hFSH-alfa compared with its biosimilars [13,16–20]. Such discrepancies may be due to differences in the primary outcomes among studies (i.e., outcomes other than live birth) and small sample sizes [13–20]. A recent pharmaco-economic review suggested that originator r-hFSH-alfa

would be the preferred strategy for ART treatment in several EU countries, likely due to its higher incremental efficacy in number of live births and its lower cost per live birth [16]. In fact, a recent meta-analysis evaluating the effectiveness of originator r-hFSH-alfa versus its biosimilars, using data from published randomized controlled trials (RCTs), demonstrated that originator r-hFSH-alfa was associated with a higher probability of live birth, clinical pregnancy and ongoing pregnancy than its biosimilars, with a similar safety profile [4]. In combination with clinical studies, economic modelling using data from large populations (particularly those included in meta-analyses) can provide useful information to help decision-makers make informed evaluations on the optimal gonadotropin for ovarian stimulation (OS). This study aimed to compare the economic implications of OS with originator r-hFSH-alfa and its biosimilars in the context of ART treatment, by evaluating the cost per live birth and cost-effectiveness of originator r-hFSH-alfa versus its biosimilars using clinical outcomes published recently in a meta-analysis [4], from the perspective of the Spanish healthcare system.

Methods

Model structure

A decision tree model was developed using Microsoft Excel (Fig. 1). The model structure comprised pregnancy and live birth rate (LBR) for one fresh embryo transfer. As the meta-analysis was not performed for outcomes prior to pregnancy, such as oocyte retrieval, embryo transfer or cancellation prior to embryo transfer, these outcomes were not included in the model. The proportion of patients at the end of each treatment pathway was multiplied by the relevant cost (i.e., the cost of stimulation, embryo transfer, pregnancy or live birth), and the total sum of all pathway costs was used to generate total costs for each intervention. Outcomes included total costs and incremental cost-effectiveness ratio (ICER), estimated as the difference in costs divided by the difference in LBRs for the two comparators. The main model outcome was the cost per live birth.

Clinical inputs

The probability of moving from pregnancy to live birth was based on a recently published meta-analysis [4], which included five unique RCTs and evaluated the efficacy and safety of the originator

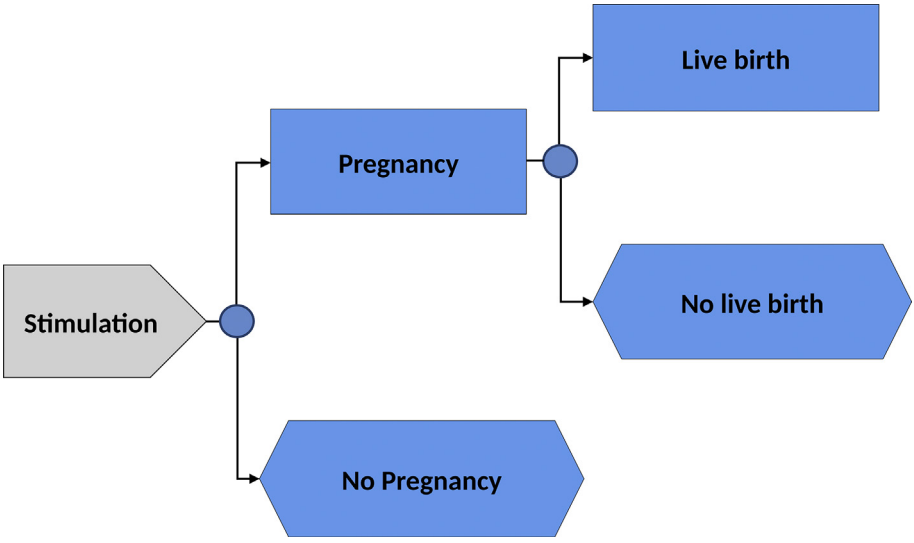

Fig. 1. Model structure (decision tree).

r-hFSH-alfa versus r-hFSH-alfa biosimilars. The probability of live birth was conditional on achieving clinical pregnancy. The primary endpoint of this meta-analysis was LBR per randomized patient following a fresh embryo transfer [4]. Although trials reporting LBR after fresh and/or frozen/thawed embryo transfers were eligible for inclusion in the meta-analysis, only four frozen/thawed embryo cycles originating from one study were included in the combined LBR estimates, which was highlighted as a potential limitation of the data for LBR in the meta-analysis. Furthermore, the evidence for cumulative outcomes in the meta-analysis was graded as low quality because, owing to cross-over of treatments after the first cycle in one of the studies, only data on the first cycle were eligible for the estimation. Secondary outcomes from this meta-analysis, including ongoing pregnancy rate, severe ovarian hyperstimulation syndrome (OHSS) rate and mean total dose of gonadotropins [4], were also used to populate the cost-effectiveness analysis reported here. Clinical model inputs from this meta-analysis are shown in Table 1.

Dosing

The dosage used for originator r-hFSH-alfa and biosimilars was based on findings from the meta-analysis [4]. The costs for originator r-hFSH-alfa and r-hFSH-alfa biosimilars were estimated according to dosage, whereby the average weighted mean total dose (SD) for originator r-hFSH-alfa was 1818.0 IU (406.01) and was assumed to be dispensed as 2 × r-hFSH 900 IU + 1 × r-hFSH 75 IU, and the average weighted mean total dose (SD) for biosimilars was 1780.5 IU (433.59) and was assumed to be dispensed as 2 × r-hFSH 900 IU.

Cost inputs

Cost inputs were categorized according to treatment phase, medication (for OS and concomitant medication), pregnancy follow-up, live birth, miscarriage and severe OHSS. Treatment costs were derived from the region-specific sources in Spain and through a targeted search of the published literature and validation by two Spanish clinical experts (Table 2).

Costs for *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) were the weighted proportion of IVF (13%) and ICSI (87%) procedures based on data from the Spanish Ministry of Health, Consumer Affairs and Social Welfare and the Fertility Spanish Society, statistical report of assisted reproductions techniques (2017) [21]. The cost of a live birth was calculated from the weighted average of vaginal and caesarean births, based on a reported proportion of 48.9% caesarean births in Spain [21]. Individual components and total costs estimated for each stage of the treatment cycle are shown in Table 2. The effect of multiple pregnancy was not included in this analysis, although no difference was expected between groups [4]. Where required, costs were subsequently inflated to current prices using the Consumer Price Index.

Validation and sensitivity analyses

Cost inputs were validated by two Spanish clinical experts with extensive experience in assisted reproduction in Spain (SI, RM). A one-way sensitivity analysis (OWSA) was conducted to test the impact

Table 1
Clinical model inputs based on a meta-analysis [4].

	Originator r-hFSH-alfa			r-hFSH-alfa biosimilars
	Rates	Events	Total	RR (upper limit; lower limit)
Ongoing pregnancy	0.35	154	436	0.81 (0.68; 0.98)
Live birth	0.26	231	875	0.83 (0.71; 0.97)
Severe OHSS	0.02	23	987	1.04 (0.63; 1.73)
Mean (SD) dose of gonadotropin, IU	1818 (406)			1780.5 (433)

OHSS, ovarian hyperstimulation syndrome; r-hFSH-alfa, recombinant human follicle-stimulating hormone follitropin alfa; SD, standard deviation; RR, relative risk.

Table 2
Estimated treatment costs for each stage of treatment cycle.

Description	Unit costs (€)
Screening before ART treatment	
General treatment; gynaecological ultrasound before starting stimulation [23]	66.55
Serological tests (HIV, HBc, HCV, syphilis, and HBs) [24]	55.00
Sub-total screening before ART treatment	*121.55*
Monitoring during ovarian stimulation	
Three oestradiol determination tests [21]	50.98
One progesterone determination test [21]	16.97
Follicular sonography (×3.5) [25]	232.00
Sub-total monitoring during ovarian stimulation	*299.95*
Ovarian stimulation medication	
Cost of originator r-hFSH-alfa per stimulation	€504.00[a]
Cost of biosimilar r-hFSH-alfa	€483.84[b]
Sub-total for ovarian stimulation medication	*€987.84*
Ovarian stimulation – concomitant medication (applied to both the originator r-hFSH-alfa and the r-hFSH-alfa biosimilar arms)	
Orgalutran: five syringes (€129.26 for 50% of population) [25]	64.63
Cetrotide: seven syringes (€248.7 for 50% of population) [25]	124.35
Ovitrelle: (one unit) 250 μg [25]	50.63
Sub-total concomitant medication:	*239.61*
Oocyte retrieval	
Outpatient surgery, post-operative monitoring [23]	334.09
Follicular aspiration: needle (clinical input and validation) [23]	25.00
Processing of sperm and processing medium [23]	156.76
Sub-total oocyte retrieval	*515.85*
Fertilization method used	
ICSI [21]	1295.72
IVF [21]	1129.67
Subtotal (weighted mean 13% IVF, 87% ICSI)	*1274.13*
Stimulation phase – no oocyte retrieval	
Follicular puncture (50% of the population)	111.48
Embryo transfer	
Embryo transfer [23]	120.92
Pregnancy	
Blood test for βHCG (pregnancy test) [21]	8.46
Utrogestan (4 boxes, 60 caps of 200 mg) [25]	167.84
Pregnancy follow-up [26]	1954.22
Sub-total pregnancy	*2130.52*
No pregnancy	
Blood test for βHCG (pregnancy test) [21]	8.46
Utrogestan (one box, 60 capsules of 200 mg) [25]	41.96
Sub-total no pregnancy	*50.42*
Live birth	
Vaginal birth (assuming 51.1%) [21]	2271.12
Caesarean section (assuming 48.9%) [21]	3598.59
Subtotal live birth (weighted mean)	*2920.25*
Miscarriage	
Miscarriage – without curettage (assuming 85%) [21]	1383.44
Miscarriage – with curettage (assuming 15%) [21]	2220.74
Subtotal miscarriage (weighted mean)	*1509.03*
Adverse event costs	
Hospitalization for severe OHSS (including vitrification) [21]	1874.86

[a] Assumed to be dispensed as 2 × r-hFSH 900 IU (€241.92 × 2) + 1 × r-hFSH 75 IU (€20.16).
[b] Assumed to be dispensed as 2 × r-hFSH 900 IU (€241.92 × 2) (costs shown are without tax). HBc, hepatitis B core antigen; HBs, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; OHSS, ovarian hyperstimulation syndrome; r-hFSH-alfa, recombinant human follicle-stimulating hormone follitropin alfa.

that changes in the clinical and cost parameters have on the outputs, by investigating the plausible upper and lower values from the reported outcomes (confidence intervals from the meta-analysis [4] for live birth and pregnancy, upper and lower 25% variance of cost input parameters).

A probabilistic sensitivity analysis (PSA) was conducted for incremental live births and costs using 1000 Monte Carlo iterations and presented as a cost-effectiveness plane. The PSA allowed quantification of the level of confidence in the output of the analysis in relation to uncertainty in the model inputs.

In addition, as willingness to pay (WTP) thresholds for fertility treatments are not established in Spain, outputs from the PSA were used to generate a cost-effectiveness acceptability curve. The aim of this was to assess the probability of cost-effectiveness of the originator compared with the biosimilars at different thresholds, representing hypothetical national health service willingness to pay limits.

Results

Costs per live birth

Costs per live birth were lower with originator r-hFSH-alfa than for r-hFSH-alfa biosimilars (€18,138 vs €20,377) (Table 3).

Total costs and cost breakdown

The total cost (source costs multiplied by the probabilities in the decision tree) were higher for originator r-hFSH-alfa than for r-hFSH-alfa biosimilars, which was due to the higher proportion of pregnancies and live births with originator r-hFSH-alfa compared with r-hFSH-alfa biosimilars (Table 3).

The largest proportion of costs for both preparations was attributed to OS-associated costs [excluding medication]/IVF/ICSI (Fig. 2), and the largest difference in costs between originator r-hFSH-alfa and r-hFSH-alfa biosimilars was for procedures related to the pregnancies and births resulting from ART treatment, such as pregnancy follow-up visits and live birth (Fig. 2).

Drug acquisition costs as a proportion of the total costs

The drug acquisition cost was €20.16 per 75 IU for all r-hFSH-alfa preparations, so total treatment costs were €504.00 for originator r-hFSH-alfa and €483.84 for r-hFSH-alfa biosimilars. As a proportion, drug costs were not the greatest contributor to the total treatment costs. Fig. 3 shows the share of the drug cost of originator r-hFSH-alfa (€504.00) in relation to the total costs. In the base case of this analysis, which reflects the probabilities of successful and unsuccessful outcomes from the decision tree, the proportion of drug acquisition costs was 10.5%. We also report the proportions represented by the drug acquisition costs when the total costs per ART treatment cycle resulting in live birth were considered (6.2%) and when the costs related to pregnancy and live birth were excluded from the total costs (16.1%; Fig. 3). The breakdown of the total costs included for these two scenarios is reported in Supplementary Table 1.

Incremental cost-effectiveness ratio

The ICER was calculated as €7208 for originator r-hFSH-alfa versus r-hFSH-alfa biosimilars.

Table 3
Model clinical inputs, cost outputs and costs per live birth.

	Originator r-hFSH-alfa	r-hFSH-alfa biosimilars	Incremental
Live birth rate	26.4%	21.9%	4.5%
Total costs (source costs multiplied by decision tree probabilities)[a]	€4789	€4465	€323
Cost per live birth	€18,138	€20,377	

[a] Higher total costs for originator r-hFSH-alfa due to its higher rate of pregnancy and live birth and conclusively more costs for these.

r-hFSH-alfa, recombinant human follicle-stimulating hormone follitropin alfa.

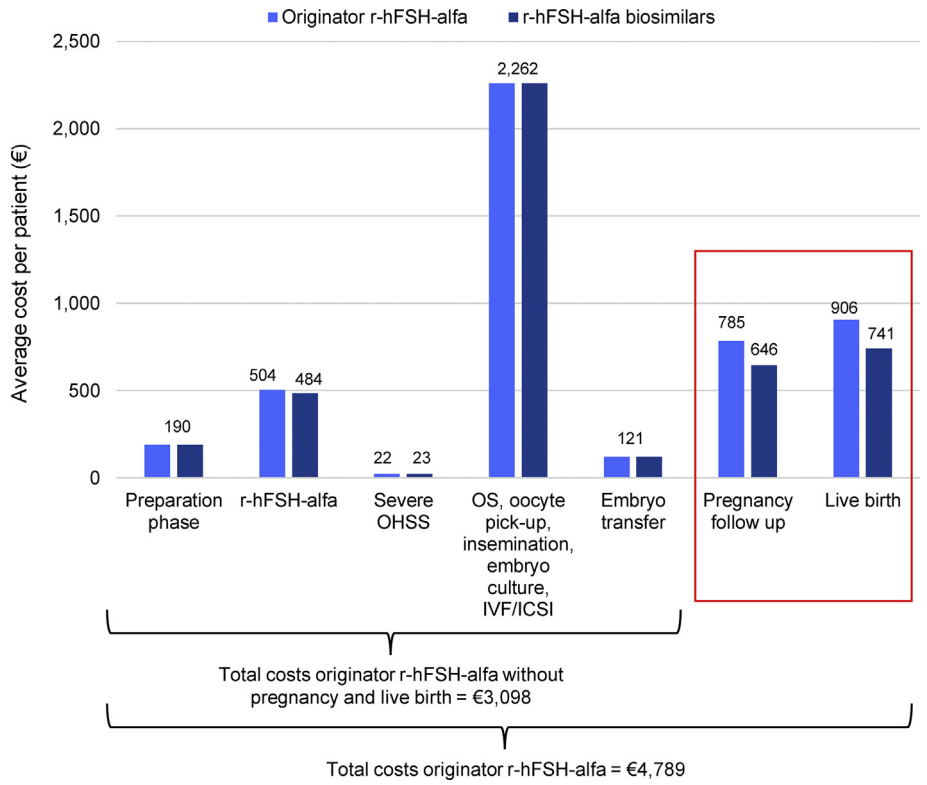

Fig. 2. Cost breakdown of total costs presented in Table 3 (source costs multiplied by decision tree probabilities). Costs for each variable were calculated as the probability of outcomes from the decision tree multiplied by mean cost per patient for originator r-hFSH-alfa or r-hFSH-alfa biosimilars, respectively (Table 3). The main differences in total costs were related to pregnancy follow-up and live birth, and they were higher for originator r-hFSH-alfa versus r-hFSH-alfa biosimilars due to its higher pregnancy and live birth rates. ART, assisted reproductive technology; IVF/ICSI, *in vitro* fertilization/intracytoplasmic sperm injection; OHSS, ovarian hyperstimulation syndrome; OS, ovarian stimulation; r-hFSH-alfa, recombinant human follicle-stimulating hormone follitropin alfa.

Sensitivity analyses

Inclusion of health status prior to pregnancy

When including the rate of embryo transfer/no embryo transfer prior to pregnancy by using data from the original trials included in the meta-analysis there was only a marginal numerical change in the results (cost per live birth €18,063 for originator r-hFSH-alfa vs €20,229 for r-hFSH-alfa biosimilars), confirming the robustness of our conclusions.

One-way sensitivity analysis

The OWSA of input parameters showed that the clinical parameters that had the most effect on the results for both comparators were the probabilities of live birth and pregnancy (Fig. 4). The cost parameters that had the most effect on the results were those associated with the costs resulting from pregnancy and live birth.

Probabilistic sensitivity analysis

In the cost-effectiveness plane of the PSA, the cluster of the outcomes from the 1000 Monte Carlo iterations remained in the North-East quadrant of the cost-effectiveness plane; therefore, the uncertainty around the final results could be considered low (Fig. 5).

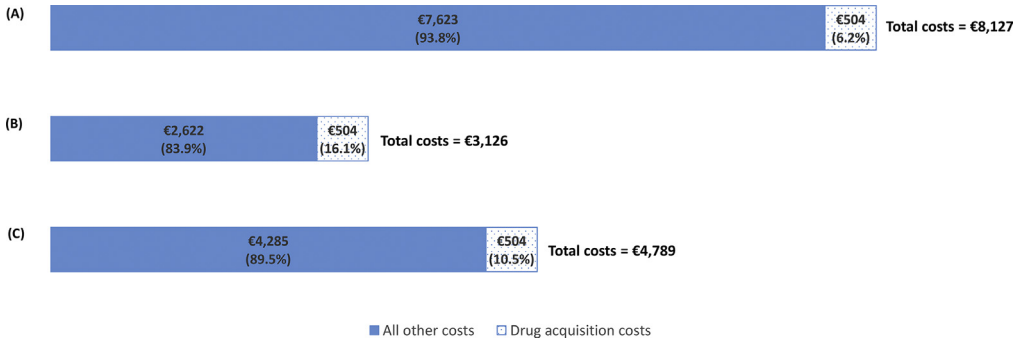

Fig. 3. Mean costs for medication of originator r-hFSH-alfa as proportion of overall costs: (A) per ART treatment cycle resulting in live birth; (B) per ART treatment cycle resulting in live birth, excluding costs for pregnancy and live birth; (C) based on cost-effectiveness analysis base case when decision tree probabilities were included. Drug costs only contributed to a small proportion of the total treatment costs; mean costs for medication of originator r-hFSH-alfa (€504) represented: (A) 6.2% of total costs per ART treatment cycle resulting in live birth (€8127; Table 2; Supplementary Table 1); (B) 16.1% of total costs per ART treatment cycle resulting in live birth, excluding costs for pregnancy and live birth (€3126; Table 2; Supplementary Table 1); (C) 10.5% of total costs per ART treatment cycle based on cost-effectiveness analysis base case (€4789; Table 3).

The cost-effectiveness acceptability curve showed the results of the multivariate PSA based on the 1000 Monte Carlo simulations, in which for each threshold there was a probability that originator r-hFSH-alfa would be considered cost effective using hypothetical WTP thresholds in the absence of defined thresholds in the Spanish setting (Fig. 5). The acceptability curve shows that according to a WTP threshold of €20,000 cost per live birth gained, the originator r-hFSH-alfa has a 100% probability of being cost effective.

Discussion

This cost-effectiveness study compared originator r-hFSH-alfa with r-hFSH-alfa biosimilars using clinical inputs from a systematic review and meta-analysis of pregnancy and live birth outcomes with these two preparations [4]. The results presented here indicate that, from a Spanish healthcare perspective, originator r-hFSH-alfa is associated with a higher LBR and a lower cost per live birth compared with r-hFSH-alfa biosimilars for fresh embryo transfer ART cycles.

The results of this study are similar to a pooled analysis from a German perspective, which reported a lower cost per live birth with originator r-hFSH-alfa compared with two biosimilar products (Ovaleap® and Bemfola®) [17]; however, the study by Xue et al. analysed only two biosimilars over one cycle using data from two RCTs [17], whereas the current study used data from a meta-analysis analysing data for four biosimilars (Bemfola®, Ovaleap®, Primapur® and Follitrope®) from 17 studies, representing five unique RCTs; therefore, the meta-analysis by Chua et al. may provide a more robust clinical dataset [4]. Our findings are also consistent with those of a recently published report, which provides an overview of the market performance of the r-hFSH-alfa biosimilars (Ovaleap® and Bemfola®) in Europe [16]. In their report, Goldstajn et al. assessed the cost-effectiveness of r-hFSH-alfa biosimilars compared with the reference r-hFSH-alfa, based on published market reports and pharmaco-economic studies; they concluded that originator r-hFSH-alfa is the first choice for national health systems, as biosimilar preparations failed to show real cost savings, with only a slight impact on cost reduction in Europe [16].

In agreement with our findings, a lower mean cost per live birth with originator r-hFSH-alfa compared with r-hFSH-alfa biosimilars has also been reported in several other previously published pharmaco-economic analyses [13,18–20,22]. The original studies used in these pharmaco-economic analyses were biosimilar registration trials [8,10], in which the number of oocytes retrieved was the primary efficacy outcome and, as such, these trials were not powered to demonstrate differences associated with LBR. An abstract published by Claus et al., in 2016 reported on a simulated budget-

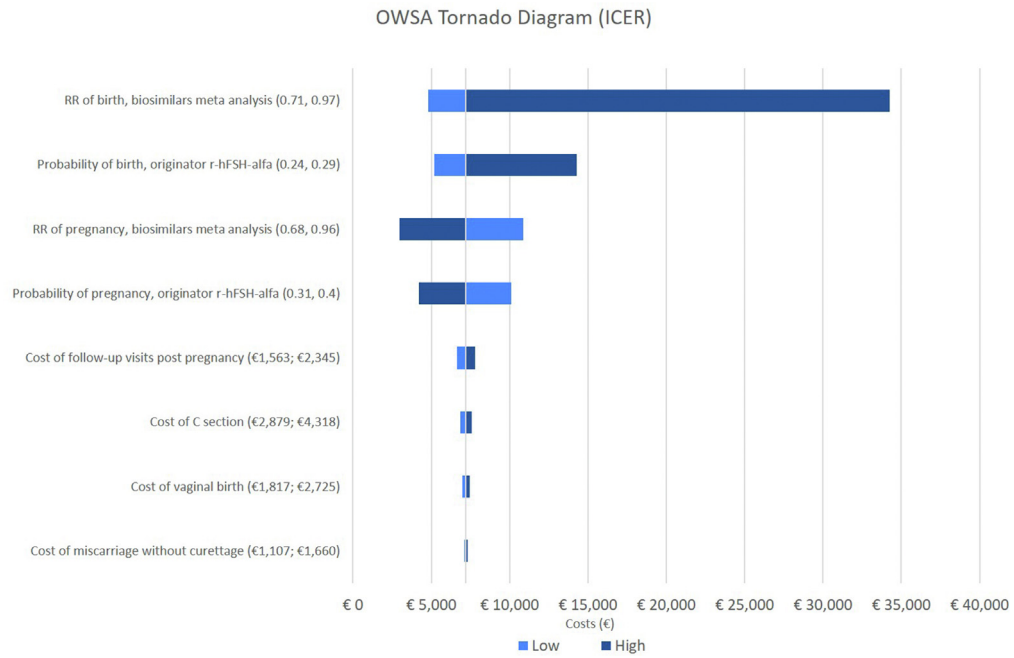

Fig. 4. One-way sensitivity analysis (Tornado diagram) of parameters with the greatest effect on the model. The Tornado diagram represents the result of multiple univariate sensitivity analyses on a single graph. It helps to assess which of the model's parameters have the greatest influence on its results. Each analysis is summarized using a horizontal bar that represents the variation in the model output (ICER) around a central value (corresponding to the base case analysis). ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; RR, relative risk.

impact analysis in Belgium, which observed cost savings for r-hFSH-alfa biosimilars when compared with originator r-hFSH-alfa if discounts were applied. It should be noted that this analysis focused purely on direct costs and therefore has limitations. The more comprehensive cost-effectiveness analysis presented here addresses a broader payer perspective beyond the focus of a single hospital or direct costs and includes the effectiveness component of products [14].

The main strength of this evaluation compared with previous studies is the robustness of the underlying clinical data, which were obtained from a meta-analysis [4] of pregnancy outcomes and live births that included a large number of patients from a population derived from different geographic and ethnic populations included in different RCTs. The Spanish setting was chosen for the analysis reported here for several reasons, including the high market uptake of r-hFSH-alfa biosimilars compared with other European countries, the general availability of health economic data (cost-effectiveness, cost consequence) in recent years in Spain, and the participation of two Spanish centres in one of the RCTs included in the meta-analysis [10]. While our results reflect the specific cost reality of ART in the Spanish context, the results could also be applicable to other healthcare markets, particularly to those with similar usage for r-hFSH-alfa biosimilars; therefore, our methodology could be applied to perform similar calculations using cost data from other countries. Furthermore, although health status prior to pregnancy, such as embryo transfer, was not included in the meta-analysis or consequently in the model, the model outputs were validated by adding the “embryo transfer/no embryo transfer” state based on results from the individual trials included in the meta-analysis to assess differences in the outcomes when this state is included, resulting in only a marginal numerical difference (cost per live birth €18,063 vs €20,229 for originator r-hFSH-alfa and r-hFSH-alfa biosimilars, respectively). The sensitivity analysis included in our analyses shows that the uncertainty around the final results could be considered low, which provides confidence in the interpretation of the data.

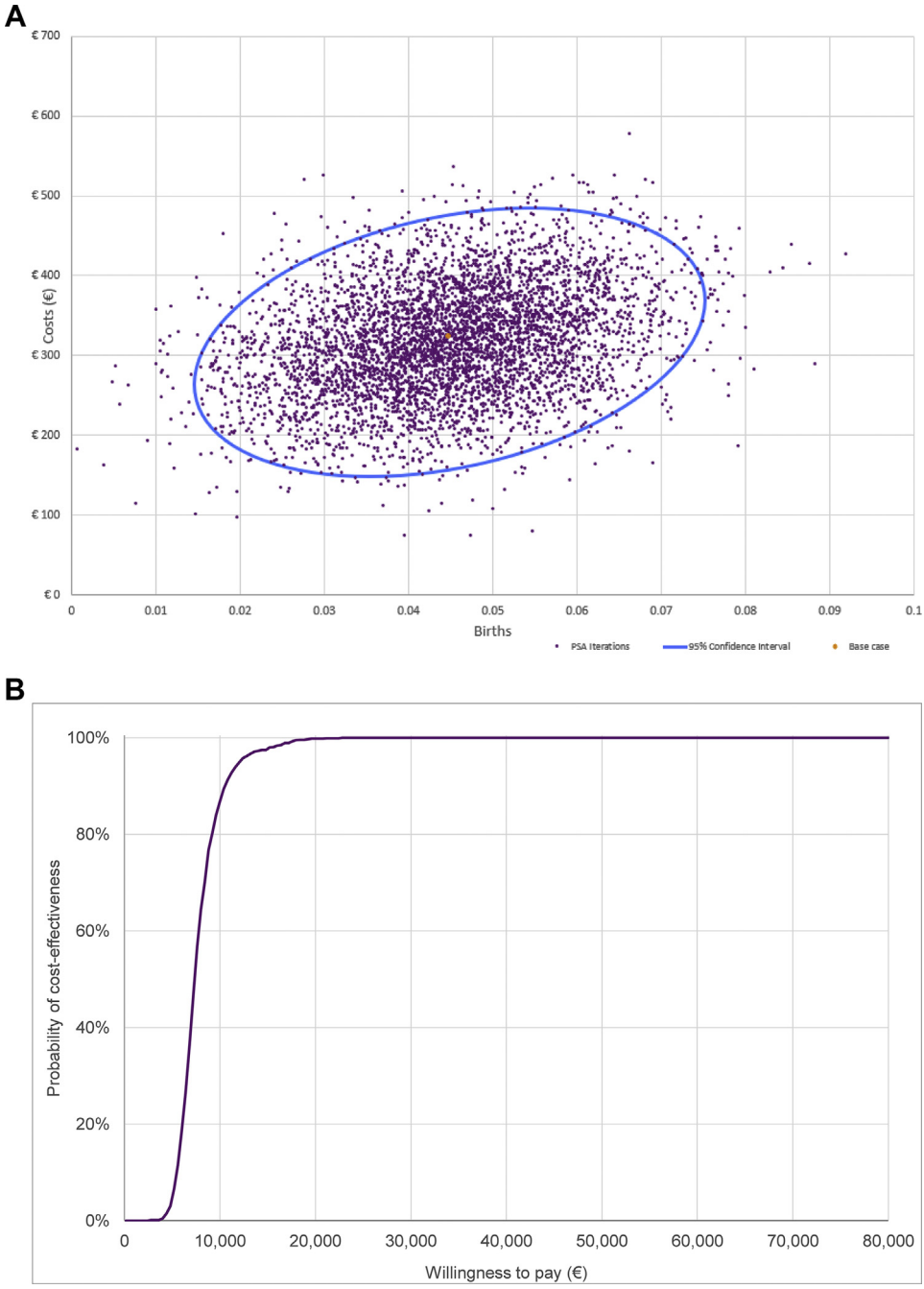

Fig. 5. Probabilistic sensitivity analysis (A) cost-effectiveness plane and (B) cost-effectiveness acceptability curve.

As reported herein, the total cost per patient was higher for originator r-hFSH-alfa than for r-hFSH-alfa biosimilars, which was the result of the increase in costs associated with a successful pregnancy and the higher proportion of live birth with originator r-hFSH-alfa compared with r-hFSH-alfa biosimilars—essentially, the costs directly linked with the higher success rate. To overcome issues of reporting and interpreting cost-effectiveness ratios, we conducted an incremental analysis that helps compare two products for establishing cost-effectiveness. We report an ICER of €7208 for originator r-hFSH-alfa compared with r-hFSH-alfa biosimilars. In the absence of defined WTP thresholds for fertility treatments in Spain, the cost-effectiveness acceptability curve based on the results of the multivariate PSA of 1000 Monte Carlo iterations showed that originator r-hFSH-alfa had 100% probability of being cost-effective at a hypothetical threshold of €20,000.

To investigate the main drivers of treatment costs, we also performed a breakdown of costs for each stage of the ART process. This showed that the largest difference in costs between originator r-hFSH-alfa and r-hFSH-alfa biosimilars was for pregnancy-related procedures, which would be expected, due to the higher successful pregnancy outcome and LBR with originator r-hFSH-alfa. Interestingly, drug acquisition costs represented only 16.1% of the overall treatment costs when the sum did not consider the costs related to pregnancy and live birth, and only 6.2% for a successful treatment resulting in a live birth (Fig. 3; Supplementary Table 1). In the base case of the cost-effectiveness analysis, drug acquisition costs for originator r-hFSH represented 10.5% of total costs per ART treatment cycle (Fig. 3).

This is noteworthy as payers and governments usually focus on drug costs as the main drivers of overall cost when determining access. By utilizing a more objective approach when evaluating the treatment pathway, this study demonstrates that the drug costs are not the main driver of overall costs for ART; rather, they only account for a small proportion of the entire treatment costs in this complex clinical pathway. Furthermore, this finding may increase the generalizability of the results presented here to other settings, as the difference in drug prices in different countries may not have a substantial effect on the results.

There are some limitations that should be considered when interpreting the results presented here. The current study only reports on the costs for first live birth following a fresh embryo transfer and does not take into account frozen embryo transfer or cumulative LBRs, which may provide a more useful assessment for decision-makers and patients. Indeed, we acknowledge that including frozen embryo transfers in the analysis would have an impact on the costs. When data on frozen embryo transfers become available, it would be valuable to expedite future analyses in which the costs for each stage in the ART process for cumulative live births could be compared. Another limitation was that multiple pregnancies were not included in the analysis, but no differences between treatment arms would be expected here because RCTs have a protocol that includes the number and stage of embryos to be transferred, and this is the main predictive factor for multiple pregnancies. Furthermore, only a small number of studies were included in the meta-analysis, although the number of participants included in these studies was sufficiently high to have the statistical power to achieve significance, with one study providing the majority of patients (n = 1100) [4]. We acknowledge that further studies based on real-world data and using cumulative pregnancy and LBR as clinical outcomes, which were not available in our study, would add value to the currently available evidence base.

Summary

To our knowledge, this study is the first cost-effectiveness analysis comparing originator r-hFSH-alfa with r-hFSH-alfa biosimilars that are based on data from a robust, recently published meta-analysis with LBR as the primary outcome. Our analysis suggests that originator r-hFSH-alfa is associated with lower costs per live birth compared with r-hFSH-alfa biosimilars in the Spanish setting. In the base case of our cost-effectiveness analysis, OS drug acquisition costs accounted for only a small proportion (10.5%) of the overall costs per ART treatment cycle, which is of interest as payers/governments usually focus on drug costs as the main drivers of overall cost when determining access. The results indicate that originator r-hFSH-alfa has a 100% probability of being cost effective considering a WTP threshold of €20,000 versus r-hFSH-alfa biosimilars for OS prior to ART treatment in fresh embryo transfer ART cycles. It would be interesting to explore the results based on a larger dataset, ideally including real-world practice, which also considers frozen embryo transfers and other outcomes, such as cumulative LBR. This would enable the comparison of cumulative outcomes.

Practice points

- Originator recombinant human follicle-stimulating hormone follitropin alfa (r-hFSH-alfa) is used to treat infertility by inducing ovarian stimulation in women undergoing medically assisted reproduction treatment.
- A number of biosimilar preparations of r-hFSH-alfa have been approved, which are required to be biologically and clinically non-inferior' to the originator product.
- Previous cost-effectiveness studies comparing originator r-hFSH-alfa with r-hFSH-alfa biosimilars have shown conflicting findings, with some studies favouring originator r-hFSH-alfa and others favouring r-hFSH-alfa biosimilars, as they are often based on a single clinical study.
- A recent meta-analysis evaluating the effectiveness of originator r-hFSH-alfa versus r-hFSH-alfa biosimilars demonstrated that originator r-hFSH-alfa was associated with a higher probability of live birth, clinical pregnancy, and ongoing pregnancy than its biosimilars, with a similar safety profile.
- Our analysis suggests that costs per live birth are lower for originator r-hFSH-alfa versus r-hFSH-alfa biosimilars in the Spanish setting, due to increased live-birth rates, despite slightly higher costs of treatments, explained by the costs related to the higher number of live births and pregnancies observed with originator r-hFSH-alfa.
- Drug acquisition costs account for only a small proportion (10.5%) of the overall costs of an ART treatment cycle, regardless of pregnant or non-pregnant outcome, which is of interest, as payers/governments usually focus on drug costs as the main drivers of overall cost when determining access.

Research agenda

- The cost per live birth and cost-effectiveness of originator r-hFSH-alfa versus r-hFSH-alfa biosimilars based on real-world data, using appropriate methodology (i.e., propensity scoring, multivariate analysis).
- Cost-effectiveness studies of originator r-hFSH-alfa versus r-hFSH-alfa biosimilars using cumulative pregnancy and live birth rates as clinical outcomes.

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Authors' contributions

All authors contributed to the interpretation of the analysis as well as drafting, critically reviewing and approving the manuscript. In addition, **TDH** was involved in the study idea and assessment of research methodology and **VL** contributed to the implementation of Spanish cost inputs in the model (adapting the model from the German health care setting to the Spanish one), quality checking the changes made and running the analysis. **SI** and **RM** provided data regarding the specific context of ART in Spain.

Data availability

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing

to Merck KGaA's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck KGaA has a co-research, co-development, co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavour to gain agreement to share data in response to requests.

Declaration of competing interest

SI has received personal fees and non-financial support from Merck Healthcare KGaA, Darmstadt, Germany, Ferring and Gedeon-Richter. **EF** is an employee of IQVIA Ltd., London, UK. **VL** was an employee of IQVIA Solutions B.V., Amsterdam, The Netherlands, at the time of the study. **CR** is an employee of Pharma Value Consulting, Switzerland, and is a consultant for Merck, KGaA Darmstadt Germany. **CAV** has received personal fees from Merck Healthcare KGaA, Darmstadt, Germany, personal fees, grant, and non-financial support from Merck Healthcare KGaA, Darmstadt, Germany, personal fees and non-financial support from Merck Sharp & Dohme, grant and non-financial support from Ferring, personal fees from Besins, personal fees and non-financial support from Gedeon-Richter, and research funding and non-financial support from Abbott. **EAC** is an employee of Merck, S.L.U., Madrid, Spain, an affiliate of Merck KGaA. **TDH** and **JES** are employees of Merck Healthcare KGaA, Darmstadt, Germany. **RM** has received personal fees, research funding, grants and non-financial support from Merck Healthcare KGaA, Darmstadt, Germany, and personal fees, grants and non-financial support from Ferring and Gedeon-Richter.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2022.01.011.

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