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Determining the cost-effectiveness of follitropin alfa biosimilar compared to follitropin alfa originator in women undergoing fertility treatment in France

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ABSTRACT

Objective: The study assessed cost-effectiveness of follitropin alfa biosimilar versus the originator in terms of cost per cumulative live-birth (CLB) for the French healthcare system based on real-world evidence. Follitropin alfa biosimilars have been shown to have comparable clinical outcomes to the originator, in both clinical studies and real-world settings, in terms of oocyte retrieval and cumulative live-birth rate (CLBR). Previous health economic studies comparing the cost-effectiveness of follitropin alfa biosimilars against the originator utilised clinical trial data, leaving ambiguity over cost-effectiveness in real-world settings. Additionally, previous cost-effectiveness analysis has been performed for live-births following only fresh embryo transfers, whereas, fresh and frozen transfers are common in clinical practice. This study investigates the cost per CLB, which more closely models clinical practice.

Study design: A decision-tree cost-effectiveness model was developed based on the total costs and CLBR per ovarian stimulation (OS) for a follitropin alfa biosimilar (Bemfola®, Gedeon Richter Plc, Budapest, Hungary) and the originator (Gonal-f®, Merck KGaA, Darmstadt, Germany). A time horizon of one year from oocyte retrieval to embryo transfer was used but costs from resulting transfers were also included. Clinical inputs were taken from the REOLA real-world study or clinician insights, while acquisition costs were taken from French public databases. The output was cost per CLB following one OS. One-way sensitivity analysis was performed to determine the largest model drivers.

Results: Cost per CLB was €18,147 with follitropin alfa biosimilar and €18,834 with the originator, saving €687 per CLB following OS with the biosimilar. When wastage estimates were considered the biosimilar cost saving is estimated to be between €796 and €1155 per CLB further increasing cost savings. Irrespective of wastage, if used ubiquitously throughout France for ART, the biosimilar could save the French health system €13,994,190 or lead to 771 more births when compared to its higher-cost originator. Sensitivity analysis showed that the originator's relative CLBR had the greatest impact on the model.

Conclusion: This analysis demonstrates that the follitropin alfa biosimilar, Bemfola®, is a more cost-effective option for OS compared with the originator from a French healthcare payer perspective, in terms of cost per CLB.

Abbreviations: ART, Assisted Reproductive Technologies; CLB, Cumulative Live-Birth; CLBR, Cumulative Live-Birth Rate; OS, Ovarian stimulation; EMA, European Medicines Agency; FSH, Follicle-Stimulating Hormone; hCG, Human Chronic Gonadotropin; HMA, Heads of Medicines Agencies; ICSI, Intracytoplasmic Sperm Injection; IVF, In Vitro Fertilisation; OHSS, Ovarian Hyperstimulation Syndrome; OWSA, One-way Sensitivity Analysis; r-hFSH, Recombinant Human Follicle Stimulating Hormone; SmPC, Summary of product characteristics; VBA, Visual Basic for Application.

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1. Introduction

Infertility affects 1 in 6 people globally and is often associated with social stigma and high treatment costs [1]. In France, ART is a common option for women struggling to conceive. Typically, ART relies upon ovarian hyperstimulation by gonadotropin FSH, to stimulate ovarian follicle development [2]. FSH makes up a significant proportion of ART costs, so lower-cost alternatives like biosimilars may create savings for the French healthcare system [3,4].

The follitropin alfa biosimilar Bemfola® (Gedeon Richter Plc, Budapest, Hungary) was the first r-hFSH alpha biosimilar launched in France in 2015 [5,6]. Several clinical trials and real-world studies demonstrated similar efficacy and safety between this follitropin alfa biosimilar and alternative FSH options [7–11], and concluded that there are no clinically relevant differences [5]. The REOLA real-world study investigated cumulative live-birth rates (CLBR), the endpoint of interest [12,13], and reported no apparent difference between the follitropin alfa biosimilar and originator in terms of CLBR according to starting dose of rFSH [7]. Clinicians consider CLBR a more meaningful outcome than LBR as it accounts for both fresh and frozen embryo transfers following stimulation with gonadotropins. Thus, CLBR has become the gold standard for determining ART success, as cryopreservation has become more effective and the prevalence of "freeze all" ART cycles is increasing [14–17].

Previous cost-effectiveness analyses between follitropin alfa originator and biosimilars used data from clinical trials and only considered outcomes from fresh embryo transfers using LBR [18–21]. Given the lower cost of the biosimilar, and the recently available data which more closely resembles clinical practice in France [7], this study aimed to perform a cost-effectiveness analysis of follitropin alfa biosimilar versus the originator in women undergoing IVF/ ICSI treatment based on real-world evidence from a French healthcare perspective in terms of cost per CLB.

2. Material and methods

2.1. Model structure

The model structure (Fig. 1) was modified from previous examples in the literature [7, 18, 19, 22, 23] to incorporate CLBR and was validated by two clinical experts. It includes all relevant clinical and economic events in ART management following one OS using either follitropin alfa originator (Gonal-f®, Merck KGaA, Darmstadt, Germany) or follitropin alfa biosimilar (Bemfola®, Gedeon Richter Plc, Budapest, Hungary). Clinical data within the model were taken from the REOLA study [7], it used different starting dose categories which are effective in defining relevant real-world populations, as treating doctors define starting dose based on anticipated ovarian responsiveness [7,10]. The model follows fresh transfers and frozen transfers until live-birth or treatment discontinuation to provide the CLBR [17], allowing the cost per CLB to be reported. All stages following embryo transfer occur either as fresh or frozen transfers and, if frozen embryos remain, women can return to the transfer stage following any failed step (Fig. 1). The model outputs include cost per CLB and the change in cost per CLB, expressed as the additional cost per CLB gained with follitropin alfa biosimilar versus follitropin alfa originator.

2.2. Time horizon and perspective

The health economic model uses a consistent time horizon of one year from oocyte retrieval to embryo transfer, fresh or frozen, plus the time until live-birth (or failure at any previous step) resulting from those transfers. This is in line with the REOLA study [7].

The model evaluates the cost effectiveness of follitropin alfa biosimilar in comparison with follitropin alfa originator on direct medical costs from the French healthcare payer perspective.

2.3. Study population

The modelled population reflects that of the REOLA study and included data from cycles of women who underwent OS either with follitropin alfa originator or with follitropin alfa biosimilar between January 1st, 2016 and February 28th, 2017 in 17 French ART centers who received the study information sheet and did not express formal opposition [7].

2.4. Model inputs

2.4.1. Clinical

The clinical efficacy data included in the model was derived from the REOLA study (Table 1) [7]. If data was unavailable from the study, expert opinion was sought to provide clinical inputs (Table 1).

Severe OHSS rates were reported in the 2017 Agence de la Biomédecine Report as 0.35% for the whole of France regardless of type of gonadotropin used, which was validated by the two clinical experts (Table 1) [24].

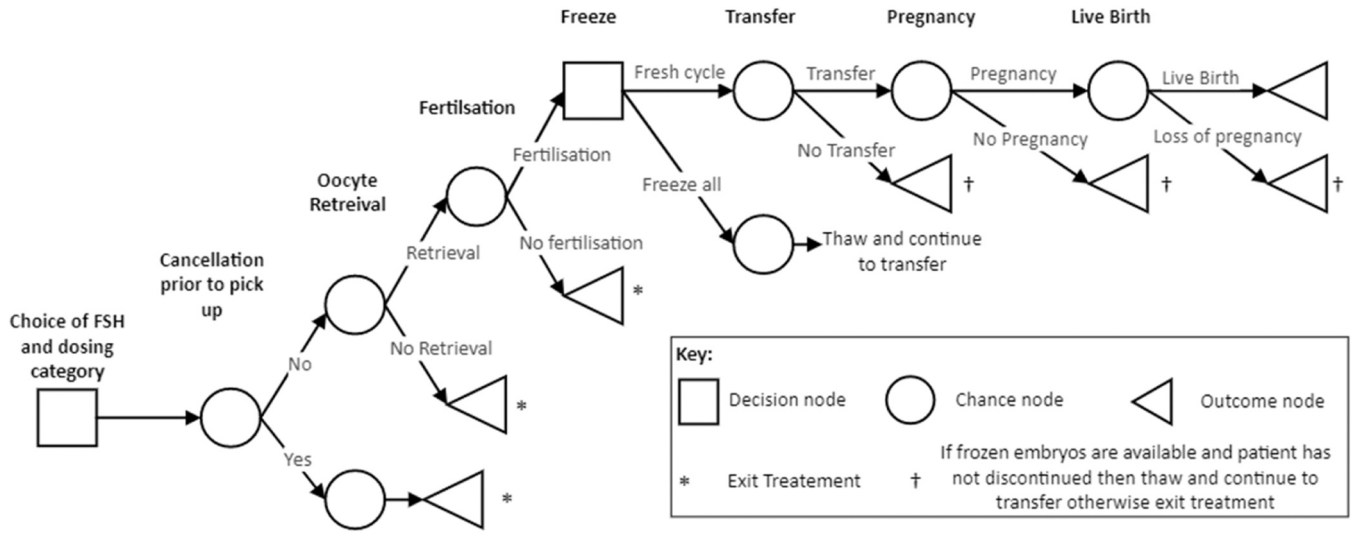

Fig. 1. Decision tree model structure to access the cost effectiveness between the follitropin alfa biosimilar and the follitropin alfa originator.

Table 1
Estimates for clinical inputs for assisted preproduction used in the model.

Category	Event	Follitropin alfa biosimilar				Follitropin alfa originator				Reference
		Input <150 IU	Input 150-244 IU	Input 225 - 299 IU	Input ≥300 IU	Input <150 IU	Input 150-244 IU	Input 225 - 299 IU	Input ≥300 IU	
Gonadotropins	Median total FSH dose	1100	1500	2250	3300	1008	1500	2250	3300	[7]
Pituitary desensitization	None	0.00	0.01	0.02	0.00	0.02	0.00	0.01	0.01	[7]
	Proportion using a long agonist protocol	0.17	0.31	0.32	0.24	0.39	0.37	0.37	0.24	[7]
	Proportion using a short agonist protocol	0.00	0.01	0.07	0.18	0.01	0.05	0.10	0.23	[7]
	Proportion using an antagonist protocol	0.83	0.66	0.60	0.58	0.67	0.58	0.52	0.53	[7]
OHSS	Proportion of cases of severe OHSS	0.0039								[24]
Cancellation	Proportion who continue treatment	0.97	0.96	0.96	0.91	0.96	0.98	0.97	0.95	[7]
Retrievals	Proportion with successful retrievals	0.99	0.99	0.99	0.98	1.00	1.00	0.99	0.98	[7]
Fertilisation	Proportion of IVF	0.30	0.38	0.39	0.38	0.31	0.39	0.42	0.42	[7]
	Proportion of ICSI	0.70	0.62	0.61	0.62	0.69	0.61	0.58	0.58	[7]
	Proportion of fertilisation of at least one embryo	0.85	0.85	0.87	0.69	0.82	0.84	0.83	0.76	[7]
Freeze	Proportion who undergo a fresh transfer	0.83	0.85	0.86	0.83	0.95	0.97	0.96	0.96	[7]
	Proportion who freeze all embryos	0.17	0.15	0.14	0.17	0.05	0.03	0.04	0.04	[7]
Fresh	Proportion with ongoing pregnancies	0.34	0.27	0.21	0.17	0.36	0.33	0.25	0.17	[7]
	Proportion of ongoing pregnancies leading to live-birth	0.87	0.95	0.92	0.94	0.92	0.95	0.93	0.90	[7]
Frozen following Fresh	Proportion with ongoing pregnancies	0.44	0.26	0.30	0.27	0.31	0.31	0.25	0.19	[7]
	Proportion of ongoing pregnancies leading to live-birth	1.00	0.85	0.94	1.00	0.92	0.89	0.80	1.00	[7]
	Proportion having 1 frozen transfer	0.64	0.79	0.77	0.86	0.82	0.77	0.85	0.82	[7]
	Proportion having 2 frozen transfers	0.24	0.15	0.18	0.14	0.13	0.17	0.15	0.18	[7]
	Proportion having 3 frozen transfers	0.08	0.04	0.05	0.00	0.05	0.05	0.00	0.00	[7]
	Proportion having 4 frozen transfers	0.04	0.02	0.00	0.00	0.00	0.01	0.00	0.00	[7]
Freeze all	Proportion with ongoing pregnancies	0.37	0.40	0.43	0.28	0.30	0.43	0.33	0.36	[7]
	Proportion of ongoing pregnancies leading to live-birth	0.90	0.94	0.96	1.00	0.90	0.89	1.00	0.92	[7]
	Proportion having 1 frozen transfer	0.56	0.45	0.62	0.66	0.61	0.67	0.71	0.73	[7]
	Proportion having 2 frozen transfers	0.11	0.36	0.16	0.26	0.24	0.14	0.24	0.24	[7]
	Proportion having 3 frozen transfers	0.22	0.10	0.17	0.03	0.12	0.12	0.05	0.03	[7]
	Proportion having 4 frozen transfers	0.07	0.07	0.03	0.03	0.03	0.05	0.00	0.00	[7]
	Proportion having 5 frozen transfers	0.04	0.01	0.02	0.01	0.00	0.02	0.00	0.00	[7]
	Proportion having 6 frozen transfers	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	[7]
Births	Proportion of single live-births	0.93	0.88	0.93	0.86	0.87	0.89	0.85	0.84	[7]
	Proportion of multiple live-births	0.07	0.12	0.07	0.14	0.13	0.12	0.15	0.16	[7]
Birth Rate	CLBR	0.30	0.25	0.21	0.12	0.27	0.27	0.20	0.12	[7]

Abbreviations: CLBR: Cumulative live-birth rate; FSH = follicle stimulating hormone; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OHSS = ovarian hyperstimulation syndrome

2.4.2. Costs

Direct costs related to ART management, using the reference year 2022, were utilized in the model with no discounting applied due to the short time horizon. Apart from drug related costs, an average of public and private procedural tariffs was used as an input to represent French healthcare practice.

r-hFSH and drug costs associated with pituitary desensitization are informed by the "Prix Public TTC" or retail price incl. VAT reported on publicly available databases (Table 2) [25]. Some pituitary desensitization costs may be dependent on drug choice, in this circumstance, a weighted average of the costs was taken according to expert opinion. Treatments prior to the beginning of OS have been excluded, as they are

Table 2
Estimated drug related costs for assisted reproduction used as input for the model including the range for sensitivity analysis.

Cost Component	Assumption	Cost (€)	Sensitivity analysis range (low-high)	Reference
Bemfola®	Per IU as an average of the different preparations available	€0.22	€0.17-€0.26	[25]
Gonal-f®	Per IU as an average of the different preparations available	€0.26	€0.21-€0.32	[25]
Long agonist protocol – Decapeptyl/ Synarel	50% Decapeptyl (3 mg, one single injection); 50% Synarel (0.2 mg one vial for 30 days of treatment)	€105.76	€89.90-€121.62	[25]; Expert opinion
Short agonist protocol- Decapeptyl	Decapeptyl 0.1 mg injection for 10 days	€45.60	€38.76-€52.44	[25]
Antagonist Protocol- Orgalutran/ Fyremadel	50% Orgalutran (0.25 mg for 5 days); 50% Fyremadel (0.25 mg for 5 days)	€113.12	€96.51-€130.09	[25]; Expert opinion

expected to be equivalent between the different interventions.

Non-drug related costs are displayed in Table 3. Where different methods could be used, with different associated costs, a weighted average was calculated based on REOLA data or expert opinion [7]. Severe OHSS costs are displayed in Table 4.

2.5. Clinical expert validation

Clinical and cost inputs, model structure, methodology, and assumptions were validated by two French clinical experts with experience in assisted reproduction in France.

The key assumption in this model was the equal distribution of women across the starting dose categories for the follitropin originator and biosimilar. This was validated by clinical experts and based on the assumption that starting dose is independent of the r-hFSH used and instead depends on the clinical parameters of the patients.

Table 4
Estimated adverse event related costs for assisted reproduction used as input for the model including the range for sensitivity analysis.

Cost Component	Assumption	Cost (€)	Sensitivity analysis range (low-high)	Reference
Severe OHSS diagnosis	Cost of one ultrasound	€52.45	€44.58-60.32	[38]
Severe OHSS related hospitalisation	Other female genital tract conditions, level 4	€5347.15	€4545.08-€6149.22	13M044 [40]

Abbreviations: OHSS = ovarian hyperstimulation syndrome

2.6. Sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted for all clinical and cost parameters by investigating the effect of inputting the plausible upper and lower values on the final outcome (Table 2, Table 3, Table 4 and Table 5). OWSA was programmed using the visual basic for application (VBA) language for Excel.

3. Results

3.1. Comparative cost effectiveness of follitropin alfa biosimilar to follitropin alfa originator

The results of the cost-effectiveness analysis are outlined in Fig. 2. The total cost per CLB is lower with follitropin alfa biosimilar than follitropin alfa originator, totaling €18,147 and €18,834, respectively, producing an incremental cost saving of €687 per CLB. The greatest

Table 3
Estimated non-drug related costs for assisted reproduction used as input for the model including the range for sensitivity analysis.

Cost Component	Assumption	Cost (€)	Sensitivity analysis range (low-high)	Reference
Stimulation follow up	Cost of one follow up per patient	€353.48	€300.46-€406.50	Expert opinion
Pre-anaesthetic consultation	Cost per patient expected in all women	€27.00	€22.95-€31.05	Expert opinion
Spermatozoid retrieval	Per patient cost of Spermatozoid retrieval by direct approach	€125.40	€106.59-€144.21	YYY027[38]
Spermatozoid preparation	Per patient cost	€54	€45.90-€62.10	0062[39]
Oocyte retrieval	Cost of Oocyte retrieval	€823.91	€703.72-€952.10	13C16J[40]
IVF	Cost per patient	€418.50	€355.73-€481.28	0060[39]
ICSI	Cost per patient	€675	€573.75-€776.25	0061[39]
Embryo cryopreservation	Freezing costs and annual fee; assumed in all women	€351.00	€298.35-€403.65	0082; 0064[39]; expert opinion
Embryo thawing	Cost of thawing	€110.7	€94.10-€127.31	0083[39]
Intrauterine Transfer	Cost of transfer	€52.25	€44.41-€60.09	JSED001[38]
Bioassays	Cost of bioassays (2 β-hCG bioassays per patient)	€13.50	€11.48-€15.52	7401[39]
Consultation pre 6 months	3,4- and 5-month consultations	€69.00	€58.65-€79.35	[41]
Consultations post 6 months	6, 7, 8 and 9th month consultations	€92.00	€78.20-€105.80	[41]
Ultrasound	1st, 2nd and 3rd trimester ultrasounds - assumes single birth	€261.87	€222.59-€301.15	JQQM010, JQQM018, JQQM016 [38]
Pregnancy loss	Cost of pregnancy loss (83% Early-stage loss; 13% Late-stage loss; 4% Still births)	€537.55	€456.92-€618.19	14Z05Z, 14C04Z, 14Z10A[40]; expert opinion
Single birth delivery	75% natural delivery; 25% caesarean delivery. 70% Primiparous; 30% multiparous women	€2048.21	€1740.98-€2355.45	14Z13A, 14Z14A, 14C08A[40]; expert opinion
Multiple birth delivery	75% natural delivery; 25% caesarean delivery. 70% Primiparous; 30% multiparous women	€2587.12	€2199.05-€2975.18	14Z11A, 14Z12A, 14C07A[40]; expert opinion

Abbreviations: β-hCG = Beta human chronic gonadotropin; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization

Table 5
Sensitivity analysis ranges for clinical inputs used in the model.

Category	Event	Follitropin alfa biosimilar				Follitropin alfa originator			
		Input <150 IU	Input 150 - 244 IU	Input 225 - 299 IU	Input ≥300 IU	Input <150 IU	Input 150 - 244 IU	Input 225 - 299 IU	Input ≥300 IU
Gonadotropins	Median total FSH dose	647.1 IU-1605.3 IU	1096.2 IU – 2029.3 IU	1708.4 IU – 2828.50 IU	2385.8 IU-3963.0 IU	573.50 IU – 1541.70 IU	953.00 IU-2088.20 IU	1378.10 IU −2698.40 IU	2332.80 IU −4063.80 IU
Pituitary desensitization	None	0.00-0.00	0.010-0.014	0.01-0.02	0.00-0.00	0.01-0.02	0.00-0.00	0.01-0.01	0.01-0.01
	Proportion using a long agonist protocol	0.14-0.2	0.27-0.36	0.27-0.37	0.20-0.27	0.33-0.45	0.31-0.43	0.31-0.42	0.20-0.27
	Proportion using a short agonist protocol	0.00-0.00	0.010-0.014	0.06-0.08	0.15-0.21	0.01-0.01	0.04-0.05	0.08-0.11	0.19-0.26
	Proportion using an antagonist protocol	0.71-0.95	0.56-0.76	0.51-0.69	0.49-0.69	0.57-0.77	0.49-0.67	0.45-0.60	0.45-0.61
OHSS	Proportion of cases of severe OHSS	0.0033-0.0045							
Cancellation	Proportion who continue treatment	0.82-1.00	0.82-1.00	0.82-1.00	0.77-1.0	0.82-1.00	0.83-1.00	0.83-1.00	0.81-0.1
Retrievals	Proportion with successful retrievals	0.85-1.00	0.84-1.00	0.84-1.00	0.84-1.0	0.85-1.0	0.84-1.00	0.84-1.00	0.83-1.0
Fertilisation	Proportion of IVF	0.26-0.35	0.32-0.44	0.33-0.45	0.32-0.44	0.27-0.36	0.33-0.44	0.35-0.48	0.35-0.48
	Proportion of ICSI	0.59-0.80	0.53-0.71	0.52-0.70	0.57-0.71	0.58-0.79	0.52-0.71	0.50-0.67	0.50-0.67
	Proportion of fertilisation of at least one embryo	0.72-0.97	0.73-0.98	0.74-1.00	0.59-0.80	0.70-0.94	0.72-0.97	0.71-0.96	0.64-0.87
Freeze	Proportion who undergo a fresh transfer	0.71-0.96	0.72-0.98	0.73-0.98	0.71-0.96	0.81-1.00	0.82-1.00	0.82-1.00	0.82-1.00
	Proportion who freeze all embryos	0.14-0.19	0.12-0.17	0.12-0.17	0.14-0.19	0.04-0.06	0.03-0.04	0.03-0.04	0.03-0.04
Fresh	Proportion with ongoing pregnancies	0.29-0.39	0.23-0.31	0.17-0.24	0.14-0.19	0.31-0.42	0.28-0.38	0.21-0.28	0.14-0.19
	Proportion of ongoing pregnancies leading to live-birth	0.74-1.00	0.81-1.00	0.78-1.00	0.79-1.00	0.78-1.00	0.80-1.00	0.79-1.00	0.77-1.00
Frozen following Fresh	Proportion with ongoing pregnancies	0.37-0.51	0.22-0.30	0.26-0.35	0.23-0.31	0.26-0.35	0.26-0.35	0.21-0.29	0.16-0.22
	Proportion of ongoing pregnancies leading to live-birth	0.85-1.00	0.72-0.97	0.59.0.80	0.85-1.0	0.78-1.00	0.76-1.00	0.68-0.92	0.85-1.00
	Proportion having 1 frozen transfer	0.54-0.74	0.67-0.91	0.65-0.88	0.73-0.99	0.70-0.94	0.66-0.89	0.72-0.98	0.70-0.95
	Proportion having 2 frozen transfers	0.20-0.28	0.13-0.17	0.15-0.21	0.12-0.16	0.11-0.15	0.14-0.20	0.13-0.17	0.15-0.20
	Proportion having 3 frozen transfers	0.07-0.09	0.03-0.05	0.05-0.06	0.00-0.00	0.04-0.06	0.04-0.05	0.00-0.00	0.00-0.00
	Proportion having 4 frozen transfers	0.03-0.05	0.02-0.02	0.00-0.00	0.00-0.00	0.00-0.00	0.01-0.01	0.00-0.00	0.00-0.00
Freeze all	Proportion with ongoing pregnancies	0.31-0.43	0.34-0.47	0.36-0.49	0.24-0.33	0.26-0.35	0.36-0.49	0.21-0.29	0.31-0.42
	Proportion of ongoing pregnancies leading to live-birth	0.77-1.00	0.80-1.00	0.82-1.00	0.85-1.00	0.77-1.00	0.76-1.00	0.68-0.92	0.78-1.00
	Proportion having 1 frozen transfer	0.47-0.64	0.38-0.52	0.53-0.71	0.56-0.76	0.52-0.70	0.57-0.77	0.61-0.82	0.62-0.84
	Proportion having 2 frozen transfers	0.09-0.13	0.30-0.41	0.13-0.18	0.22-0.30	0.21-0.28	0.12-0.16	0.20-0.27	0.21-0.28
	Proportion having 3 frozen transfers	0.19-0.26	0.08-0.11	0.15-0.20	0.03-0.04	0.10-0.14	0.10-0.14	0.04-0.05	0.03-0.03
	Proportion having 4 frozen transfers	0.06-0.09	0.06-0.08	0.03-0.04	0.03-0.04	0.03-0.03	0.04-0.05	0.00-0.00	0.00-0.00
	Proportion having 5 frozen transfers	0.03-0.04	0.01-0.01	0.01-0.02	0.01-0.01	0.00-0.00	0.02-0.03	0.00-0.00	0.00-0.00
	Proportion having 6 frozen transfers	0.00-0.00	0.01-0.01	0.00-0.00	0.00-0.00	0.00-0.00	0.00-0.00	0.00-0.00	0.00-0.00
Births	Proportion of single live-births	0.79-1.00	0.75-1.00	0.79-1.00	0.73-0.99	0.74-1.00	0.75-1.00	0.73-0.98	0.00-0.00
	Proportion of multiple live-births	0.06-0.08	0.10-0.14	0.06-0.08	0.12-0.16	0.11-0.15	0.10-0.13	0.12-0.17	0.00-0.00
Cumulative live birth rate	Cumulative live birth rate	0.26-0.35	0.22-0.29	0.18-0.25	0.10-0.14	0.23-0.31	0.23-0.31	0.17-0.23	0.10-0.14

Abbreviations: FSH = follicle stimulating hormone; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OHSS = ovarian hyperstimulation syndrome

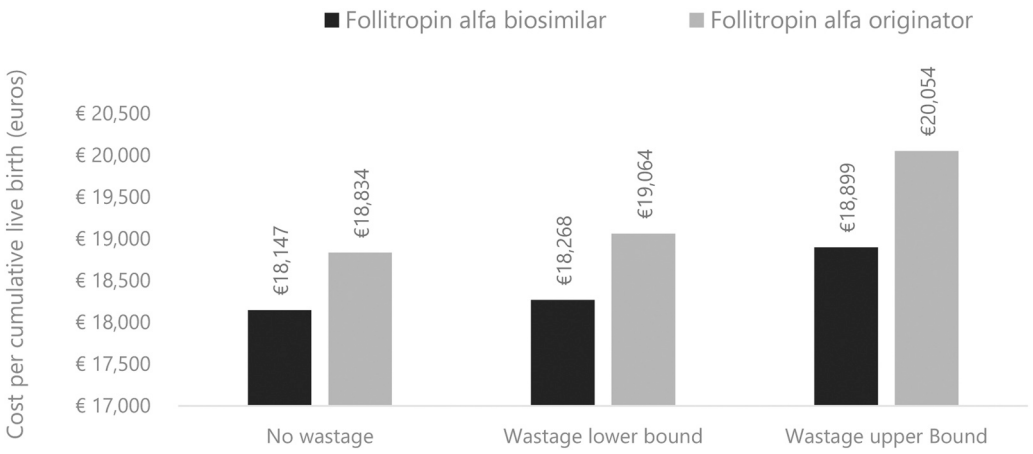

Fig. 2. Comparative cost effectiveness of follitropin alfa biosimilar over follitropin alfa originator across different wastage scenarios including no wastage, the wastage lower bound as based on Foxon *et al.* and the upper bound of wastage as reported in Somigliana *et al.* [26,27].

difference for the average woman between the originator and the biosimilar was during the stimulation phase. Reduced drug costs for follitropin alfa biosimilar contributed to the stimulation being €95.48, (9.1%) cheaper than the originator.

3.2. Wastage

Previous studies have demonstrated lower drug wastage with follitropin alfa biosimilar in a single use delivery system than follitropin alfa originator [26,27]. This lower level has been factored into a hypothetical wastage analysis where wastage was added to the median dose per woman. The upper bound of drug wastage was taken from an Italian study between follitropin alfa biosimilar and follitropin alfa originator [27], whilst the lower bound was taken from a study conducted in the UK [26]. The average lower drug wastage value for follitropin alfa biosimilar was 104 IU per woman and 160 IU for follitropin alfa originator in comparison to 650 IU (Follitropin alfa biosimilar) and 850 IU (follitropin alfa originator) for the average upper bound values [26,27]. When the lower bound for wastage was considered, on top of the median dose, there was a difference in cost per CLB of €796.08, in favor of the biosimilar (Fig. 2). When the upper bound for wastage was considered on top of the median dose there was a difference in cost per CBL of €1155.40 of in favor of the biosimilar (Fig. 2).

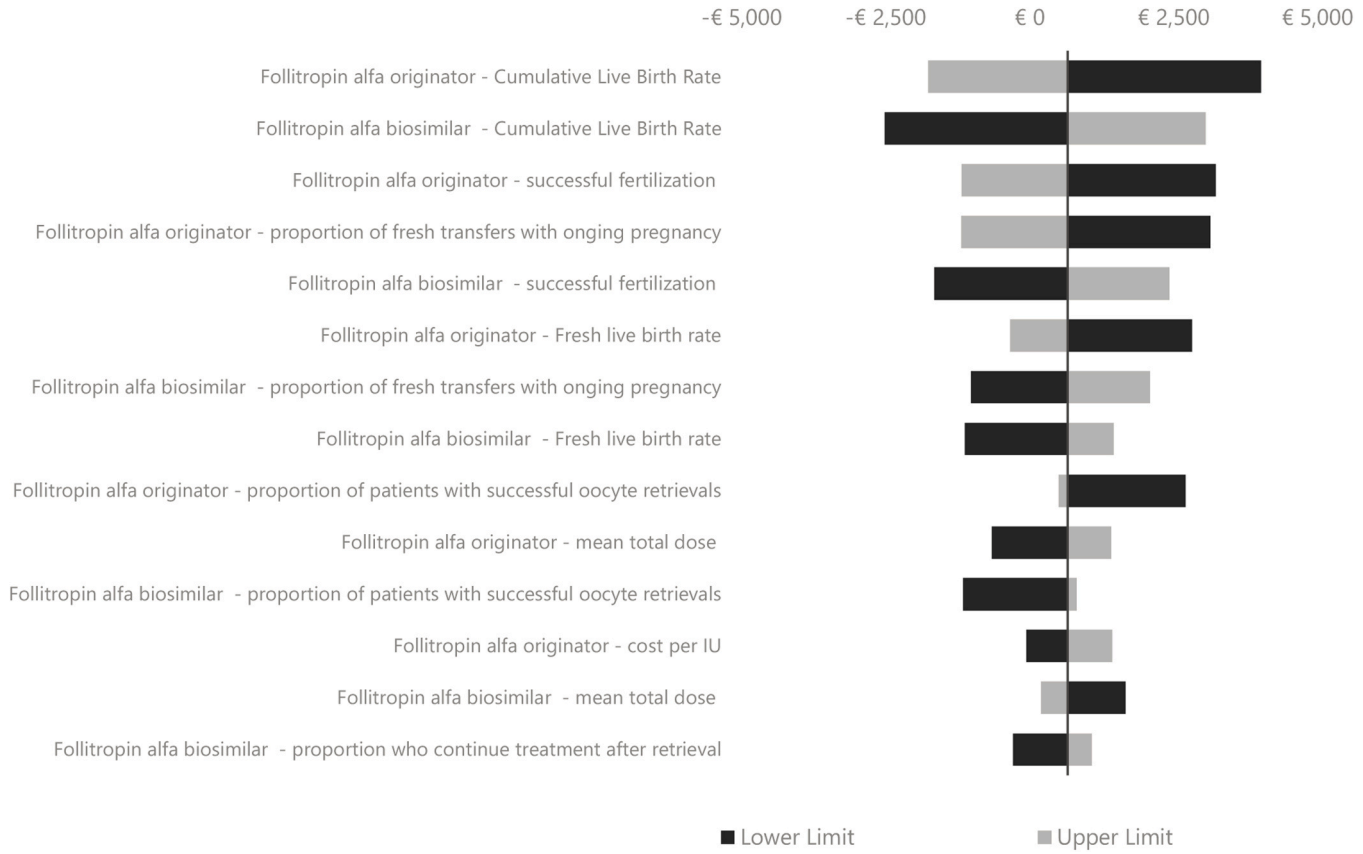

Fig. 3. The upper and lower bounds for inputs with the top twenty highest sensitivity when calculating cost per cumulative live-birth.

3.3. Sensitivity analysis

OWSA analysis was performed on the incremental cost per CLB for follitropin alfa biosimilar versus the originator. The top twenty results are displayed in Fig. 3 and show the key drivers were always higher for the follitropin alfa originator arm, this is thought to be driven by higher follitropin alfa originator acquisition costs.

4. Discussion

This study investigates the cost-effectiveness of follitropin alfa biosimilar versus the originator in a French healthcare setting using inputs from real-world data and CLBR. As follitropin alfa biosimilar has previously shown non-inferiority to the originator in terms of oocyte retrieval and CLBR per ART ovarian stimulation cycle [7–11], which is supported by the recommendation of interchangeability within the EU of all biosimilars with their originator [28], differences in the overall ART costs originate mostly from the r-hFSH drug costs.

The cost per CLB is €18,147 with follitropin alfa biosimilar and €18,834 with follitropin alfa originator, leading to a saving of €687 per CLB following OS with the biosimilar. There was a large difference in the stimulation costs, primarily due to the lower drug costs of follitropin alfa biosimilar compared to the originator; these are further increased in favor of the biosimilar if wastage is also considered. Differences in type of pituitary desensitization used may contribute to differences in costs at this stage but were not the driving factor. Results displayed here are supported by similar cost savings analysis looking at gonadotropin costs only [29], which aligns with the clinical equivalence between the two r-hFSH [5, 7–10] and a previous cost effectiveness study which shows cost per live-birth is lower with follitropin alfa biosimilars than with follitropin alfa originator [18].

A recent French study, based on clinical trial data and cost per live-birth following a fresh transfer, showed a similar difference in cost per live birth as this analysis with a difference of €512.90 per live-birth in favor of the follitropin alfa biosimilar, calculated from the cost per live-birth reported in table three of the publication [18]. Studies from other markets have tried to suggest that follitropin alfa originator is cost-effective over the biosimilar, though their arguments are built on studies with non-statistically significant differences in the birth rate [19–21]. A recent meta-analysis has suggested statistically significant differences between pooled biosimilars and pooled originators [30], however the conclusions of this meta-analysis should be viewed with caution due to the validity of some of the methodology used in the analysis and as some of the studies included do not reflect current clinical practice [31]. In addition, previous studies have not considered the wastage of rFSH and on occasions made unrealistic assumptions on how the rFSH is provided to women, by suggesting the use of an ideal number of pens plus follitropin alfa originator vials to top up as needed, which does not reflect real clinical practice [18].

The birth rates used in previous cost-effectiveness studies range from 26%– 52% for follitropin alfa originator and 32%– 47% for the biosimilar [18–23]. These rates were extrapolated from clinical trials where they are known to be higher than clinical practice due to highly selected subjects [9,31], exemplified by lower birth rates observed in French registry data with deliveries per oocyte retrieval of 18.3% for IVF and 18.8% for ICSI [32]. The birth rates from the real world REOLA study (Table 1) are more consistent with birth rates from French registry data than those reported during the clinical trials, providing results more relevant to clinical practice in France [7,9]. Therefore, allowing a more relevant assessment of the cost effectiveness of the follitropin alfa biosimilar [16,17]. Considering that biosimilars are recommended to be used interchangeably with the originators in the EU, provided sound scientific rationale and comparable clinical outcomes, [28] and that real-world data from the REOLA study demonstrated no meaningful clinical difference between follitropin alfa originator and follitropin alfa biosimilar [7], the driving factor behind the cost-effectiveness is the lower acquisition costs of follitropin alfa biosimilar. Although drug wastage is another important factor to consider.

Follitropin alfa biosimilar has a cost saving per CLB of €687 compared to the originator, if follitropin alfa biosimilar was used to treat every woman in the REOLA study (6606 women) then €4538,322 could have been saved, equivalent to 250 live-births, compared to if all women were treated using follitropin alfa originator. If we apply the same logic to France as a whole, and follitropin alfa biosimilar was used ubiquitously for ART compared to the originator being used ubiquitously, €13,994,190 could have been saved for the French healthcare system. Given that 20,370 babies are born each year via ART [33], this saving would be sufficient to fund 21,141 live-births, a ~4% (771) increase in live-births following OS (Fig. 4).

The follitropin alfa biosimilar and follitropin alfa originator differ regarding their delivery system, which can impact the r-hFSH drug wastage. The follitropin alfa originator is provided in multidose, multiuse pens, unlike the follitropin alfa biosimilar, Bemfola®, where doctors can choose the appropriate follitropin alfa biosimilar pen size to fit the woman's daily r-hFSH need with minimum r-hFSH wastage. In real practice, typically higher dosed pens are prescribed for follitropin alfa originator to be used over a period of several days. The SmPC advises that the follitropin alfa originator dose be taken over two pens if one does not contain sufficient r-hFSH [34], but this approach risks dosing errors [35]. In standard practice in France the pen is discarded if it contains insufficient r-hFSH for the next dose, leading to wastage. We used the results from wastage studies published on the originator and biosimilar as the upper and lower bounds of wastage [26,27]. In both the upper and lower bound simulations there was a large increase in the difference in cost per CLB in follitropin alfa biosimilar's favor, further supporting cost-effectiveness over follitropin alfa originator. Therefore, a switch to follitropin alfa biosimilar could save the French healthcare system money due to both reduced drug costs and reduced wastage.

The authors acknowledge study limitations such as using assumptions to fill data gaps, which risks bias despite being essential to build a model. To reduce this, expert opinion validated any assumptions and clinical and economic data, whilst OWSA was performed by varying parameters individually to assess their impact (Fig. 3). Additionally, a larger data set from a registry in France has been published [36], which could have increased the number of cases in this model. However, it was not considered appropriate, compared to the RELOA study, as it showed less granularity, lacked critical variables, and among other issues the data collection period varied between originator and biosimilars [37].

5. Conclusion

This is the first health economic study utilizing real world data and CLBR enabling a more representative analysis of the cost-effectiveness of infertility treatments utilized in French clinical practice [7, 16, 17]. Overall, the model demonstrated that follitropin alfa biosimilar is a more cost-effective option for ovarian stimulation in France compared to follitropin alfa originator in terms of costs per cumulative live-birth, due to its lower drug costs. If used ubiquitously throughout France for ART, follitropin alfa biosimilar could save the French health system €13,994,190 or lead to 771 more births when compared to the higher cost follitropin alfa originator, whilst the single use delivery system of the follitropin alfa biosimilar could reduce wastage furthering cost savings.

CRediT authorship contribution statement

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

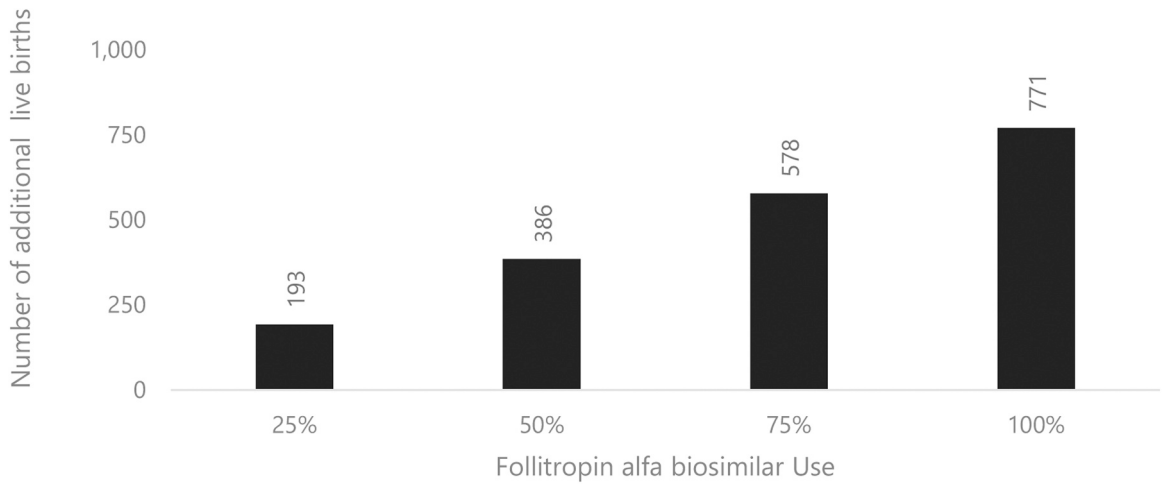

Fig. 4. Number of additional annual live-births following ovarian stimulation with differing proportions of follitropin alfa biosimilar. Based on cost savings from if all women were previously receiving follitropin alfa originator.

review & editing.

Declaration of Competing Interest

ML is an employee of GR, and JJ is a scientific advisor to GR. EA was an employee of GR and is now an external consultant. PB received fees as a consultant and/or speaker for Merck, Genevrier, Ferring, Teva, MSD and GR. JLP received fees as a consultant and/or speaker for GR. LAB and SGB are employees of Remap Consulting who were commissioned to perform this piece of work.

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