Journal of **R**eproduction & **I**nfertility
Volume 22, Issue no. 2
http://dx.doi.org/10.18502/jri.v22i2.5798

Original Article

Check for updates

Clinical Efficacy of Follitropin Alfa in GnRH-Antagonist Protocols: A Prospective Observational Phase IV Study on the Use of Biosimilar Follitropin Alfa r-hFSH in Assisted Reproductive Technology in a Routine Care Setting

Georg Griesinger [1*], Thilo Schill [2], Michael Sator [3], Michael Schenk [4], Jan-Steffen Krüssel [5]

1- Sektion Für Gynaekologische Endokrinologie und Reproduktionsmedizin, Klinik Für Frauenheilkunde & Geburtshilfe (Gynaekologie), Universitaetsklinikum Schleswig-Holstein-Campus Luebeck, Luebeck, Germany
2- MVZ Kinderwunschzentrum Langenhagen-Wolfsburg, Langenhagen, Germany
3- Kinderwunsch im Zentrum GmbH, Tulln an der Donau, Austria
4- Das Kinderwunsch Institut Schenk GmbH, Dobl b. Graz, Austria
5- Universitaeres interdisziplinäres Kinderwunschzentrum Duesseldorf (UniKiD), Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Duesseldorf, Duesseldorf, Germany

** Corresponding Author:*
Georg Griesinger,
Sektion Für Gynaekologische Endokrinologie und Reproduktionsmedizin, Klinik Für Frauenheilkunde & Geburtshilfe (Gynaekologie), Universitaetsklinikum Schleswig-Holstein-Campus Luebeck, Luebeck, Germany
E-mail:
georg.griesinger@uni-luebeck.de

Received: Jun. 14, 2020
Accepted: Nov. 10, 2020

Abstract

Background: This phase IV routine care study evaluated ovarian responses when using a biosimilar follitropin alfa r-hFSH (Bemfola®) for controlled ovarian stimulation (COS) in women undergoing assisted reproductive technology (ART) treatment who were pituitary-suppressed with a gonadotrophin-releasing hormone (GnRH) antagonist.

Methods: This multicenter, prospective, non-comparative, non-interventional study (Germany/Austria) was conducted with 885 women (Mean age of 34.0±4.4 years) for whom COS with Bemfola® and GnRH-antagonist for pituitary suppression were applied as part of in vitro fertilization (IVF) treatment with/without intracytoplasmic sperm injection (ICSI) observing routine clinical-practice protocols. Primary endpoint was the number of retrieved cumulus-oocyte-complexes (COCs).

Results: Among 986 ART cycles, COS was given for 9.9±1.8 days (First-day r-hFSH dose of 220.7±68.9 *IU*; mean total dose of 2184.3±837.5 *IU*). It was revealed that 99.1% of cycles resulted in follicular puncture, with mean of 10.7±6.6 oocytes retrieved. Successful fertilization took place after IVF/ICSI in 93.8% of follicular punctures. Freeze-all was performed in 14.2% of cycles. Fresh embryo transfer was performed in 76.9% of cycles with follicular puncture; mean day of transfer was 3.5±1.3 and average number of transferred embryos was 1.76±0.50. Clinical pregnancy rate was 30.2% of embryo-transfer cycles and 23.4% of started cycles. Sixty-nine reports of ovarian hyperstimulation syndrome (7.0% of started cycles) were documented.

Conclusion: COS with Bemfola® in GnRH-antagonist IVF/ICSI protocols in a routine care setting led to an appropriate ovarian response allowing oocyte retrieval in 99.1% of initiated cases.

Keywords: Assisted reproductive technology, Biosimilar pharmaceuticals, Follitropin alfa, Gonadotropin-releasing hormone antagonist.
To cite this article: Griesinger G, Schill T, Sator M, Schenk M, Krüssel JS. Clinical Efficacy of Follitropin Alfa in GnRH-Antagonist Protocols: A Prospective Observational Phase IV Study on the Use of Biosimilar Follitropin Alfa r-hFSH in Assisted Reproductive Technology in a Routine Care Setting. J Reprod Infertil. 2021;22(1):116-124. http://dx.doi.org/10.18502/jri.v22i2.5798.

Introduction

Recombinant human follicle-stimulating hormone (r-hFSH) has been used as part of assisted reproductive technology (ART) since the 1990s. Recently, biosimilar versions of r-hFSH preparations have been developed to provide high-quality alternatives to established prod-

ucts. Bemfola® (Gedeon Richter, Hungary) is a biosimilar follitropin alfa r-hFSH. It has been shown to have similar pharmacological, pharmacokinetic and toxicological profiles, as well as clinical bioequivalence, to the originator reference product [Gonal-f®; Merck Serono, the Netherlands] (1, 2). Bemfola® was developed as a prefilled single-use pen, available in five dosages, each with the option of additional flexible dosage adjustment. The complexity of ovarian stimulation regimens can lead to patient non-compliance (3), and easy-to-use devices could potentially help improve compliance with treatment. The Bemfola® pen scored well in user acceptance studies (4-6).

Controlled ovarian stimulation protocols are not standardized across centers, and therefore it is helpful to obtain information about how individual products are used in routine clinical practice. Moreover, in the pivotal clinical trial demonstrating the efficacy and safety of Bemfola®, pituitary suppression was performed using gonadotropin-releasing hormone (GnRH) agonists, whereas an increasing number of ART cycles are currently being performed using GnRH-antagonists. According to the German IVF Registry, 69% of ART cycles used GnRH-antagonists in 2017 (7). Consequently, data relating to the use of Bemfola® within GnRH-antagonist protocols would be of interest.

A post marketing surveillance study (Phase IV) is an important phase of drug development since effectiveness of a drug in routine care, as evaluated in an observational, non-interventional trial in a "real world" setting complements efficacy data from a pre-marketing randomized controlled trial. Therefore, to gather further information on the use of Bemfola® for the treatment of infertility, a study was performed in a routine care setting to evaluate ovarian response (Characterized by the number of oocytes retrieved) when using Bemfola® for ovarian stimulation in women undergoing ART who were pituitary-suppressed with a GnRH-antagonist.

Methods

This multicenter, prospective, non-comparative, non-interventional post-authorization, phase IV study was conducted at 24 ART centers in Germany and Austria.

Participants: Women aged at least 18 years who underwent ovarian stimulation with Bemfola® monotherapy and pituitary suppression with a GnRH-antagonist as part of in vitro fertilization (IVF) treatment with or without intracytoplasmic sperm injection (ICSI) were eligible for the study and were enrolled consecutively. Women were excluded from the study if they had hypersensitivity to follitropin alfa, FSH or any associated excipients; tumors of the hypothalamus or pituitary gland; ovarian enlargement or ovarian cysts not due to polycystic ovary syndrome; gynecological hemorrhage of unknown etiology; or ovarian, uterine or breast carcinoma.

Study design: Patients underwent ART according to the investigators' local routine clinical practice; no additional treatment or diagnostic procedures were performed specifically for the study. The decision to start ART treatment and to use Bemfola® for controlled ovarian stimulation in conjunction with a GnRH-antagonist protocol was made independently by investigators in accordance with their ART center's standard protocol and before patients were enrolled into the study.

Patients attended the usual number and pattern of visits arranged at their ART center. Data were collected at three points during the IVF cycle: screening visit (First visit), once ovarian stimulation had been completed (Second visit), and once the results of ART (Pregnancy test/ultrasound) were known (Third visit).

The study was performed in accordance with the ethical principles outlined in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996). The study was approved by the relevant Independent Ethics Committees, and all patients provided written informed consent before being enrolled into the study. The trial is registered at ClinicalTrials.gov (Trial registration number: NCT 02942849). Communications and transfer of personal data complied with the stipulations of the European Data Protection Directive (Directive 95/46/EC) and the German Federal Data Protection Act (Bundesdatenschutzgesetz).

Treatment: Pituitary suppression was induced by a GnRH-antagonist and ovarian stimulation was induced by Bemfola®. Doses were selected by the treating physician. Bemfola® (r-hFSH produced in Chinese hamster ovary cells by recombinant DNA technology) was administered subcutaneously once daily with a single-use pen device. Only those treatments in which Bemfola® was administered as monotherapy were included in the analysis.

Assessments and endpoints: Data were obtained from medical records completed as part of routine healthcare practice. Demographic and diagnostic parameters were collected at the first visit. Information relating to ovarian stimulation was collected at the second visit. Information relating to ART and outcomes, as well as adverse events, was collected at the third visit (Which took place 90 days after the initial visit).

The primary endpoint was the number of cumulus-oocyte-complexes (COCs) retrieved. Demographic variables collected and secondary endpoints analyzed were age, body mass index (BMI), anti-Müllerian hormone (AMH) level, antral follicle count (Total number of follicles 2–10 *mm* in diameter during cycle days 1–3), basal FSH level (Cycle days 1–3), number of previous fresh ART cycles, r-hFSH dose (First/last day of stimulation; total dose), days of FSH stimulation, type of triggering of final oocyte maturation, type of ART, number of oocytes fertilized, number of pronuclear stage 2 (2PN) cells cryopreserved, number of embryos transferred, day of embryo transfer, biochemical pregnancy rate, clinical pregnancy rate (Presence of a gestational sac on ultrasound during weeks 5–7 of gestation or 3–5 weeks after embryo transfer; rate per cycle started/per embryo transfer), implantation rate, and adverse events (Including ovarian hyperstimulation syndrome, OHSS).

Statistical methods: Data were analyzed descriptively. Summary statistics included means, standard deviations and 95% confidence intervals (CIs) for quantitative variables, and absolute and relative frequencies for qualitative variables.

Results

Between September 2016 and August 2018, a total of 885 women who met all inclusion criteria and initiated 986 ART treatment cycles were enrolled in the study.

Baseline characteristics and diagnostic parameters are summarized in table 1. The mean patient age across all cycles was 34.0±4.4 years (95% CI 33.8–34.3). The youngest patient was 18 years and the oldest was 45 years; most women were aged between 30 and 40 years. Mean BMI was 24.7±5.3 kg/m^2 (95% CI 24.4–25.1) and women had a normal weight (BMI 20 to <25 kg/m^2) at the start of 46.3% of cycles. Of the started cycles, 63.8% (629/986) were first fresh ART treatment cycles. Mean AMH level across all cycles was 2.8±2.4 *ng/ml* (95% CI 2.7–3.0) and mean basal FSH level was 7.1±2.7 *mIU/ml* (95% CI 6.8–7.3). The most common type of ART planned was ICSI performed alone (72.4% of started cycles [714/986]).

Ovarian stimulation: Follicular puncture was performed in 99.1% (977/986) of started cycles. Among the nine cycles in which ovarian stimulation was cancelled, the most common reason was "poor response" (6 of 9 cycles); no cancellations were due to imminent OHSS.

Doses, duration and type of ovarian stimulation are summarized in table 2 both for the overall population and according to the type of ART planed. The trigger for final oocyte maturation was β-human chorionic gonadotropin (β-hCG) in 79.6% of started cycles (785/986), and GnRH agonists in 19.4% (191/986). The mean r-hFSH dose on the first day of controlled ovarian stimulation was 220.7±68.9 *IU* (95% CI 216.4–225.0) and on the last day of stimulation was 218.9±68.3 *IU* (95% CI 214.7–223.2). Ovarian stimulation was given for a mean of 9.9±1.8 (95% CI 9.8–10.0) days and patients received a mean total r-hFSH dose of 2184.3±837.5 *IU* (95% CI 2131.9–2236.7).

Egg retrieval and fertilization: Overall, 99.1% of all started cycles (977/986) resulted in follicular puncture, and oocytes were retrieved in 98.9% (966/977) of these punctures. A mean of 10.7±6.6 (95% CI 10.3–11.1) oocytes were retrieved, with similar numbers obtained for IVF and ICSI treatments (Table 3). An *in vitro* fertilization by IVF or ICSI procedure was performed in 956 cycles. Successful fertilization after an *in vitro* fertilization procedure was achieved in 916 cycles, representing 95.8% (916/956) of cycles in which such a procedure was performed and 93.8% (916/977) of cycles with follicular puncture. The mean number of 2PN cells cryopreserved was 2.6±4.1 (95% CI 2.3–2.8). No cryopreservation was done in more than half of cycles with fertilization (57.4%, 526/916) because there were no surplus 2PN oocytes available for freezing or the patient had opted against cryopreservation of surplus 2PN oocytes.

Freeze-all strategy: Cryopreservation of all available entities (*e.g.* 2PN oocytes or embryos) was performed in 14.2% (140/986) of all started ART cycles during the study period (Table 3). A trend towards increased use of a freeze-all protocol was observed over time, with the rate increasing more than 2-fold between 2016 and 2018, such that

Table 1. Baseline characteristics: demographics, diagnostic parameters, planned ART

Parameter	Value (n=986)
Age (years), mean±SD (95% CI)	34.0±4.4 (33.8–34.3)
Age categories, number of cycles (%)	
<20	2 (0.2)
20 to <25	7 (0.7)
25 to <30	166 (16.8)
30 to <35	338 (34.3)
35 to <40	398 (40.4)
40 to <45	74 (7.5)
45 to <50	1 (0.1)
Body mass index (*kg/m²*), mean±SD (95% CI)	24.7±5.3 (24.4–25.1)
BMI categories, number of cycles (%)	
<20	152 (15.4)
20 to <25	456 (46.3)
25 to <30	226 (22.9)
30 to <40	133 (13.5)
≥40	16 (1.6)
Missing	3 (0.3)
AMH level (*ng/ml*) [a], mean±SD (95% CI)	2.8±2.4 (2.7–3.0)
Basal FSH level (*mIU/ml*) [b], mean±SD (95% CI)	7.1±2.7 (6.8–7.3)
Mean antral follicle count [c], mean±SD (95% CI)	11.5±5.4 (11.0–12.0)
Fresh ART cycle rank, number of cycles (%)	
First	629 (63.8)
Second	220 (22.3)
Third	79 (8.0)
Fourth	46 (4.7)
Fifth or higher	12 (1.2)
Type of ART, number of cycles (%)	
IVF	190 (19.3)
ICSI	714 (72.4)
IVF+ICSI	52 (5.3)
None	30 (3.0)

a: n=862 cycles. b: n=522 cycles. c: n=453 cycles. AMH=Anti-Müllerian Hormone; ART= Assisted Reproductive Technology; BMI=Body Mass Index; CI=Confidence Interval; FSH= Follicle-stimulating Hormone; IVF=*In vitro* fertilization; ICSI=Intracytoplasmic sperm injection; n=number of cycles

Table 2. Ovarian stimulation

Parameter	IVF (n=190)	ICSI (n=714)	IVF+ICSI (n=52)	No IVF/ICSI (n=30)	Total (n=986)
r-hFSH dose (*IU*)					
First day, mean±SD (95% CI)	212.0±57.1 (203.8–220.1)	221.1±71.1 (215.9–226.3)	227.4±73.8 (206.9–248.0)	255.0±67.1 (230.0–280.5)	220.7±68.9 (216.4–225.0)
Last day, mean±SD (95% CI)	208.0±61.9 (199.2–216.9)	220.5±70.7 (215.3–225.7)	214.4±43.3 (202.4–226.5)	257.4±67.4 (232.2–282.6)	218.9±68.3 (214.7–223.2)
Total r-hFSH dose (IU), mean±SD (95% CI)	2004.7±709.6 (1903.2–2106.3)	2216.0±873.7 (2151.7–2280.2)	2241.8±553.3 (2087.8–2395.9)	2469.6±953.7 (2113.5–2825.7)	2184.3±837.5 (2131.9–2236.7)
Number of days of COS, mean±SD (95% CI)	9.6±1.9 (9.3–9.8)	10.0±1.7 (9.9–10.1)	10.4±1.6 (9.9–10.8)	9.7±2.6 (8.7–10.7)	9.9±1.8 (9.8–10.0)
Trigger of final oocyte maturation (number of cycles, %)					
β-HCG	152 (80.0)	604 (84.6)	12 (23.1)	17 (56.7)	785 (79.6)
GnRH agonist	38 (20.0)	109 (15.3)	40 (76.9)	4 (13.3)	191 (19.4)

CI=Confidence Interval; COS=Controlled Ovarian Stimulation; β-HCG=β-human Chorionic Gonadotropin; GnRH=Gonadotropin-releasing Hormone; n=Number of cycles; r-hFSH= Recombinant Human Follicle-stimulating Hormone; SD=Standard Deviation

Table 3. Egg retrieval and fertilization

Parameter	IVF n=190	ICSI n=714	IVF+ICSI n=52	No IVF/ICSI n=30	Total n=986
Oocytes retrieved, mean±SD (95% CI)	10.7±6.7 (9.7–11.6)	10.7±6.2 (10.2–11.1)	14.6±8.3 (12.2–16.9)	4.1±6.8 (0.9–7.2)	10.7±6.6 (10.3–11.1)
Freeze-all, number of cycles (%)	29 (15.3)	80 (11.2)	26 (50.0)	5 (16.7)	140 (14.2)
	n=190 [a]	n=714 [a]	n=52 [a]	-	n=956 [a]
Successful fertilization [b], number of cycles (%)	181 (95.3)	685 (95.9)	50 (96.2)	-	916 (95.8)
Number of oocytes fertilized [c], mean±SD (95% CI)	5.9±4.4 (5.2–6.5)	5.8±3.7 (5.5–6.1)	7.9±5.0 (6.5–9.4)	-	5.9±3.9 (5.7–6.2)

In addition to the cryopreservation of fertilized oocytes or embryos after IVF or ICSI treatment, the freeze-all procedures included the cryopreservation of all retrieved eggs on the day of ovarian puncture; in each case, all available eggs or embryos were frozen – and no fresh embryo transfer took place.
a: Number of cycles in which an in vitro fertilization procedure was performed. b: One or more 2PN stages. c: Among cycles in which at least one oocyte was fertilized. CI=Confidence Interval; n=number of cycles

Figure 1. Rate of use of a freeze-all protocol over time (2016–2018): Rate per cycle with follicular puncture

freeze-all was performed in 26.7% of all cycles during the last quarter of 2018 (Figure 1).

Embryo transfer: Embryo transfers were performed in 751 cycles (76.9% [751/977] of all follicular punctures and 77.7% [751/966] of cycles with successful egg retrievals) (Table 4). The mean day of embryo transfer was day 3.5±1.3 (95% CI 3.4–3.6). The average number of embryos transferred was 1.76±0.50 (95% CI 1.72–1.79), with two embryos transferred in 69.4% of transfers. For cycles with follicular puncture in which embryo transfer was not performed (n=226), the reasons for cancellation included risk of OHSS (6.4% of all cycles with follicular puncture), elective freeze-all protocol (6.1%), lack of embryos (4.4%), and other reasons (6.2%). For cycles with follicular puncture and without freeze-all (n=837), embryo transfer was performed in 89.7% of cycles.

Pregnancy: Pregnancy rates are summarized in table 4 for the overall population and according to type of ART. Pregnancy was confirmed biochemically in 29.9% (295/986) of all cycles and in 38.7% (291/751) of cycles with embryo transfer. Pregnancy was confirmed clinically in 23.4% of all cycles (231/986) and in 30.2% of cycles with embryo transfer (227/751). Multiple gestation occurred in 20.3% of cycles with confirmed clinical pregnancy (47/231); no triplet pregnancy was documented. The clinical pregnancy rate decreased with increasing maternal age (Figure 2).

Adverse drug reactions: A total of 106 adverse drug reactions were recorded in 104 cycles (10.5% of all cycles [104/986]). Six adverse drug reactions were considered serious. There were 69 reports of OHSS (65.0% of adverse drug reactions; 7.0% of all cycles). The severity of OHSS was mild in 25 cases (36.2% of OHSS reports; 2.5% of all cycles), moderate in 42 cases (60.9% of OHSS reports; 4.3% of all cycles) and severe in 2 cases (2.9% of OHSS reports; 0.2% of all cycles); three cases of OHSS were reported as serious adverse drug reactions.

Discussion

This study in a routine care setting found that in IVF/ICSI patients treated with a GnRH-antagonist protocol, individualized ovarian stimulation with Bemfola® led to the retrieval of an appropriate number of oocytes, demonstrated clinical efficacy in terms of pregnancy rates, and had an acceptable safety/tolerability profile. Bemfola® is a biosimilar h-rFSH (Active ingredient follitropin alfa) manufactured in the European Union. Studies showed that it has similar pharmacokinetics, efficacy and safety to the originator product (Gonal-f®, Merck Serono) (1, 2). It is available as a

Table 4. Embryo transfer and pregnancy

Parameter	IVF n=190	ICSI n=714	IVF+ICSI n=52	Total n=966
Embryo transfer performed [a], number of cycles (%)	148 (77.9)	579 (81.1)	24 (46.2)	751 (77.7)
Day of embryo transfer, mean±SD (95% CI)	3.6±1.3 (3.3–3.8)	3.5±1.3 (3.4–3.6)	4.7±0.9 (4.4–5.1)	3.5±1.3 (3.4–3.6)
Days between egg retrieval and embryo transfer [b]				
Day 0	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.4)
Day 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 2	38 (25.7)	177 (30.6)	1 (4.2)	216 (28.8)
Day 3	47 (31.8)	153 (26.4)	2 (8.3)	202 (26.9)
Day 4	6 (4.1)	43 (7.4)	1 (4.2)	50 (6.7)
Day 5	53 (35.8)	183 (31.6)	19 (79.2)	255 (34.0)
Day 6	2 (1.4)	13 (2.3)	1 (4.2)	16 (2.1)
Missing	2 (1.4)	7 (1.2)	0 (0.0)	9 (1.2)
	n=148	n=579	n=24	n=751
Number of embryos transferred [b], mean±SD (95% CI)	1.72±0.48 (1.65–1.80)	1.76±0.50 (1.72–1.80)	1.75±0.44 (1.56–1.94)	1.76±0.50 (1.72–1.79)
One embryo, number of transfers (%)	43 (29.1)	158 (27.3)	6 (25)	207 (27.6)
Two embryos, number of transfers (%)	103 (69.6)	400 (69.1)	18 (75.0)	521 (69.4)
Three embryos, number of transfers (%)	2 (1.4)	21 (3.6)	0 (0)	23 (3.1)
Biochemical pregnancy rate (After embryo transfer) [b], number of cycles (%)	62 (41.9)	218 (37.7)	11 (45.8)	291 (38.7)
Clinical pregnancy rate (After embryo transfer) [b], number of cycles (%)	47 (31.8)	173 (29.9)	7 (29.2)	227 (30.2)
	n=190	n=714	n=52	n=956
Clinical pregnancy rate (All cycles) [c], number of cycles (%)	48 (25.3)	176 (24.7)	7 (13.5)	231 (23.4)
Number of gestational sacs [d]	N=48	N=176	N=7	N=231
Single, number of cycles (%)	37 (77.1)	141 (80.1)	6 (85.7)	184 (79.7)
Multiple, number of cycles (%)	11 (22.9)	35 (19.9)	1 (14.3)	47 (20.3)
	n=148	n=579	n=24	n=751
Implantation rate [e], mean±SD (95% CI)	0.24±0.38 (0.18–0.30)	0.21±0.36 (0.19–0.24)	0.21±0.36 (0.06–0.36)	0.22±0.36 (0.19–0.25)

There were no embryo transfers in the 10 cycles without IVF or ICSI. a: Among cycles with successful egg retrievals after an in vitro fertilization procedure. b: Among cycles with embryo transfer. c: Among cycles in which an in vitro fertilization procedure was performed. d: Among cycles with confirmed clinical pregnancies. e: Gestational sacs with heartbeat per total number of embryos transferred.
CI=Confidence Interval; n=Number of cycles

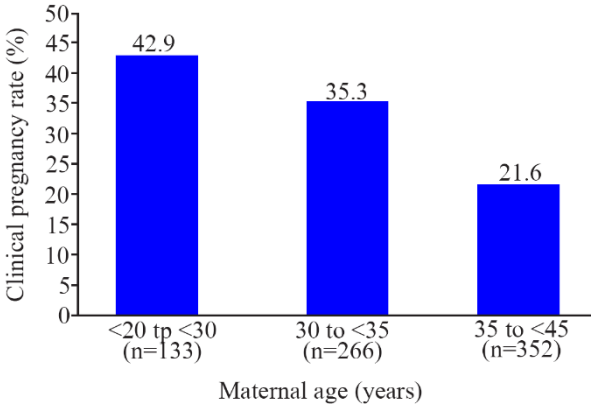

Figure 2. Clinical pregnancy rate (based on cycles with embryo transfer), according to maternal age

prefilled single-use pen which provides a simple to-use alternative to other pens (4-6).

Data on the use of ART-associated medications in a routine care setting is important in order to understand their use in routine practice, particularly within GnRH-antagonist protocols for IVF, which are now widely performed. In Germany, two-thirds of IVF/ICSI treatments in 2017 involved GnRH-antagonists (7). Therefore, the current study evaluated the clinical effectiveness of Bemfola® for ovarian stimulation in the context of a GnRH- antagonist protocol.

Since in our study the sample was drawn arbitrarily, this might introduce a selection bias. A

comparison between morphometric patient data from our study with the pivotal phase III clinical study by Rettenbacher et al. showed a few differences in characteristics (2). The mean age of women at baseline was 34 years in the current study (with 52% aged <35 years) compared with approximately 32 years in the pivotal trial (With 75% aged <35 years). Mean BMI was 24.7 kg/m^2 in the current study and approximately 22.5 kg/m^2 in the phase III trial. In the current study, 86.1% of women were in their first or second fresh ART cycle compared with 100% of participants in phase III trial. The mean antral follicle count was 11.5 in the current study versus 15 in the phase III trial. Comparison with data from the 2017 German IVF-Registry annual report indicates that the mean age in our study (34 years) was lower than that for the overall population of infertile women in Germany (35.7 years) (7). Furthermore, in our study population, the 95% CI for the mean AMH level (2.7–3.0) and the mean antral follicle count (11.5) indicate a positive selection of patients in terms of age and the associated ovarian response and treatment outcome.

The primary endpoint data from the current study confirm that Bemfola® provides adequate stimulation of follicular development during IVF/ICSI cycles using a GnRH-antagonist protocol in routine clinical practice. The mean number of oocytes retrieved (10.7) was similar to that reported in the 2017 German IVF-Registry annual report (9.6), which reflects routine care practice in Germany (7). As a measure of the success of ART, the clinical pregnancy rate of 30.2% per transfer seen in the study is consistent with the clinical pregnancy rate per fresh cycle transfer of 31.4% reported in the German IVF-Registry annual report (7). A direct comparison of the findings from this study in a routine care setting with the results of the pivotal clinical trial for Bemfola® (2) would not be appropriate because of the different settings, and differences in patient demographics, FSH doses and luteal-phase support.

The information the current analysis provides about the Bemfola® dosages used during ovarian stimulation in routine practice may be useful for clinicians. The mean doses of Bemfola® on the first and last days of dosing were comparable (220.7 *IU* and 218.9 *IU*, respectively). Taken together with the mean total r-hFSH dose (2184.3± 837.5 *IU*) and duration of ovarian stimulation (9.9±1.8 days), this might indicate a significant use of fixed-dose stimulation regimes, which were proven effective in the general IVF/ICSI population (8). In the future, further analysis of the study data with respect to the need/frequency of dosage adjustments, and evaluation of whether particular daily dosages were useful in specific subgroups, could be of interest.

The study also provides additional information on the safety profile of Bemfola®, including OHSS, in a routine care setting. Moderate to severe OHSS has been reported to occur in 3–10% of ART cycles, and the use of GnRH-antagonist protocols can reduce the risk of OHSS without affecting the clinical pregnancy rate (9). In the current study, OHSS (All severity levels) occurred in 7.0% of cycles, with severe OHSS reported in 0.2% of cycles. The grading of severity may differ depending on the classification system used; however, the rate in our study is consistent with the 2017 German IVF-Registry annual report, which indicated that severe OHSS during GnRH-antagonist protocols with FSH-only ovarian stimulation occurred at a rate of 0.3% (7).

Freeze-all protocols, in which all embryos are cryopreserved to be transferred in later cycles with a more physiological endometrial environment, are being used increasingly often (10, 11). Consistent with this, our analysis indicated that the use of freeze-all protocols in routine clinical practice has increased at our centers in recent years, with a doubled frequency between 2016 and the end of 2018.

The current study has several limitations which should be considered. It was a non-interventional observational study performed at a limited number of fertility centers and therefore outcomes are subject to bias in terms of differences in treatment habits between centers and differences in patient morphometric and lifestyle variables. The explorative and non-interventional nature of the study limits the generalizability of data. However, it was a large study, covering approximately 1000 treatment cycles. This also enabled valid subgroup analyses (*e.g.* by age group) to be undertaken. Overall, this prospective non-interventional study provides useful information on routine care practice.

Conclusion

This large observational study provided additional evidence for the clinical efficacy of Bemfola®, a biosimilar follitropin alfa r-hFSH, in ART routine daily practice. Ovarian stimulation with Bemfola®, when used as part of a GnRH-anta-

gonist protocol, led to the retrieval of an appropriate number of oocytes. Treatment courses and outcomes in the study were comparable with those in routine care practice in Germany. No safety concerns were observed.

Acknowledgement

This study was sponsored by Gedeon Richter, Germany and prepared in line with Good Publishing Practice-3 (GPP-3) recommendations. The authors thank Drs Kathy Croom, Steve Clissold and Peter Weber (Content Ed Net, Germany) for editorial support. The authors also thank the Bemfola® Study group listed below for their contribution, and without whose help this publication would not be possible: Tim Cordes and Andreas Thiemann (Kinderwunschzentrum Altonaer Strasse, Hamburg); Stefan Dieterle (Kinderwunschzentrum, Dortmund); Georg Griesinger (Universitäres Kinderwunschzentrum UKSH, Lübeck); Jörg Hennefründ and Saskia Katmann (Tagesklinik, Oldenburg); Swetlana Hoffmann (MVZ für Gynäkologie Helle-Mitte, Berlin); Axel Kamischke, Alexander Niehoff, Kathrin Reinermann and Sandra Weis (MVZ Kinderwunschzentrum, Münster); Thomas Katzorke (Novum Zentrum für Reproduktionsmedizin, Essen); Jan-Steffen Krüssel and Barbara Mikat-Drozdzynski (UniKid UKD, Düsseldorf); Dieter B. Mayer-Eichberger (Kinderwunschpraxis Villa Haag, Stuttgart); Daniel Noss and Julia Bauer (MVZ Reproduktionsmedizin, München); Kazem Nouri and Sabine Hauer (Universitätsklinik für Frauenheilkunde, Wien); Hans-Ulrich Pauer (Kinderwunschzentrum an der Oper, München); Gerhard Pohlig (Team Kinderwunsch, Oldenburg); Rainer Rau (Kinderwunschzentrum, Aalen); Michael Sator (Kinderwunsch im Zentrum, Tulln a. d. Donau); Michael Schenk and Gregor Weiss (Kinderwunschinstitut, Dobl b. Graz); Thilo Schill (MVZ Kinderwunschzentrum, Langenhagen); Bernd Seifert and Tanja Ignatov (MVZ KITZ, Regensburg); Michael Sommergruber, Martina Kusmitsch and Vlatka Tomic (Uniklinikum, Salzburg); Erwin Strehler (Praxisklinik Frauenstrasse, Ulm); Sascha Tauchert (IVF Saar, Saarbrücken); Sören von Otte (Universitäres Kinderwunschzentrum, Kiel); Volker Ziller (Uniklinikum, Marburg).

Conflict of Interest

The authors declare that they have no conflicts of interest.

Funding: This study was funded by Gedeon Richter, Germany.

References

1. Wolzt M, Gouya G, Sator M, Hemetsberger T, Irps C, Rettenbacher M, et al. Comparison of pharmacokinetic and safety profiles between Bemfola(®) and Gonal-f(®) after subcutaneous application. Eur J Drug Metab Pharmacokinet. 2016;41(3):259-65.
2. Rettenbacher M, Andersen AN, Garcia-Velasco JA, Sator M, Barri P, Lindenberg S, et al. A multi-centre phase 3 study comparing efficacy and safety of Bemfola(®) versus Gonal-f(®) in women undergoing ovarian stimulation for IVF. Reprod Biomed Online. 2015;30(5):504-13.
3. Niederberger C, Pellicer A, Cohen J, Gardner DK, Palermo GD, O'Neill CL, et al. Forty years of IVF. Fertil Steril. 2018;110(2):185-324.e5.
4. Imthurn B, McVeigh E, Stiller R, Arnold M, Pringle F, Irps C, et al. Evaluation of the use and handling of three different pen systems considered for in vitro fertilization treatment. Expert Opin Drug Deliv. 2014;11(12):1859-64.
5. Quintero LA, Verdú Merino V, Olivares Vela R, Rayward J, Torres Afonso A, Báez Quintana D, et al. An evaluation by potential IVF/donor oocyte patients of the use and handling of the Bemfola® Pen compared with the Gonal-f® Pen and Puregon Pen®. Revista Iberoamericana de Fertilidad y Reproducción Humana. 2017; 34:64-73.
6. Saunders H, de la Fuente Bitaine L, Eftekhar C, Howles CM, Glaser J, Hoja T, et al. Functionality of a novel follitropin alfa pen injector: results from human factor interactions by patients and nurses. Expert Opin Drug Deliv. 2018;15(6):549-58.
7. Blumenauer V, Czeromin U, Fehr D, Fiedler K, Gnoth C, Krüssel JS, et al. D.I.R annual 2017 - the German IVF-registry. J Reproduktionsmed Endokrinol. 2018;15:217-50.
8. Van Tilborg TC, Oudshoorn SC, Eijkemans MJ, Mochtar MH, Van Golde RJ, Hoek A, et al. Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis. Hum Reprod. 2017;32(12):2485-95.
9. Nastri CO, Teixeira DM, Moroni RM, Leitão VM, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology, staging, prediction and prevention. Ultrasound Obstet Gynecol. 2015;45(4):377-93.
10. Roque M, Valle M, Kostolias A, Sampaio M, Geber S. Freeze-all cycle in reproductive medicine: current perspectives. JBRA Assist Reprod. 2017;21 (1):49-53.

11. Griesinger G, Von Otte S, Schroer A, Ludwig AK, Diedrich K, Al-Hasani S, et al. Elective cryopreservation of all pronuclear oocytes after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS: a prospective, observational proof-of-concept study. Hum Reprod. 2007;22(5):1348-52.