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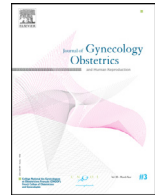
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## Original Article

## A real-world study of ART in France (REOLA) comparing a biosimilar rFSH against the originator according to rFSH starting dose



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## ABSTRACT

**Background:** Since the first launch of a biosimilar recombinant follicle stimulating hormone (rFSH), Bemfola<sup>®</sup>, in Europe in 2014, it has been possible to study in routine clinical care throughout France the effectiveness of a biosimilar rFSH including according to different rFSH starting doses.

**Methods:** REOLA was a non-interventional, retrospective, real world study using anonymized data from 17 Assisted Reproductive Technology (ART) centres' data management systems across France including 2,319 ART ovarian stimulation cycles with Bemfola<sup>®</sup> and 4,287 ART ovarian stimulation cycles with Gonal-f<sup>®</sup>. For both products, four populations were studied according to starting dose of rFSH: < 150 IU, 150 - 224 IU, 225 - 299 IU and ≥ 300 IU. The primary endpoint was the cumulative live birth rate (cLBR) per commenced ART ovarian stimulation cycle including all subsequent fresh and frozen-thawed embryo transfers starting during a follow up period of at least 1 year following oocyte retrieval.

**Results:** A direct relationship of increasing rFSH starting dose with increasing age, increasing basal FSH, decreasing AMH and increasing body mass index was noted. No clinically relevant differences were seen in all outcomes reported, including the cLBR, between Bemfola<sup>®</sup> and Gonal-f<sup>®</sup>, but for both drugs, an association was seen with increasing rFSH starting dose and decreasing cLBR.

**Conclusions:** The REOLA study demonstrates that the cLBR with Bemfola<sup>®</sup> is very similar to Gonal-f<sup>®</sup> across all patient subpopulations. The cLBR is inversely related to the rFSH starting dose irrespective of the drug used, and the REOLA study provides reassurance of the clinical effectiveness of a biosimilar rFSH used in a real world setting.

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## Background

For 2015 France reported to the European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) 68,258 cycles of IVF/ICSI including oocyte

donors; following which, when including frozen embryo replacement cycles, 19,181 infants were born, equivalent to 2.4% of all births in France [1]. Gonadotrophin therapy is a significant proportion of Assisted Reproductive Technology (ART) costs, which in France are generously reimbursed by the state [2], thus the introduction of rFSH

**Abbreviations:** AMH, Anti-Mullerian Hormone; ART, Assisted Reproductive Technology; CEREEES, Committee for Expertise in Research, Studies and Evaluations in the field of Health; CI, Confidence interval; cLBR, Cumulative live birth rate; ET, Embryo transfer; FH, Foetal heart; FSH, Follicle stimulating hormone; INDS, National Institute for Health Data; CNIL, Commission National Data Protection Authority; EIM, European IVF-monitoring Consortium; Ph.Eur, European Pharmacopoeia; EDQM, European Directorate for the Quality of Medicines and Healthcare; MESA, Microscopic Epididymal Sperm Aspiration; OS, Ovarian stimulation; PESA, Percutaneous Epididymal Sperm Aspiration; rFSH, Recombinant follicle stimulating hormone; TESA, Testicular Sperm Aspiration; TESE, Testicular Sperm Extraction; US, Ultrasound

<sup>1</sup> A full list of the REOLA Study Group can be found at the end of the article, in Appendix 1.

(recombinant follicle stimulating hormone) biosimilars such as Bemfola<sup>®</sup>, the first rFSH alpha biosimilar launched in Europe in 2014, [3] could have a positive impact on public health care funding [4].

The approval of Bemfola<sup>®</sup> by the European Medicines Agency was primarily based on extensive physicochemical and biological comparisons to the originator Gonal-f<sup>®</sup>, further supported by clinical studies [5, 6], leading to the conclusion that there were no clinically relevant differences between Bemfola<sup>®</sup> and Gonal-f<sup>®</sup> [3]. Beyond the strictly controlled studies demonstrating the efficacy of Bemfola<sup>®</sup> [5, 6], the effectiveness of Bemfola<sup>®</sup> with respect to clinical pregnancy rates following embryo transfer has also been demonstrated in four populations of differing ovarian responsiveness in a real world study of 1,222 women treated in Spain [7].

A preliminary report of the REOLA study was presented at the 2020 annual meeting of ESHRE of very similar cumulative live birth rates with Bemfola<sup>®</sup> compared to other rFSH alpha options; cumulative live birth rates per stimulated cycle of 20.0% (95% CI: 18.4%-21.5%) with Bemfola<sup>®</sup> (n=2,478) and 20.8% (95% CI: 19.7%-21.9%) with other follitropin alfas (n=4,970) [8]. However, this data was criticised in that the “other follitropin alfas” population included both Gonal f<sup>®</sup> and Ovaleap<sup>®</sup> (Theramex, UK) and there were slight imbalances in the populations compared with respect to the starting dose of rFSH used. To correct these issues the present paper presents only data from Bemfola<sup>®</sup> and Gonal-f<sup>®</sup> treatment and this data is presented according to rFSH starting dose to ensure homogeneity in the populations being compared. Real world studies provide the opportunity to assess the effectiveness of new drugs in different populations [9]. Although the patient's age is generally the top prognostic factor for ART outcome, numerous other factors are relevant, although incorporation of many further factors to define prognostic groups presents significant challenges [10]. With regard to the assessment of the effectiveness of Bemfola<sup>®</sup> the starting dose for ovarian stimulation chosen by doctors defines relevant real-world populations, as the chosen rFSH starting dose is ultimately an overall assessment by the treating doctor of anticipated ovarian responsiveness, which is not the sole but a critical factor influencing prognosis [7]. Thus, this paper analyses the effectiveness of Bemfola<sup>®</sup> with respect to cumulative live birth rates per stimulated cycle according to the rFSH starting dose in comparison to the originator Gonal-f<sup>®</sup>.

## Methods

### Study design

The REOLA study was a non-interventional, retrospective, observational study conducted in 17 French ART centres, which had used Bemfola<sup>®</sup> for at least 100 IVF/ICSI cycles.

In accordance with French legislation on non-interventional studies anonymized data from women, who received the REOLA information sheet at least one month prior to the data collection and did not express formal opposition to the use of their data, were extracted from the data management system of the ART centres. Each clinic used one of three different ART database software packages, Medifirst (<https://www.medifirst.fr/>, n=11), InfoFIV (<http://www.infofiv.org/>, n=5) and BabySentry (<http://www.babysentry.com/>, n=1). Data were collected from cycles of women who underwent ovarian stimulation (OS) between January 1st, 2016 and February 28th, 2017 and also including a follow-up to livebirth of all pregnancies following embryo transfer within 12 months of oocyte retrieval. The following treatments were excluded from the analyses: 1) OS with follitropin alfa in association with another gonadotropin; 2) cycles with sperm obtained by Microscopic Epididymal Sperm Aspiration (MESA), Testicular Sperm Extraction (TESE), Testicular Sperm Aspiration (TESA), Percutaneous Epididymal Sperm Aspiration (PESA); 3) cycles with oocytes from donors; 4) cycles with genetic preimplantation diagnosis; 5) cycles with female fertility preservation. Further this paper

presents only cases treated with Bemfola<sup>®</sup> (Gedeon Richter Plc, Budapest, Hungary) or Gonal-f<sup>®</sup> (Merck KGaA, Darmstadt, Germany). For both Bemfola<sup>®</sup> and Gonal-f<sup>®</sup> four populations were studied according to starting dose of rFSH: < 150 IU, 150 - 224 IU, 225 - 299 IU and ≥ 300 IU.

### Measurements

The primary endpoint was the cumulative live birth rate (cLBR) per started ART ovarian stimulation cycle including all subsequent fresh and frozen-thawed embryo transfers during a follow up period of at least 1 year following oocyte retrieval. A live birth was defined as a delivery of at least 24 weeks gestation with a heartbeat. Demographic data and secondary endpoints were limited to variables collected consistently across the three databases by the different centres and these included number of days of rFSH stimulation, total dose of rFSH administered, number of oocytes retrieved, number of MII oocytes, and number of fertilized oocytes.

### Statistical analysis

Since the purpose of this study was descriptive, no formal sample size calculations were conducted, instead the sample size was based on ensuring adequate numbers to describe the effectiveness of Bemfola<sup>®</sup> in routine use. As doctors had treated patients as they felt appropriate it would be anticipated that there would be considerable heterogeneity within populations, which might be subject to both overt and covert biases. Thus, to avoid misleading the reader with comparative analyses, particularly if logistic regression is applied potentially introducing distortions, comprehensive data is provided descriptively with continuous data expressed as mean ± standard deviation or, if non-normally distributed, by median [interquartile ranges]. Nevertheless, to appreciate the similarity of the Bemfola<sup>®</sup> and Gonal-f<sup>®</sup> subpopulations the primary endpoint (cLBR) is presented with the 95% Confidence Intervals (CI), which are relatively narrow given the large sample size. Statistical analyses were performed using SAS<sup>®</sup> Version 9.4, and SAS/STAT 14.1 software under Windows (SAS Institute, North Carolina USA).

## Results

The REOLA study results presented included 2,049 women treated for 2,319 ART OS cycles with Bemfola<sup>®</sup> and 3,731 women treated for 4,287 ART OS cycles with Gonal-f<sup>®</sup>. Note patients may have had more than 1 cycle of ART OS and multiple frozen embryo cycles.

Similar baseline characteristics were seen for the populations receiving Bemfola<sup>®</sup> and those receiving Gonal-f<sup>®</sup> but differed according to the starting dose of rFSH (see Table 1). There were direct relationships of increasing age, increasing basal FSH, decreasing AMH and increasing body mass index (BMI) with increasing rFSH starting dose. Primary infertility and ovulatory dysfunction were commoner with the lowest rFSH starting doses, whereas the duration of infertility was longest and the diagnosis of endometriosis were commoner with the highest rFSH starting doses.

Pituitary desensitization was used in almost all ART cycles, although short agonist protocols were commoner in patients on higher rFSH starting doses and antagonist protocols were commoner with lower rFSH starting doses (see Table 2). Irrespective of rFSH starting dose the median duration of rFSH stimulation was 10 days for both Bemfola and Gonal-f, except for Gonal-f <150 IU, which had a median value of 11 days of FSH stimulation. Moreover, irrespective of rFSH starting dose the interquartile range of the duration of rFSH stimulation fell within 9 to 12 days for both products. The median values of total rFSH administered were the same for Bemfola and Gonal-f and increased with the rFSH starting doses.

Irrespective of rFSH starting dose no appreciable difference was seen in number of oocytes retrieved between Bemfola® and Gonal-f®, but for both products there was a trend of decreasing number of oocytes retrieved with increasing rFSH starting dose (see Table 3). Similar trends were seen for the numbers of metaphase II oocytes and numbers of embryos. For both products the proportion of embryos transferred at the blastocyst stage declined and the number of embryos per embryo transfer increased with increasing rFSH starting dose.

Irrespective of rFSH starting dose no significant difference was seen in cLBR between Bemfola® and Gonal-f®, but for both products there was a trend of decreasing cLBR with increasing rFSH starting dose (see Fig. 1).

**Discussion**

The REOLA study presents results of the initial use of a biosimilar rFSH, Bemfola®, against the originator Gonal-f® in 17 ART centres across France while studying the variation of the rFSH starting dose, which is an important and controversial topic. The REOLA study confirms the similar efficacy of Bemfola® vs the originator Gonal-f® supporting prior studies [6, 7] but on a much larger number of cases and in real life. The analyses according to starting rFSH dose provides homogeneity of the comparative populations and interesting data on the relationship between FSH dose, conditions of use of these doses and results.

There is a clear relationship between higher total dose of rFSH and lower chance of livebirth [11]. Further there is a significant inverse relationship between the starting daily dose of gonadotrophins and pregnancy rates, whereas there is no significant difference in pregnancy rates between women who were stimulated for <9 days, 10–11 days or >12 days. [12]. As the REOLA study demonstrates, the total dose of rFSH is driven principally by the daily rFSH dose as the duration of rFSH stimulation remains relatively constant, thus confirming the starting dose of rFSH defines populations of interest to study the clinical effectiveness of Bemfola®. It is more likely that the relationship between higher total dose of rFSH and lower chance of cLBR is due to the patients' prognoses rather than an adverse effect of higher doses of rFSH. A study of oocyte donors found no adverse effect from higher rFSH doses during stimulation; aneuploidy rates not showing any relationship with either total FSH dose or number of oocytes [13]. Although the latter study does not confirm for an individual patient that obtaining more oocytes will increase her chance of pregnancy, it suggests that higher doses of FSH do not have an adverse effect on oocytes. Further the REOLA study suggests a relationship in ART between higher prescribed rFSH doses and lower patient fertility evidenced by patient age and biomarkers of ovarian response.

With increasing embryo cryopreservation effectiveness and the trend to “freeze all” cycles the clinical pregnancy rate per fresh embryo transfer is becoming less relevant as a measure of clinical effectiveness, as good responding patients likely to achieve a pregnancy may not have the opportunity for pregnancy in the fresh ART cycles [14]. Although the retrieval of up to 12 to 18 oocytes is associated with the maximal fresh LBR, when including cryopreserved embryo cycles there is a continuing positive association between the number of oocytes retrieved and cLBR [15]. Note for biosimilar rFSH development the European Medicines Agency (EMA) recommends the “number of oocytes retrieved” as the primary endpoint to demonstrate comparability of clinical efficacy against the reference product, as pregnancy rates are influenced by multiple factors unrelated to ovarian stimulation [16]. The clinical development program of Bemfola® confirmed an equivalent number of oocytes retrieved between Bemfola® and Gonal-f® [6] and the REOLA study now provides evidence of clinical effectiveness with respect to similar cLBRs in actual clinical practice across a range of patient populations.

The goal of setting the rFSH starting dose is to achieve an adequate response to ovarian stimulation while minimising the risk of ovarian hyperstimulation syndrome and numerous factors are relevant including age, BMI, weight, polycystic ovarian syndrome, smoking history, severe endometriosis, prior ovarian response, prior pelvic surgery, AFC, ovarian volume, ovarian stromal blood flow, serum AMH, serum FSH, serum LH, serum oestradiol, serum inhibin B, serum testosterone and various dynamic tests of ovarian reserve [17–19]. Although various predictive algorithms are available to help the determination of the rFSH starting dose [17–19], in clinical practice patients are very heterogeneous. In addition, the interaction between prognostic factors is complex, hence no simple consistent way has been widely adopted to set the rFSH alpha starting dose for all patients, which has ultimately relied on the professional judgement of the treating doctor. During the recent development of rFSH delta (Rekovel®; Ferring Pharmaceuticals) due to differences in pharmacokinetic and pharmacodynamic properties of rFSH delta compared to rFSH alpha [20] it was necessary to introduce a new dosing algorithm for OS with rFSH delta, which was proposed from a phase 2 study based on achieving a desired number of oocytes according to a patient's body weight and serum AMH [21]. However, in the confirmatory phase 3 trial of this dosing algorithm 33.2% of investigators would have preferred to alter the dose of rFSH delta during OS from that determined by the algorithm, illustrating the challenge of selecting the “ideal” starting rFSH dose [22].

When considering the relevance of the rFSH starting dose to ART treatment outcome, it is important to question if the daily rFSH dose should be adjusted during stimulation. Although it is tempting to

**Table 1**  
Baseline characteristics of women according to the starting dose of Bemfola® or Gonal F®.

N	Bemfola® (n=2319)				Gonal F® (n=4287)			
	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU
	197	698	527	897	834	1518	730	1205
Age (years)	30.6 ± 4.4	32.4 ± 4.3	34.0 ± 4.3	36.0 ± 4.3	31.4 ± 4.2	32.8 ± 4.3	34.8 ± 4.2	36.4 ± 4.2
Dysovulation	37.6%	24.3%	20.5%	21.8%	41.8%	25.9%	28.2%	32.3%
Primary infertility	74.9%	74.7%	76.7%	64.5%	81.9%	71.9%	70.6%	63.0%
Duration of infertility (months)	41 [30-63]	42 [30-64]	44 [32-72]	48 [30-73]	45 [31-69]	47 [32-73]	49 [32-76]	52 [35-78]
Body Mass Index (kg/m <sup>2</sup> )	23.0 ± 3.81	23.8 ± 4.7	24.2 ± 5.0	24.4 ± 4.8	22.5 ± 3.8	23.9 ± 4.7	24.3 ± 4.7	24.8 ± 5.2
Obesity*	6.0%	11.5%	15.7%	13.8%	6.3%	13.0%	14.3%	16.2%
Smoker	24.1%	23.4%	23.1%	18.6%	18.4%	19.2%	20.1%	16.6%
Basal FSH concentration (IU/L)	6.01 ± 1.56	6.43 ± 1.92	7.05 ± 2.16	7.42 ± 2.50	6.14 ± 1.68	6.52 ± 1.91	7.05 ± 2.08	7.84 ± 2.58
Basal AMH concentration (ng/mL)	6.86 ± 4.28	4.44 ± 3.59	2.96 ± 2.12	1.72 ± 2.03	7.95 ± 6.43	4.54 ± 4.46	3.00 ± 2.94	1.85 ± 2.46
Male Infertility	17.7%	32.3%	27.1%	18.1%	27.6%	34.9%	30.2%	21.1%
Female Infertility	50.4%	40.1%	42.9%	50.4%	35.9%	33.7%	37.5%	45.7%
Both Infertility	21.2%	16.0%	16.7%	21.9%	28.6%	19.0%	20.0%	22.4%
Idiopathic Infertility	10.6%	11.6%	13.4%	9.6%	7.8%	12.4%	12.4%	10.8%
Endometriosis	7.1%	12.4%	13.1%	19.0%	5.8%	7.4%	6.8%	12.6%

**Table 2**  
Details of ovarian stimulation cycles according to the starting dose of Bemfola® or Gonal F®.

	Bemfola® (n=2319)				Gonal F® (n=4287)			
	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU
N	197	698	527	897	834	1518	730	1205
Pituitary desensitization								
Short agonist	0%	1.2%	6.6%	17.9%	0.6%	4.7%	9.9%	22.7%
Long agonist	17.0%	31.3%	31.8%	23.9%	30.9%	37.0%	36.7%	23.8%
Antagonist	83.0%	66.3%	60.0%	58.1%	66.8%	58.0%	52.4%	52.9%
Days of rFSH stimulation								
Median	10	10	10	10	11	10	10	10
Interquartile range	9-11	9-11	9-12	9-12	9-12	9-11	9-12	9-12
Total rFSH dose IU								
Median	1100	1500	2250	3300	1008	1500	2250	3300
Interquartile range	825 -1313	1350 - 1800	2025 -2700	2700 -4200	700 - 1275	1200 - 1900	1800 - 2625	2700 - 4400

Data are displayed as: number, % cycles or medians and interquartile ranges based on the number of patients with non-missing data.

adjust the rFSH dose during stimulation when the ovarian response does not meet expectations, ovarian biology makes such change futile within the timescale of an ART cycle. After adjusting the daily dose of rFSH in view of FSH pharmacokinetics there is a delay of 3 to 4 days for the circulating FSH levels to increase to a new stable level [23] and it takes a further 4 days to achieve pharmacodynamic responses of the ovary with respect to follicular growth and increased oestradiol levels [24]. Moreover, the REOLA study demonstrates that the daily dose of rFSH has little impact on the duration of rFSH stimulation.

Although the starting rFSH stimulation dose varies significantly, it has been suggested this variation may in fact have little impact on the ultimate outcome of an ART cycle [25]. For anticipated poor responder patients, the OPTIMIST study did not find any increase in livebirth rates in those patients receiving an increased FSH daily dose of 225 IU or 445 IU compared to a standard daily dose of 150 IU FSH daily [26]. Also, for anticipated hyper responder patients the OPTIMIST study comparing a reduced dose of 100 IU daily versus a standard dose 150 IU FSH daily did not find any difference in cumulative live birth rate nor occurrence of severe OHSS, although the occurrence of any grade of OHSS was lower with reduced FSH dose [27]. Further in cases considered at particular risk of OHSS avoiding an injection of HCG and instead using GnRH agonist trigger with cryopreservation of all embryos for delayed transfer may largely eliminate the risk of OHSS [14]. REOLA shows that varying the rFSH starting dose according to the anticipated ovarian response does not

normalise the number of oocytes obtained suggesting an inevitability of outcome such that the precise rFSH starting dose may not be critical. However, if there had been no dose adjustment according to anticipated ovarian response in the ART cycles reported by the REOLA study, the differences in number of oocytes obtained might have been even greater. Taken into account the views of international experts in ART regarding the FSH starting dose, ESHRE proposes to optimally use a GnRH antagonist protocol from 150 IU FSH daily for anticipated high responders up to a maximum of 300 IU FSH daily for anticipated low responders based on serum AMH or AFC determination by ultrasound, advising against changing the FSH dose during stimulation [28]. The REOLA study would further support the ESHRE guidance as duration of rFSH stimulation does not appear to relate to daily rFSH dose, thus changing dose during stimulation is unlikely to be helpful.

No formal cost efficiency analysis was performed, as this would require further details that were not available; for instance, in addition to the total amount of rFSH administered it would be important to consider the rFSH dose wasted. However, within each REOLA study subpopulation comparing Gonal-f® and Bemfola® the total rFSH administered and cumulative cLBR are similar. Further a real-world study of 4,078 IVF cycles in five UK clinics modelled the actual usage of Gonal-f® including wastage against potential usage of Bemfola® suggesting a 5.7% greater rFSH wastage in Gonal-f® pens than Bemfola® pens, even if patients administered two Gonal-f® injections

**Table 3**  
Outcomes of oocytes retrievals according to the starting dose of Bemfola® or Gonal F®.

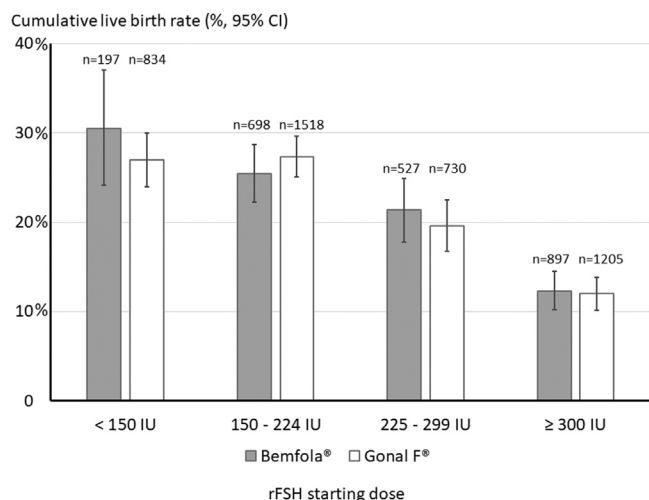
	Bemfola®				Gonal F®			
	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU
Oocyte retrieval (n)	191	673	508	812	801	1484	709	1148
Number of oocytes retrieved	14.1 ± 7.4	12.9 ± 7.2	10.1 ± 5.8	6.6 ± 5.1	13.0 ± 7.1	12.1 ± 6.3	10.3 ± 6.0	7.4 ± 5.0
Number of metaphase II oocytes	9.8 ± 6.7	9.9 ± 6.1	7.8 ± 4.7	4.9 ± 4.0	9.9 ± 6.0	9.3 ± 5.4	8.0 ± 5.0	5.6 ± 4.1
Fertilisation rate*								
IVF	66.6%	64.0%	68.0%	64.0%	62.7%	69.6%	69.6%	70.1%
ICSI	72.4%	66.7%	67.2%	65.0%	70.2%	67.8%	70.2%	65.1%
Number of embryos	7.9 ± 5.2	7.2 ± 5.1	5.7 ± 4.0	3.3 ± 3.1	7.0 ± 5.1	6.7 ± 4.8	5.6 ± 4.0	3.8 ± 3.3
Stage of ET								
Cleavage stage	62.1%	73.3%	82.0%	89.8%	60.1%	73.0%	76.8%	90.0%
Blastocyst	37.9%	26.7%	18.0%	10.2%	39.9%	27.0%	23.2%	10.0%
Number of embryos per ET								
Mean	1.37	1.34	1.47	1.49	1.41	1.47	1.57	1.61
<b>1</b>	63.3%	66.5%	55.3%	54.3%	59.9%	54.0%	45.5%	43.3%
<b>2</b>	36.7%	32.7%	42.6%	42.3%	39.0%	44.7%	51.8%	52.2%
<b>3</b>	0.0%	0.8%	2.2%	3.2%	1.1%	1.3%	2.7%	4.4%
<b>4</b>	0.0%	0.0%	0.0%	0.2%	0.0%	0.0%	0.0%	0.1%

Data are displayed as: n (%) or by their mean ± standard deviation based on the number of patients with non-missing data.

ET: embryo transfer

\* Fertilization rate % was calculated as the number of oocytes with 2 pronuclei (PN) on day 1 divided by the number of injected or inseminated oocytes





**Fig. 1.** Cumulative live birth rate (%; 95% CI) following fresh and all cryopreserved embryo transfer cycles starting within at least 1 year post oocyte retrieval per commenced ART ovarian stimulation cycle according to the starting dose (IU rFSH) of Bemfola® or Gonal F®.

on days when the residual rFSH in the Gonal-f® pen was inadequate for that day's prescribed dose to reduce wastage [4]. The routine practice in France, where rFSH costs are fully reimbursed, if the residual rFSH in the Gonal-f® pen should be inadequate to administer that days FSH dose would be usually to give only one injection and discard the pen with the inadequate Gonal-f dose to reduce the risk of dosing errors.

Beyond potential reduced rFSH wastage a single use, multidose rFSH pen product was considered to have several advantages over multiple use rFSH pens in a comparative study of different types of FSH delivery [29]. In particular, the simplicity of a single use pen that does not require a treatment diary to keep a record of the residual rFSH to determine whether it is adequate for the next injection or whether two injections may be required was seen as important factor to reduce the risk of dosing errors. Further an easier-to-use FSH administration option was seen as preferable to shorten the time required for training thereby reducing the number of persons simultaneously present in the IVF centre, which is a recommendation to reduce the risk of Covid-19 transmission [30].

There are limitations with the REOLA dataset reflecting real world clinical practice where patients may have multiple cycles of ART with different treatment protocols, different ART laboratories and even moving between clinics. Further not all relevant data to ART outcome may be captured by different clinics' databases consistently [31], for instance embryological data was not collected consistently hence has been omitted from this paper. Consequently, the REOLA study data is presented transparently using appropriate descriptive statistics with a sufficiently large sample size to provide helpful information to guide clinical practice when considered with other relevant publications [3, 5, 6]. Although logistic regression could have been applied to this real-world data attempting to correct for imbalances between groups to make comparative analyses, the lack of randomisation between groups risks significant imbalances arising between groups that may not even be recognised leading to misleading comparisons. The impact of such potential imbalances between groups may be increased by the many challenges of applying logistic regression to ART real world data including multicollinearity of variables (e.g. age, oocyte number and AMH are highly correlated yet also have non-redundant contribution to outcomes), non-linear relationship between variable and outcome (eg age and pregnancy rate), the need to use both continuous and categorical variables (e.g. age, AMH and BMI are continuous; whereas diagnosis and treatments are discrete), and the impacts of outliers and missing data [10, 32]. At the time of

completion of the REOLA study there were still cryopreserved embryos that could allow patients to have further treatment, hence the ultimate cumulative livebirth rate per stimulated cycle might increase slightly, and some patients might eventually even have more than one livebirth per stimulation cycle. However, French ART regulations require all cryopreserved embryos to be transferred prior to further fresh ART attempt and there was a follow up period of one year following the oocyte retrieval to transfer cryopreserved embryos, hence the number of further livebirths outside the study period would be expected to be low and not make a significant difference to the results.

Although for demonstration of a fertility drug's effectiveness the cLBR is a relevant measure, it is important to note that in view of multiple confounding factors, an even more important and sensitive comparison of the similarity of a biosimilar to an originator product is provided by extensive, meticulous laboratory comparisons [3]. Taken this into account, it is interesting to note that for any follitropin that a gold standard for comparisons of the active drug substance (the follitropin for peptide mapping and glycan analysis chemical reference substance) according to the European Pharmacopoeia (Ph.Eur) of the European Directorate for the Quality of Medicines and Healthcare (EDQM) since 2018 has been the Bemfola® drug substance [33, 34].

## Conclusions

The REOLA study demonstrates that the CLBR with Bemfola® is very similar to Gonal-f® across all patient subpopulations. Complementary to the Bemfola® clinical development program [3, 5, 6] and other real-world studies [4, 7] the REOLA study provides further support for the clinical effectiveness of Bemfola® across different populations of patients undergoing ART from patients receiving a low rFSH starting dose to those patients receiving a high rFSH starting dose. The cLBR is inversely related to the daily dose of rFSH administered, which has little influence on the duration of rFSH stimulation, and this inverse relationship appears to result from worse prognoses of the patients who are given higher rFSH doses. The results of the REOLA study support the simplified approach to OS for ART suggested by ESHRE guidance that is based on sound scientific evidence and international expert opinion [28].

## Authors' contributions

All authors contributed to the design of the study, execution of the study and/or drafting of the publication and all authors confirm the validity of the results.

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The REOLA study was funded by Gedeon Richter France, 103 Boulevard Haussmann, 75008 Paris.

## Ethics approval and consent to participate

The non-interventional study protocol received a positive opinion of the Committee for Expertise in Research, Studies and Evaluations in the field of Health (CEREES), on 26 September 2017, a positive opinion on the public interest nature of the study by the National Institute for Health Data (INDS) on 17 October 2017, as well as the authorization of the Commission National Data Protection Authority (CNIL) on 23 March 2018. Further, a non-opposition form was sent to all patients informing them that their data would be used for a research purpose unless they declined for such use. Data were collected retrospectively in 2018 and therefore the study did not influence drug prescription nor medical practice.

## Competing interests

EA is an employee of Gedeon Richter, and JJ is a scientific advisor to Gedeon Richter. SH received funding for scientific projects from Gedeon Richter, Merck and Ferring. MG received fees from Merck Serono, Ferring, MSD, Besins, GE, Samsung and Gedeon Richter. PB received fees as consultant and/or speaker for Merck, Genevrier, Ferring, Teva, MSD and Gedeon Richter. CA received consulting fees from Gedeon Richter. The other co-authors declare that they have no competing interests.

The data analysis was performed by the Contract Research Organisation, Monitoring Force, under the direction of the Medical Affairs department of Gedeon Richter France and the final manuscript was drafted by the Medical Affairs department in collaboration with the authors; in both cases there was no involvement of Gedeon Richter marketing or commercial teams.

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