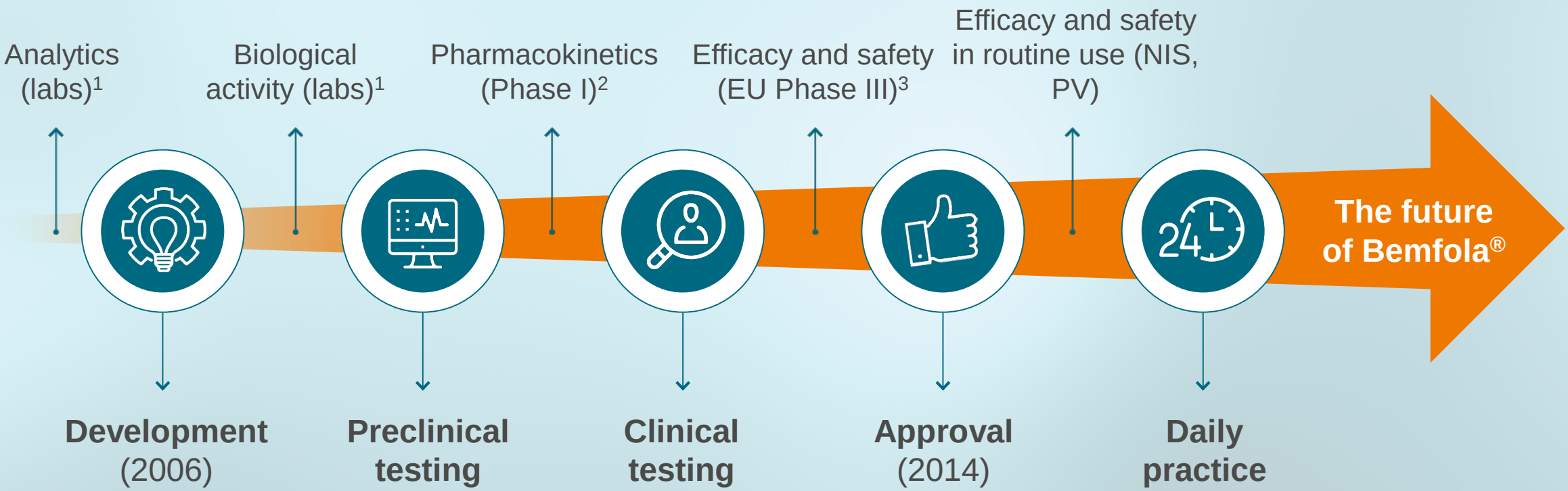
Bemfola®
Development and use

GEDEON RICHTER

Bemfola®: 8 years of development, over 5 years of routine use



NIS, non-interventional study; PV, pharmacovigilance.

1. de Mora F, Fauser BCJM. *Reprod Biomed Online.* 2017;35(1):81–86; 2. Wolzt M, et al. *Eur J Drug Metab Pharmacokinet*. 2016;41(3):259–265; 3. Rettenbacher M, et al. *Reprod Biomed Online.* 2015;30(5):504–513.

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Bemfola®: development and use

Background to Bemfola® development

Bemfola® clinical development

Real-world experience with Bemfola®

Benefits of the Bemfola® pen

Potential to reduce drug wastage

Simplification of ovarian stimulation by avoiding dose changes

Is there any value adding LH to Bemfola®?

LH, luteinising hormone.

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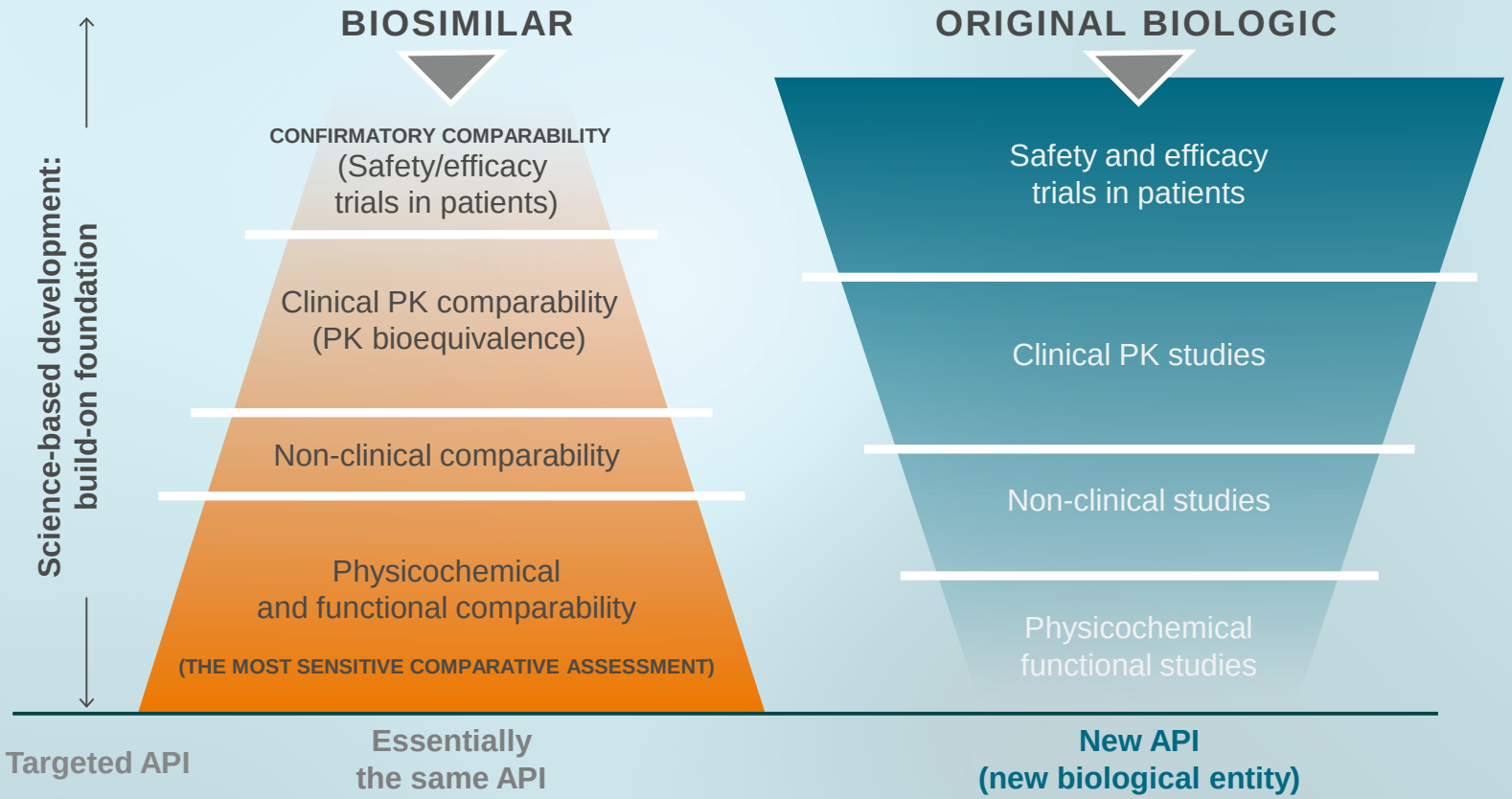
The science behind the differential regulatory requirements for biosimilar and original biologic medicines[1]

Equivalence between a biosimilar and reference product relies mainly on physicochemical and biological activity comparability assessments.

Demonstration of a favourable risk-to-benefit balance of an original biologic resides mainly in clinical trials in patients.



Adapted from de Mora, Fauser. 2017.

API, active pharmaceutical ingredient.

1. de Mora F, Fauser BCJM. *Reprod Biomed Online.* 2017;35(1):P81–P86.

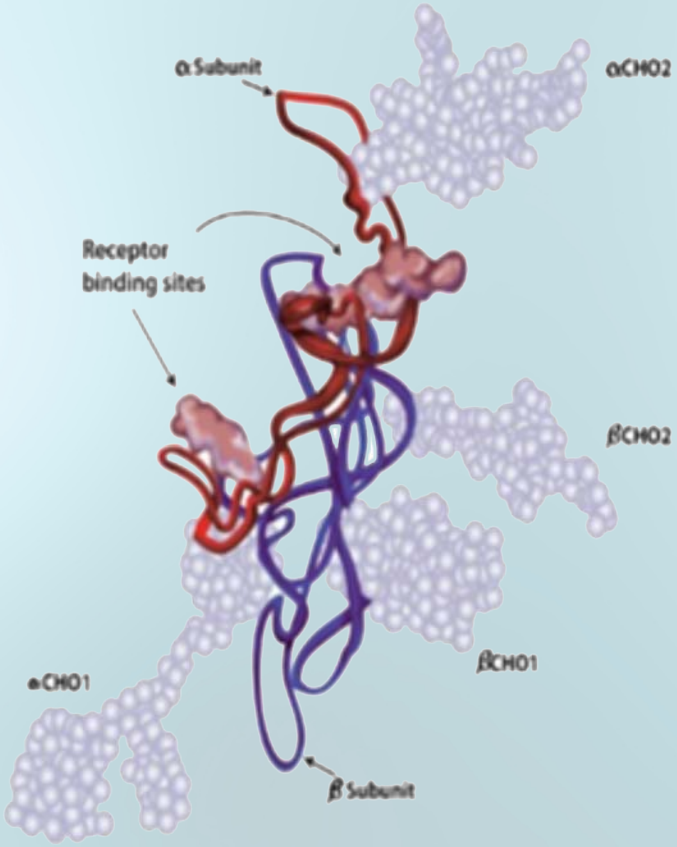
Follicle-stimulating hormone (FSH)[1]

Glycoprotein composed of two non-covalently bound polypeptide chains

- Alpha chain 92 amino acid residues
- Beta chain 111 amino acid residues

Four glycosylation sites

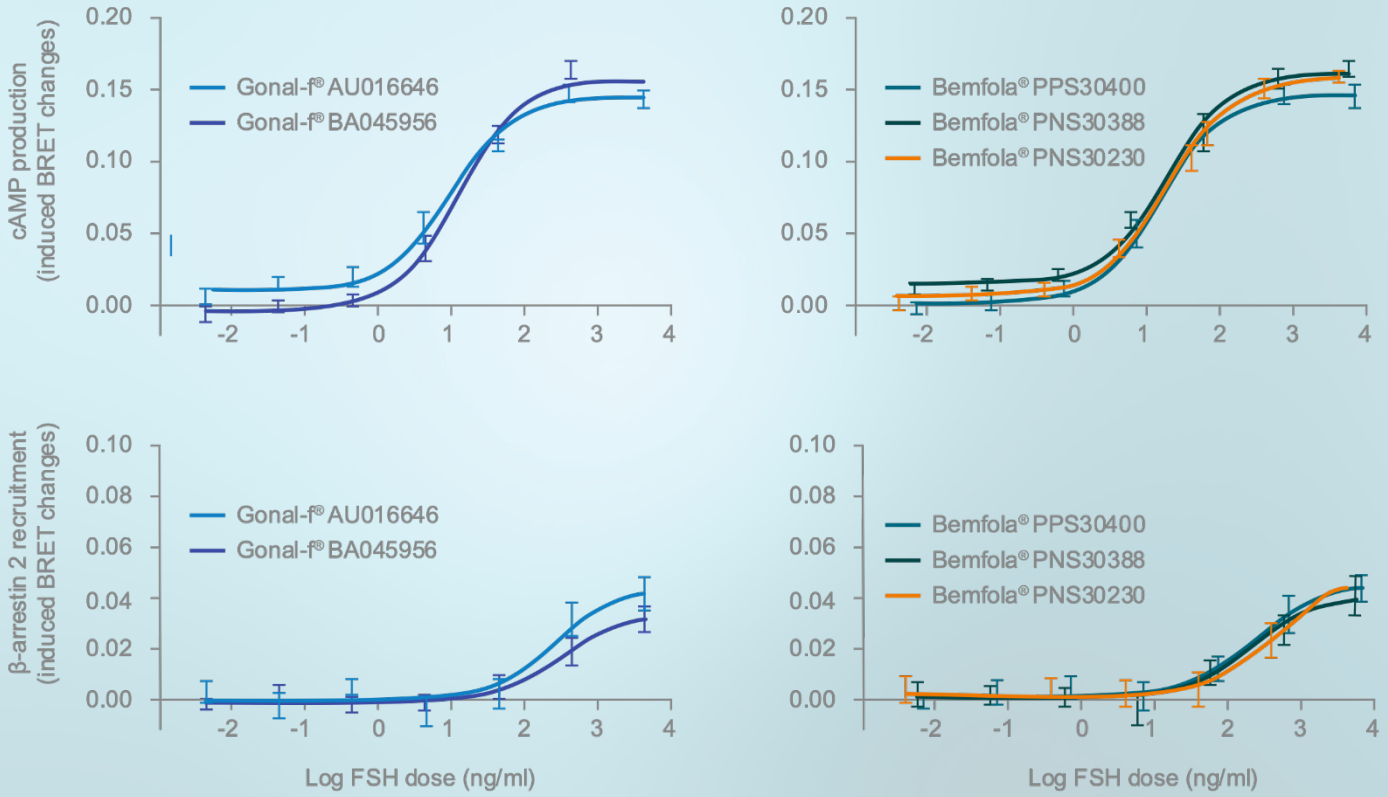
- Confer variability to circulating FSH isohormones with little biological effect at the receptor[1]
- Different glycosylation profiles are characteristic of follitropin alfa preparations[2]



1. Alfredo UA, Timossi C. *Hum Reprod.* 1998;4(3):260–283; 2. Riccetti L, et al. *Front Endocrinol.* 2019; doi: 10.3389/fendo.2019.00503 [and supplementary material].

Bemfola® and Gonal-f® demonstrated similar intracellular signalling patterns[1]

The differing glycosylation patterns between follitropin alfa and biosimilars result in similar intracellular level signalling and steroid synthesis at physiological concentrations.[1]



Adapted from Riccetti et al. 2019.

Gonal-f® (follitropin alfa) is a registered trademark of Merck KGaA.
BRET, bioluminescence resonance energy transfer; cAMP, cyclic adenosine 3′,5′-mono-phosphate.
1. Riccetti L, et al. *Front Endocrinol.* 2019; doi: 10.3389/fendo.2019.00503 [and supplementary material].

GEDEON RICHTER

Determination of FSH activity in Europe in 2019

FSH activity expressed in IUs

Assessed by Steelman-Pohley bioassay using reference standards of NIBSC

- NIBSC code 08/282 for IUs of rFSH[1]
- In 2009, the above standard replaced the original rFSH standard 92/642 established in 1995 by WHO Expert Committee on Biological Standardization
- By demonstrating that the mass of a batch of Gonal-f® or Bemfola® equals the bioactivity of the relevant standard, the drugs may be filled and dosed according to mass (or IUs)

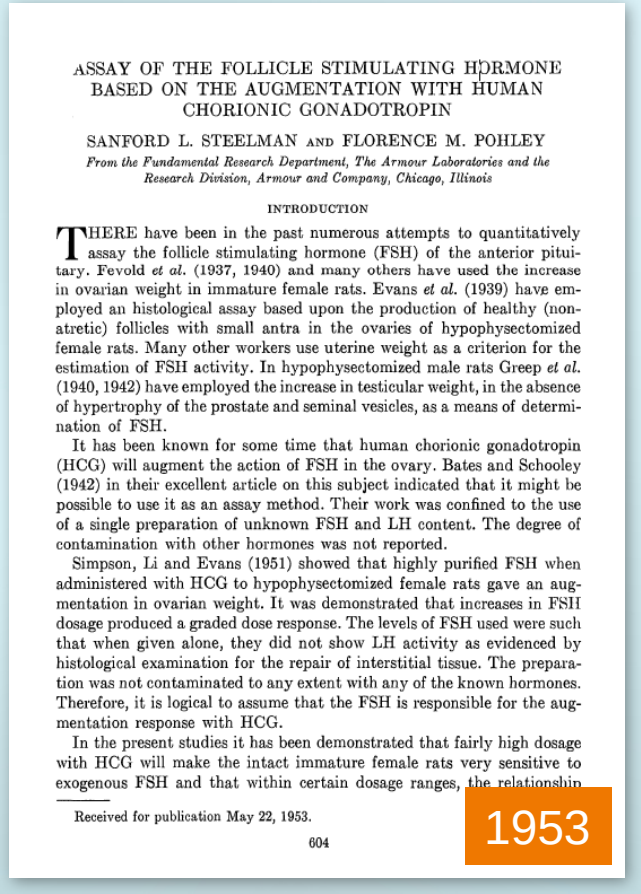
Note: uFSH (including HMG) requires a different standard, which has been in use for much longer; hence, it is now on its fifth version

- NIBSC code 10/286 for IUs of both uFSH and LH, if needed

HMG, human menopausal gonadotropin; LH, luteinising hormone; NIBSC, National Institute for Biological Standards and Control; uFSH, urinary follicle stimulating hormone; WHO, World Health Organization.

1. NIBSC. Follicle Stimulating Hormone, Luteinizing Hormone human, urinary for bioassay (5th International Standard). Available at https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=10/286. Accessed April 2021.

The activity of FSH is still determined by the rat bioassay described by Steelman and Pohley in 1953[1]



ASSAY OF THE FOLLICLE STIMULATING HORMONE BASED ON THE AUGMENTATION WITH HUMAN CHORIONIC GONADOTROPIN

SANFORD L. STEELMAN AND FLORENCE M. POHLEY

From the Fundamental Research Department, The Armour Laboratories and the Research Division, Armour and Company, Chicago, Illinois

INTRODUCTION

THERE have been in the past numerous attempts to quantitatively assay the follicle stimulating hormone (FSH) of the anterior pituitary. Fevold *et al.* (1937, 1940) and many others have used the increase in ovarian weight in immature female rats. Evans *et al.* (1939) have employed an histological assay based upon the production of healthy (non-atretic) follicles with small antra in the ovaries of hypophysectomized female rats. Many other workers use uterine weight as a criterion for the estimation of FSH activity. In hypophysectomized male rats Greep *et al.* (1940, 1942) have employed the increase in testicular weight, in the absence of hypertrophy of the prostate and seminal vesicles, as a means of determination of FSH.

It has been known for some time that human chorionic gonadotropin (HCG) will augment the action of FSH in the ovary. Bates and Schooley (1942) in their excellent article on this subject indicated that it might be possible to use it as an assay method. Their work was confined to the use of a single preparation of unknown FSH and LH content. The degree of contamination with other hormones was not reported.

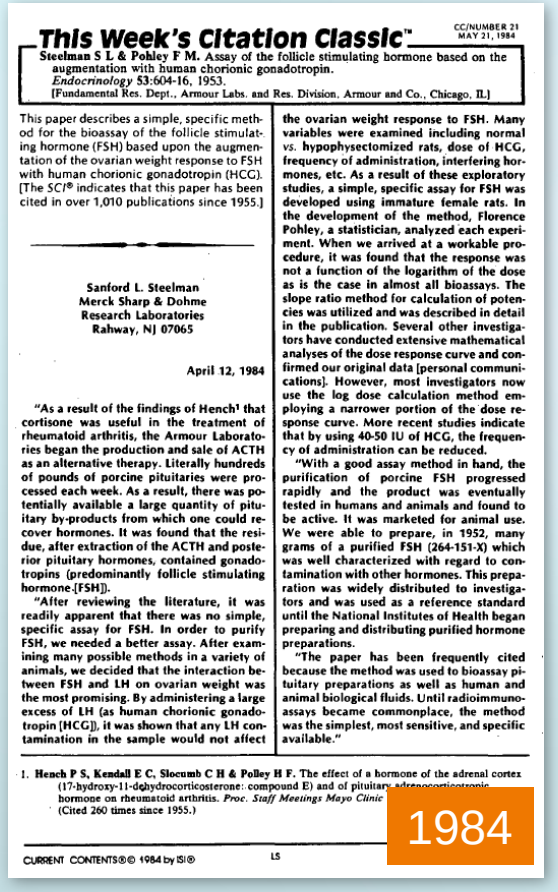
Simpson, Li and Evans (1951) showed that highly purified FSH when administered with HCG to hypophysectomized female rats gave an augmentation in ovarian weight. It was demonstrated that increases in FSH dosage produced a graded dose response. The levels of FSH used were such that when given alone, they did not show LH activity as evidenced by histological examination for the repair of interstitial tissue. The preparation was not contaminated to any extent with any of the known hormones. Therefore, it is logical to assume that the FSH is responsible for the augmentation response with HCG.

In the present studies it has been demonstrated that fairly high dosage with HCG will make the intact immature female rats very sensitive to exogenous FSH and that within certain dosage ranges, the relationship

Received for publication May 22, 1953.

604

1953



This Week's Citation Classic™

CC/NUMBER 21
MAY 21, 1984

Steelman S L & Pohley F M. Assay of the follicle stimulating hormone based on the augmentation with human chorionic gonadotropin.
Endocrinology 53:604-16, 1953.
[Fundamental Res. Dept., Armour Labs. and Res. Division, Armour and Co., Chicago, IL]

This paper describes a simple, specific method for the bioassay of the follicle stimulating hormone (FSH) based upon the augmentation of the ovarian weight response to FSH with human chorionic gonadotropin (HCG). [The *SCI*® indicates that this paper has been cited in over 1,010 publications since 1955.]

Sanford L. Steelman
Merck Sharp & Dohme
Research Laboratories
Rahway, NJ 07065

April 12, 1984

"As a result of the findings of Hench[1] that cortisone was useful in the treatment of rheumatoid arthritis, the Armour Laboratories began the production and sale of ACTH as an alternative therapy. Literally hundreds of pounds of porcine pituitaries were processed each week. As a result, there was potentially available a large quantity of pituitary by-products from which one could recover hormones. It was found that the residue, after extraction of the ACTH and posterior pituitary hormones, contained gonadotropins (predominantly follicle stimulating hormone-[FSH]).

"After reviewing the literature, it was readily apparent that there was no simple, specific assay for FSH. In order to purify FSH, we needed a better assay. After examining many possible methods in a variety of animals, we decided that the interaction between FSH and LH on ovarian weight was the most promising. By administering a large excess of LH (as human chorionic gonadotropin [HCG]), it was shown that any LH contamination in the sample would not affect the ovarian weight response to FSH. Many variables were examined including normal *vs.* hypophysectomized rats, dose of HCG, frequency of administration, interfering hormones, etc. As a result of these exploratory studies, a simple, specific assay for FSH was developed using immature female rats. In the development of the method, Florence Pohley, a statistician, analyzed each experiment. When we arrived at a workable procedure, it was found that the response was not a function of the logarithm of the dose as is the case in almost all bioassays. The slope ratio method for calculation of potencies was utilized and was described in detail in the publication. Several other investigators have conducted extensive mathematical analyses of the dose response curve and confirmed our original data [personal communications]. However, most investigators now use the log dose calculation method employing a narrower portion of the dose response curve. More recent studies indicate that by using 40-50 IU of HCG, the frequency of administration can be reduced.

"With a good assay method in hand, the purification of porcine FSH progressed rapidly and the product was eventually tested in humans and animals and found to be active. It was marketed for animal use. We were able to prepare, in 1952, many grams of a purified FSH (264-151-X) which was well characterized with regard to contamination with other hormones. This preparation was widely distributed to investigators and was used as a reference standard until the National Institutes of Health began preparing and distributing purified hormone preparations.

"The paper has been frequently cited because the method was used to bioassay pituitary preparations as well as human and animal biological fluids. Until radioimmunoassays became commonplace, the method was the simplest, most sensitive, and specific available."

1. **Hench P S, Kendall E C, Slocumb C H & Polley H F.** The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. *Proc. Staff Meetings Mayo Clinic* (Cited 260 times since 1955.)

LS

1984

- A group of immature rats is injected subcutaneously with hCG, and then injected with the international standard of FSH once daily for 3 days
- A second group of rats is injected with the same amount of hCG, and then, with the preparation to be tested, once daily for 3 days
- Autopsy is performed 72 h after the first injection, at which time the ovaries were dissected, weighed and compared between the above groups

2021

hCG, human chorionic gonadotropin.

1. Steelman SL, Pohley FM. *Endocrinology*. 1953;53(6):604–616.

Determination of rFSH quality in Europe in 2020

Drug substance

The drug substance, depending on its purity, is mostly composed of the API or the ‘naked’ drug without excipients. The API is what will have a therapeutic effect inside the body, as opposed to the excipients, which serve to package and deliver the API.

Drug product

The drug product is the formulated mixture of the drug substance and excipients either as a prototype or as the final marketed dosage form.

Quality attributes of rFSH drug substance

The quality and consistency of rFSH drug substance prior to release of final rFSH drug product may be further assessed against the FOLLITROPIN CRS according to the European Pharmacopoeia of the EDQM

- Note: since Nov 2017, the FOLLITROPIN CRS is Bemfola® drug substance[1–3]

API, active pharmaceutical ingredient; CRS, Chemical Reference Substance; EDQM, European Directorate for the Quality of Medicines and Healthcare.

1. EDQM. Information Leaflet Ph. Eur. Reference Standard. Follitropin for peptide mapping and glycan analysis CRS batch 2. Available at https://crs.edqm.eu/db/4DCGI/db/4DCGI/leaflet?leaflet=Y0001627 2. Accessed April 2021; 2. EDQM. Laboratory Report: Establishment of follitropin for peptide mapping and glycan analysis follitropin CRS batch 2. European Pharmacopoeia Commission. Strasbourg: EDQM report; 2018. Available at https://crs.edqm.eu/db/4DCGI/View=Y0001629 Accessed April 2021. 3. Ferrando M, et al. *Fertil Res Pract.* 2020;6:13.

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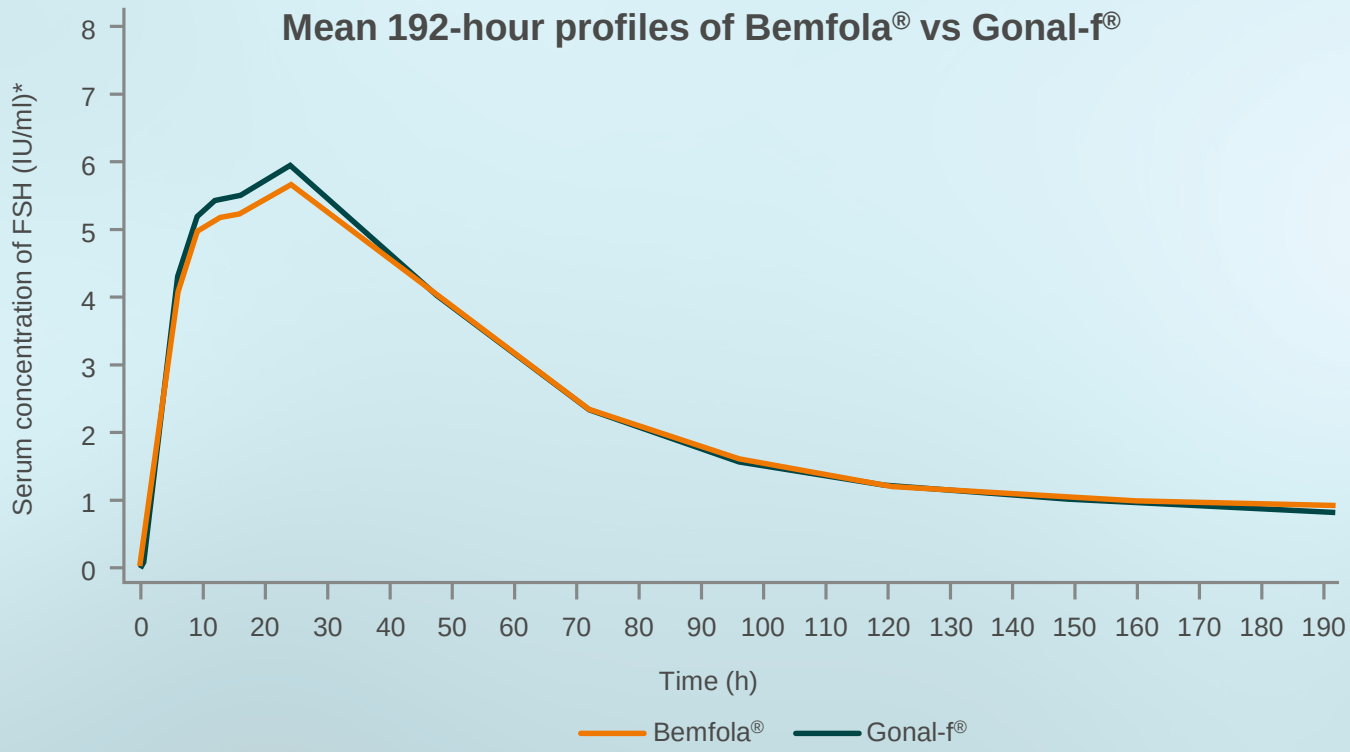
Phase I study[1]
Pharmacokinetics of Bemfola® vs Gonal-f®



Adapted from Wolzt et al. 2016.

Parameter	Bemfola® (n=24)	Gonal-f® (n=23)
$AUC_{0–192}$ (IU h/l)*	424.90	432.75
T_{max} (h)	24 (6–24)	24 (9–24)
C_{max} (IU/l)*	5.69	6.01
$T_{1/2}$ (h)	43.58 (14.7)	42.58 (16.47)

Proven bioequivalence between Bemfola® and Gonal-f® for $AUC_{0–192}$ and C_{max} after subcutaneous 225 IU rhFSH

*Geometric mean.
C_{max}, maximum drug concentration; rhFSH, recombinant human FSH; $T_{1/2}$, elimination half-life; T_{max}, time to reach maximum drug concentration.
1. Wolzt M, et al. *Eur J Drug Metab Pharmacokinet*. 2016;41(3):259–265.

Gedeon Richter

Follitropin alfa EU Phase III registration studies comparison

In 1995, originator rFSH (follitropin alfa):[1]

- **60 patients:** rFSH, vs
- **63 patients:** uFSH

In 2015, Bemfola® (follitropin alfa):[2]

- **249 patients:** new rFSH, vs
- **123 patients:** originator rFSH

Study Drugs

Recombinant hFSH was used as a lyophilized powder in vials containing either 75 or 150 IU of FSH bioactivity. Commercially available urinary hFSH was used as a lyophilized powder in ampules containing 75 IU of FSH bioactivity. The commercially available GnRH-a buserelin acetate was purchased from Hoechst (Suprefact; Frankfurt, Germany) as ampules containing 1 mg of peptide in a 1-mL solution.


ELSEVIER

ARTICLE

A multi-centre phase 3 study comparing efficacy and safety of Bemfola® versus Gonal-f® in women undergoing ovarian stimulation for IVF

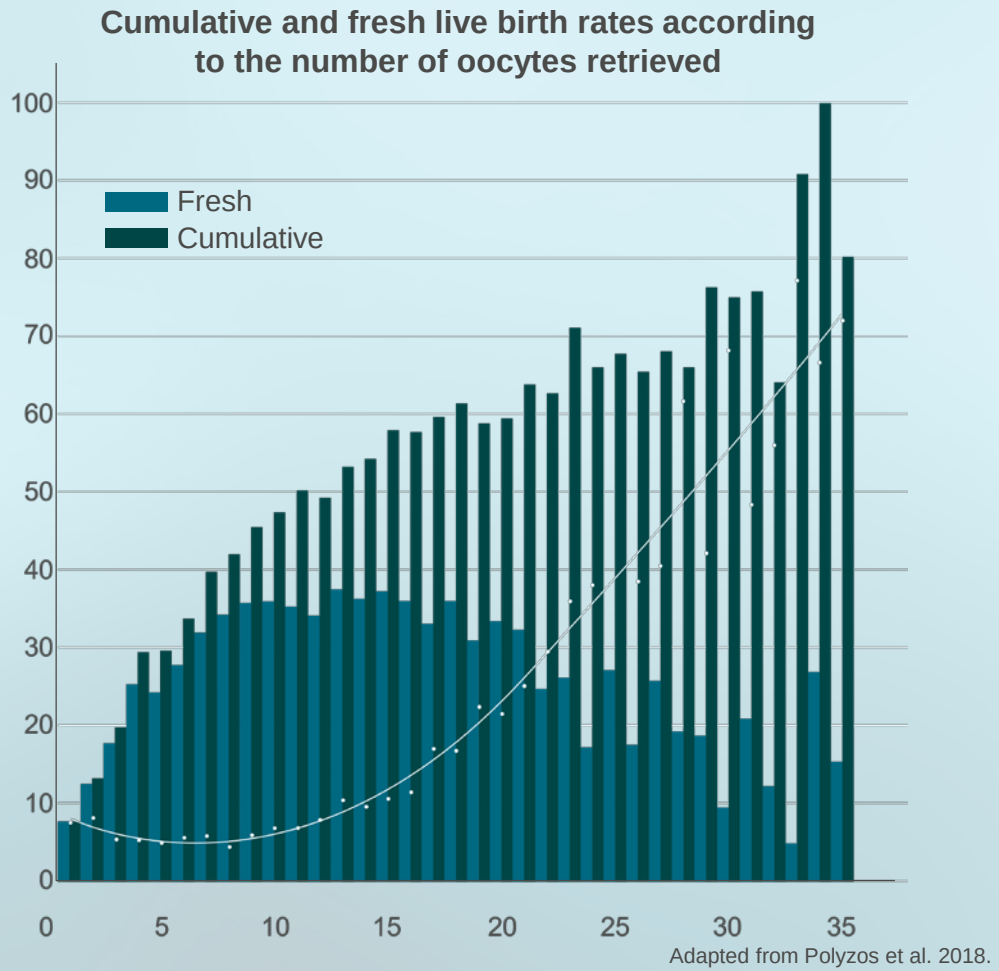
M. Rettenbacher, A.N. Andersen, J.A. Garcia-Velasco, M. Sator, P. Barri, S. Lindenberg, K. van der Ven, Y. Khalaf, U. Bentin-Ley, A. Obruca, G. Tews, M. Schenk, T. Strowitzki, N. Narvekar, K. Sator, B. Imthurn

uFSH, urinary follicle stimulating hormone.

1. Recombinant Human FSH Study Group. *Fertil Steril.* 1995;63(1):77–86; 2. Rettenbacher M, et al. *Reprod Biomed Online.* 2015;30(5):504–513.

GEDEON RICHTER

Why does the EMA require oocytes rather than pregnancy as the primary endpoint?



Adapted from Polyzos et al. 2018.

- Clear relationship between oocyte number and pregnancy rates[1]
- Pregnancy rates are influenced by the overall success rate in the treating clinic and the characteristics of couples seeking treatment[2]
- Critical stages to success follow oocyte collection:
  - *In vitro* fertilisation and embryo development
  - Transfer to patient
  - Implantation
  - *In vivo* growth and differentiation

EMA, European Medicines Agency.

1. Polyzos NP, et al. *Fertil Steril*. 2018;110:661–670; 2. Templeton A, et al. *Lancet.* 1996;348(9039):1402–1406.

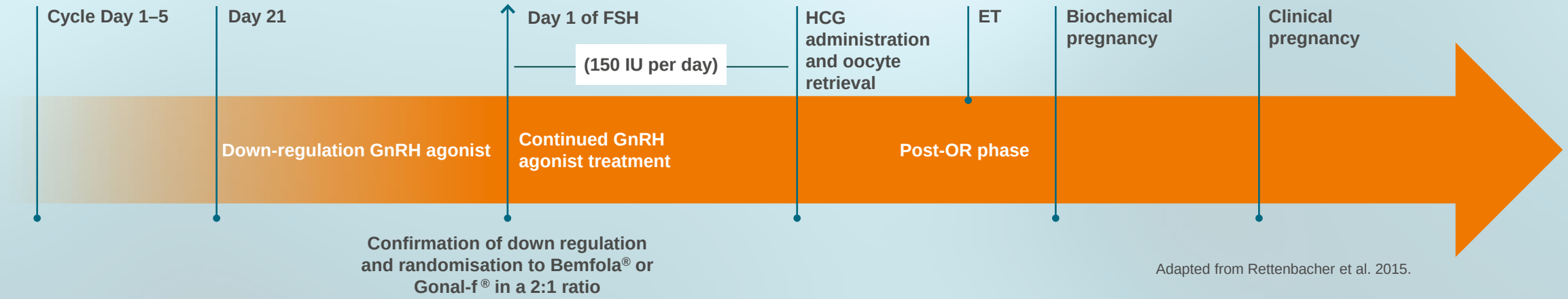
Bemfola® Phase III study design[1]

Key inclusion criteria

- Age 20–38 years
- First or second IVF cycle
- BMI ≥18 to ≤30 kg/m^2
- Basal FSH <10 IU/l
- AFC >10 to ≤25 follicles

Key study features

- Fixed daily dose of 150 IU FSH
- Could only be reduced after 6 days of FSH administration if safety concerns
- Down-regulation with GnRH agonist



Adapted from Rettenbacher et al. 2015.

AFC, antral follicle count; BMI, body mass index; ET, embryo transfer; GnRH, gonadotropin-releasing hormone; HCG, human chorionic gonadotropin; OR, oocyte retrieval.

1. Rettenbacher M, et al. *Reprod Biomed Online.* 2015;30(5):504–513.

GEDEON RICHTER

Bemfola® Phase III study primary endpoint: similar number of oocytes retrieved[1]

	Bemfola®	Originator rhFSH	(95% CI)
Primary cycle			
ITT population (n=372)	n=249	n=123	
No. of oocytes retrieved ± SD	**10.7±5.62**	**10.4±6.14**	(−1.29, 1.34)
PP population (n=333)	n=220	n=113	
No. of oocytes retrieved ± SD	**10.8±5.11**	**10.6±6.06**	(−1.34, 1.32)

Adapted from Rettenbacher et al. 2015.

Bemfola® treatment resulted in a number of oocytes statistically equivalent (*p*=0.0003) to that of patients treated with Gonal-f®

CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; rhFSH, recombinant human follicle stimulating hormone.

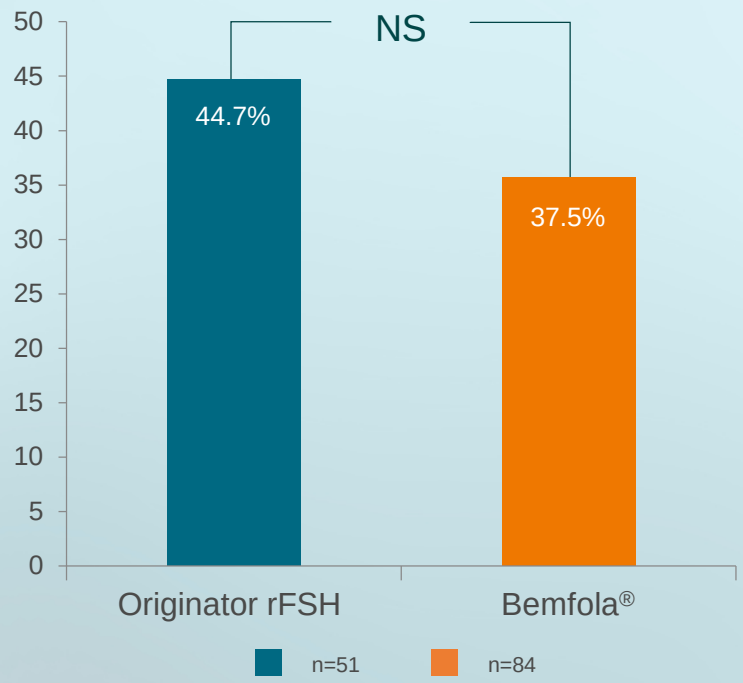
1. Rettenbacher M, et al. *Reprod Biomed Online.* 2015;30(5):504–513.

Gedeon Richter

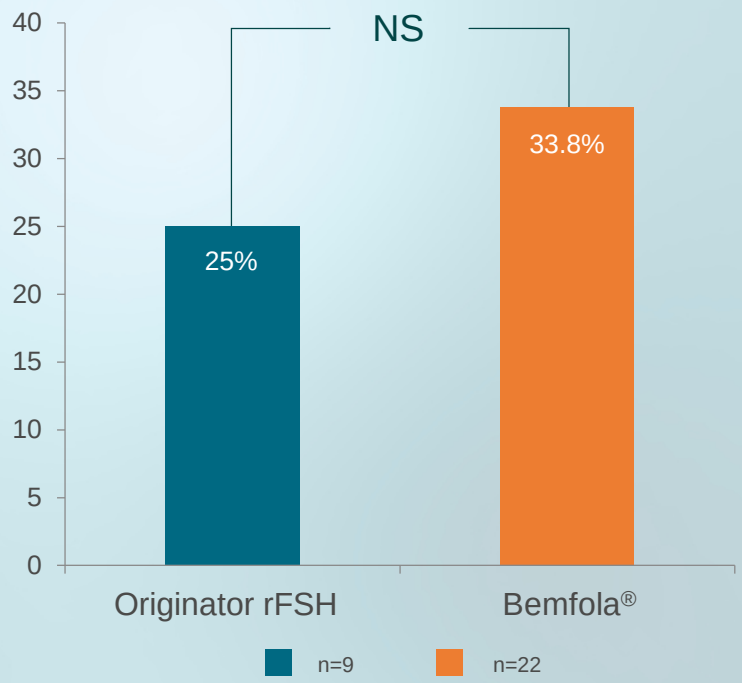
Bemfola® Phase III study secondary endpoints: ongoing pregnancy rate per embryo transfer[1]

PP population (patients with oocyte retrieval after completed treatment cycle)

First treatment cycle
Ongoing pregnancy rate (%)



Second treatment cycle
Ongoing pregnancy rate (%)



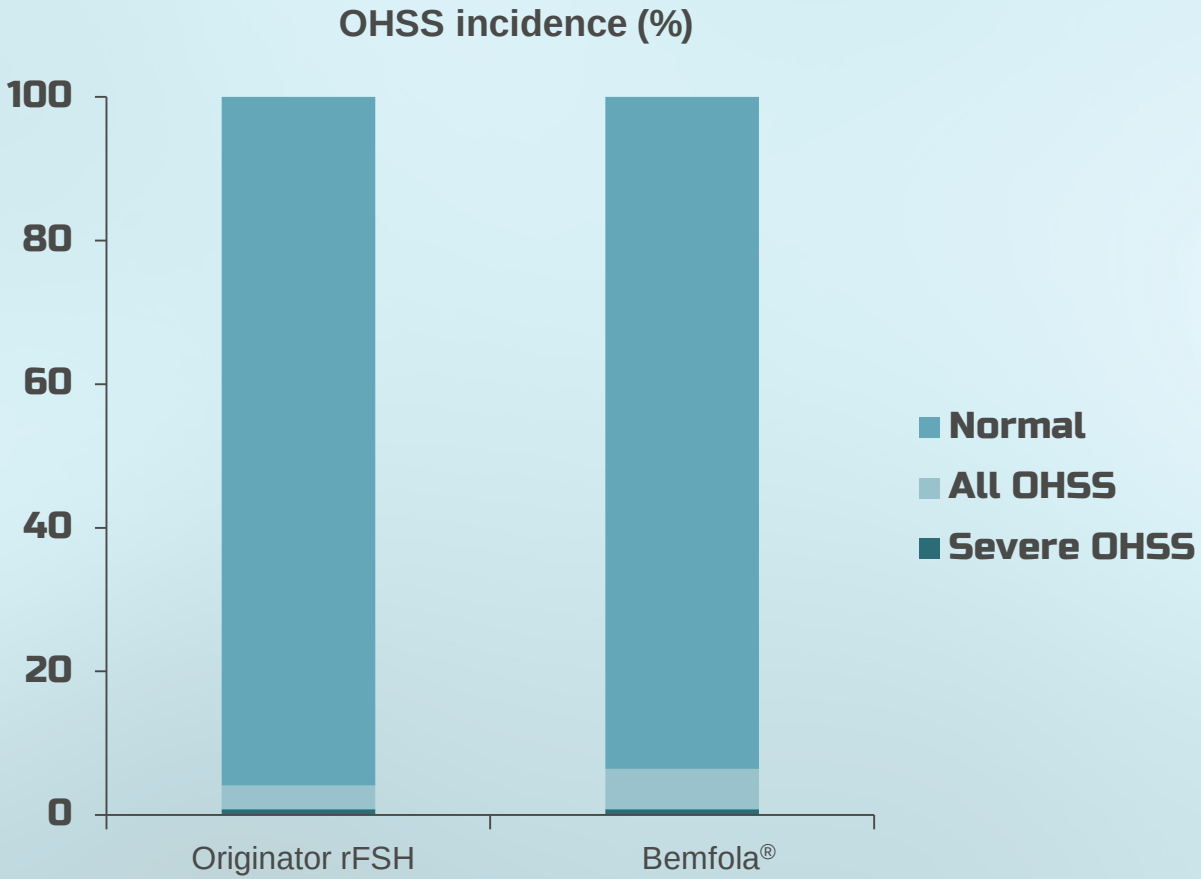
Adapted from Rettenbacher et al. 2015.

NS, non significant; PP, per protocol.

1. Rettenbacher M, et al. *Reprod Biomed Online.* 2015;30(5):504–513.

GEDEON RICHTER

Bemfola® Phase III study secondary endpoints: no significant difference in OHSS incidence[1]



The incidence of severe OHSS* was 0.8% in both groups

Adapted from Rettenbacher et al. 2015.

*As defined by The Practice Committee of the American Society for Reproductive Medicine, 2004.[1]
OHSS, ovarian hyperstimulation syndrome.

1. Rettenbacher M, et al. *Reprod Biomed Online* 2015;30(5):504–513

GEDEON RICHTER

Bemfola® shows similar efficacy and safety profiles to Gonal-f®[1]

- Clinical equivalence in terms of primary endpoint: number of oocytes retrieved[1]
- All secondary endpoints were similar[1]
- Incidence of adverse events reported were as anticipated in ART[1]
- No formation of anti-FSH antibodies (data not shown)[1]

Conclusion of EMA:

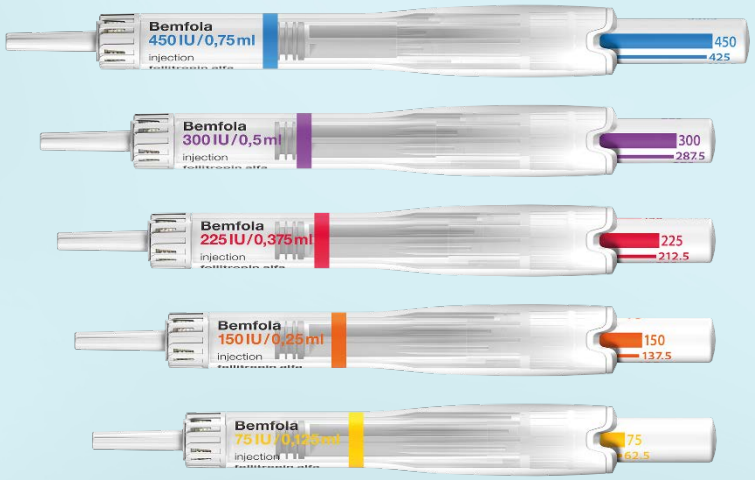
Biosimilarity with the reference medicinal product Gonal-f® has been sufficiently demonstrated[2,3]

ART, assisted reproductive technology; EMA, European Medicines Agency.

1. Rettenbacher M, et al. *Reprod Biomed Online.* 2015;30(5):504–513; 2. Bemfola Summary of Product Characteristics. May 2014; 3. EMA. Committee for medical products for human use (CHMP). EMEA/H/C/002615. Available at https://www.ema.europa.eu/en/documents/minutes/minutes-chmp-meeting-20-23-july-2020_en.pdf. Accessed April 2021.

GEDEON RICHTER

Bemfola® pen device is available for routine use



reddot design award
winner 2011

- Five single-use pens for common rFSH doses, with the option to make fine adjustments:[1]
  - Bemfola® 75 (37.5–75 IU)
  - Bemfola® 150 (75–150 IU)
  - Bemfola® 225 (150–225 IU)
  - Bemfola® 300 (225–300 IU)
  - Bemfola® 450 (300–450 IU)
- Shelf life of 3 years[1] (1 year longer than Gonal-f®)[2]

1. Bemfola Summary of Product Characteristics. May 2014; 2. Gonal-f® Summary of Product Characteristics. January 2020.

GEDEON RICHTER

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Is there any value adding LH to Bemfola®?

LH, luteinising hormone.

Randomised controlled trial vs real-world data

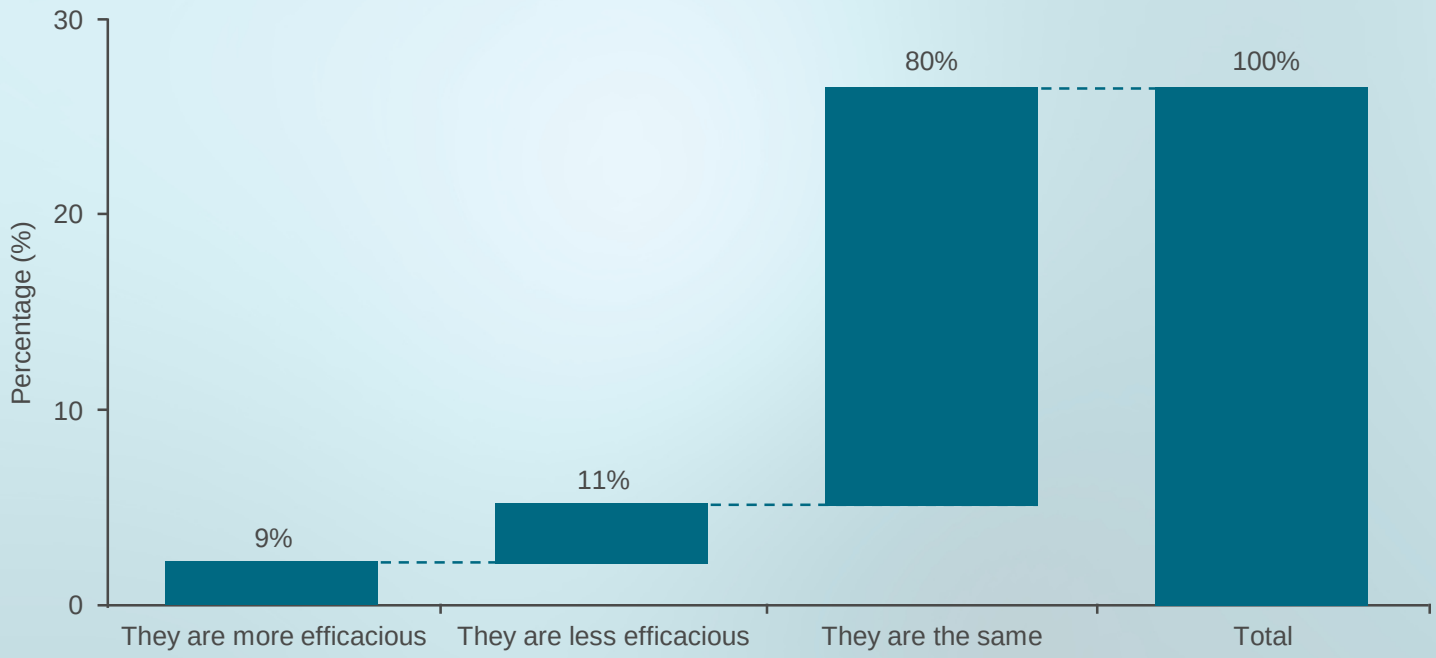
VS

Efficacy:
Randomised controlled trials reflect ideal patients in clinical trial circumstances

Effectiveness:
Real-world data provides insight into how drugs behave in the real world with all patients

Online survey in 2015 of 314 IVF units with cumulatively over 200,000 IVF cycles[1]

Graph showing results for the survey question:
If you have used the new recombinant FSH biosimilars, what is your view on their efficacy compared to previously-used gonadotrophins in a similar patient group?



Adapted from IVF Worldwide.

1. IVF Worldwide The use of gonadotropins and biosimilars in ART treated cycle. Available at http://www.ivf-worldwide.com/survey/the-use-of-gonadotropins-and-biosimilars-in-art-treated-cycles/results-the-use-of-gonadotropins-and-biosimilars-in-art-treated-cycles.html. Accessed April 2021.

GEDEON RICHTER

No difference in clinical outcomes using follitropin alfa biosimilar compared to follitropin alfa or follitropin beta for COS in oocyte donation-recipient cycles[1]

Parameter	Gonal-f®	Puregon®	Bemfola®
Mean total FSH dose (IUs)	2014±529	1824±559	2084±677
ITT population (N=372)	21±10	26±10	21±11
IU FSH/oocyte retrieved	117 IU	89 IU	98 IU
Ongoing pregnancy (%)	50.7	51.3	52.8

Adapted from Bosch, Howles. 2018.

Acknowledgement

- IVI-RMA Valencia

COS, controlled ovarian stimulation; ITT, intention-to-treat.

1. Bosch E, Howles C. *Fertil Steril.* 2018;110(4):e336.

Bemfola® has demonstrated real-world efficacy in a range of patients[1]

Population*	Number of oocytes retrieved ± SD
Normal responders (n=378)	12.2±7.2
Suboptimal responders (n=274)	8.6±6.0
Poor responders (n=88)	4.1±2.7
Oocyte donors (n=429)	19.5±9.5

Adapted from Ferrando et al. 2020.

*Poor responders were defined as (≥2 of the following): ≥40 years old (or any other risk for poor ovarian response); ≤3 oocytes with a conventional stimulation protocol; AFC <5 to 7 follicles or AMH <0.5–1.1 ng/ml. Suboptimal responders were defined as: either, <38 years old with ≤3 oocytes with a conventional stimulation protocol or AFC <5 follicles or AMH <0.5 ng/ml; or, >37 years old without previous features and stimulated with >225 IU FSH in combination with LH activity from HMG or rLH. Normal responders were defined as: either, <38 years old with AMH <1.5 ng/ml and no risk factors of poor ovarian response (endometriosis grade I–II, previous poor ovarian response); or, women with high ovarian reserve.
†Quality was assessed according to the criteria of the Asociación para el Estudio de la Biología de la Reproducción (ASEBIR).
AFC, antral follicle count; AMH, anti-Müllerian hormone; HMG, human menopausal hormone; LH, luteinising hormone; rLH, recombinant luteinising hormone.
1. Ferrando M, et al. *Fertil Res Pract*. 2020;6:13.

- BIRTH: a non-interventional, real-world study of 1,222 women treated in 26 centres across Spain[1]
- Bemfola met treatment requirements for all patient types, including embryo quality† and fertility rates[1]

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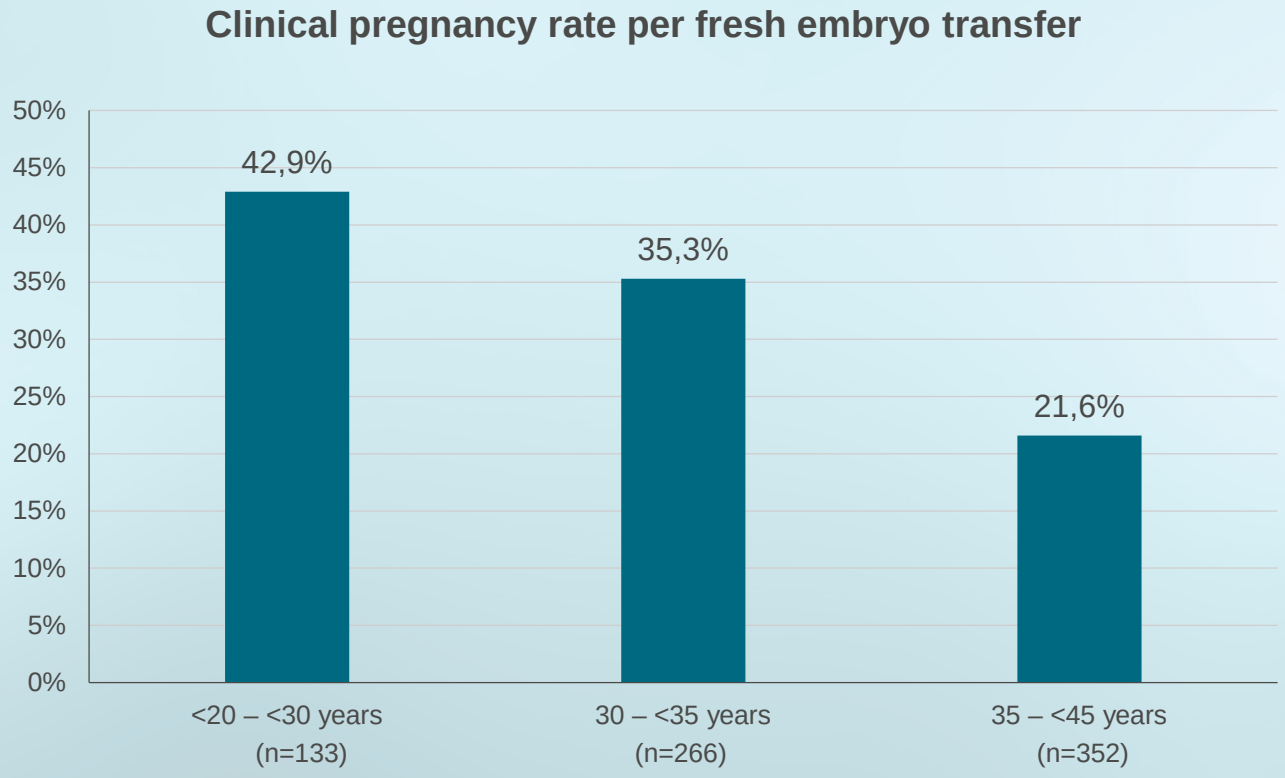
NIS: 977 ovarian punctures in 20 sites in Germany and 4 sites in Austria[1]



Adapted from Griesinger et al. 2021.

Mean number of eggs retrieved 10.7 (±6.6)	
OHSS	69 (7.0% of all cycles)
Mild	25 (2.5% of all cycles)
Moderate	42 (4.3% of all cycles)
Severe	2 (0.2% of all cycles)

CI, confidence interval; NIS, non-interventional study; OHSS, ovarian hyperstimulation syndrome.

1. Griesinger G, et al. *J Reprod Infertil*. 2021; doi: 10.18502/jri.v22i2.5798.

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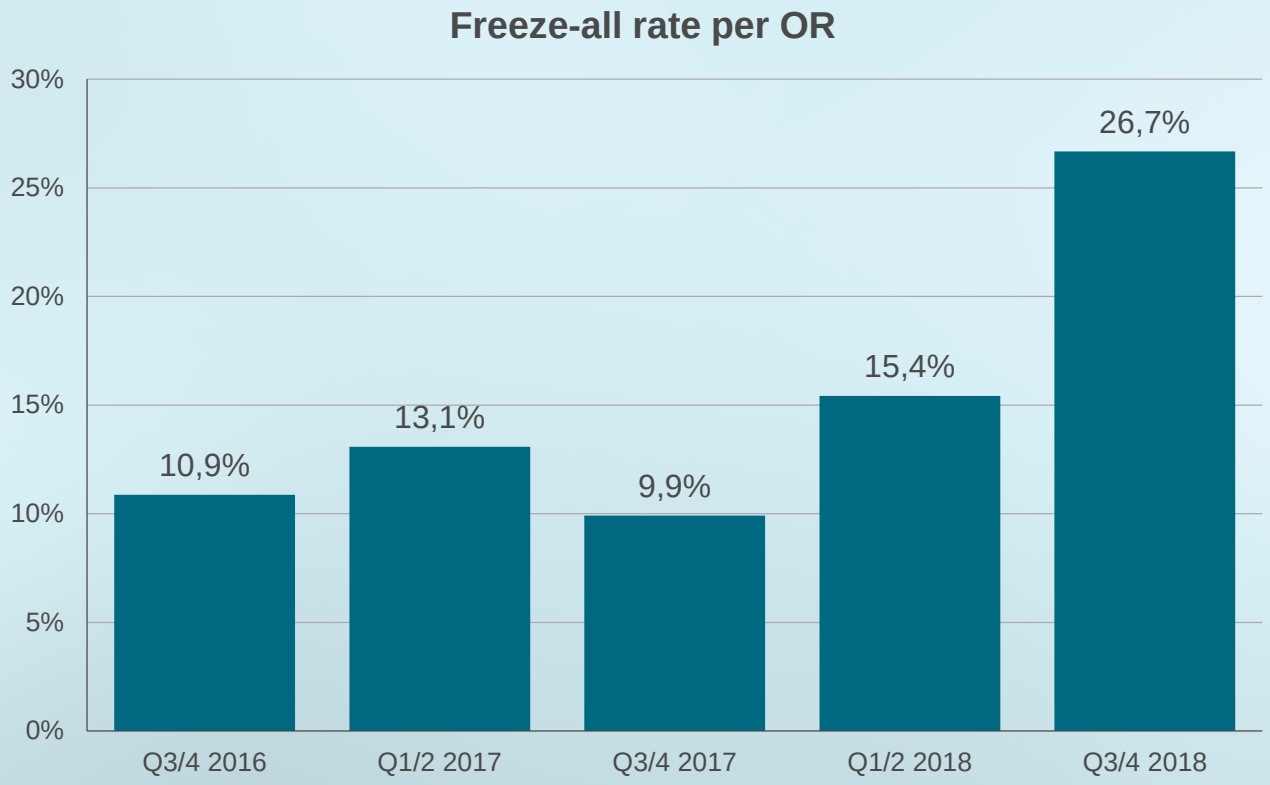
Trend towards increasing use of freeze-all cycles[1]



Adapted from Griesinger et al. 2021.

Freeze-all

- All ORs: 14.2% (140/986)
- IVF: 15.3% (29/190)
- ICSI: 11.2% (80/714)
- IVF+ICSI: 50.0% (26/52)
- No IVF/ICSI: 16.7% (5/30)

ICSI, intracytoplasmic sperm injection; OR, oocyte retrieval.

1. Griesinger G, et al. *J Reprod Infertil*. 2021; doi: 10.18502/jri.v22i2.5798.

Non-interventional study on freeze-all therapies in Germany and Austria

Freeze-all treatments in Germany and Austria have become more and more widespread;[1] however, incidence, indications, treatment burden and benefits are still not very well evaluated

- A prospective, observational post-authorisation study on fresh-transfer and freeze-all treatments of assisted reproductive technology patients undergoing controlled ovarian stimulation with follitropin alfa (Bemfola®)[1]
  - ART patients stimulated with Bemfola® (fresh-transfer and freeze-all cycles plus corresponding FETs)[1]
  - >900 COS cycles in 24 study centres across Germany and Austria[1]
  - PI: Prof. Georg Griesinger, Lübeck

ART, assisted reproductive technology; COS, controlled ovarian stimulation; FET, frozen embryo transfer.

1. Griesinger G, et al. *J Reprod Infertil*. 2021; doi: 10.18502/jri.v22i2.5798.

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LH, luteinising hormone.

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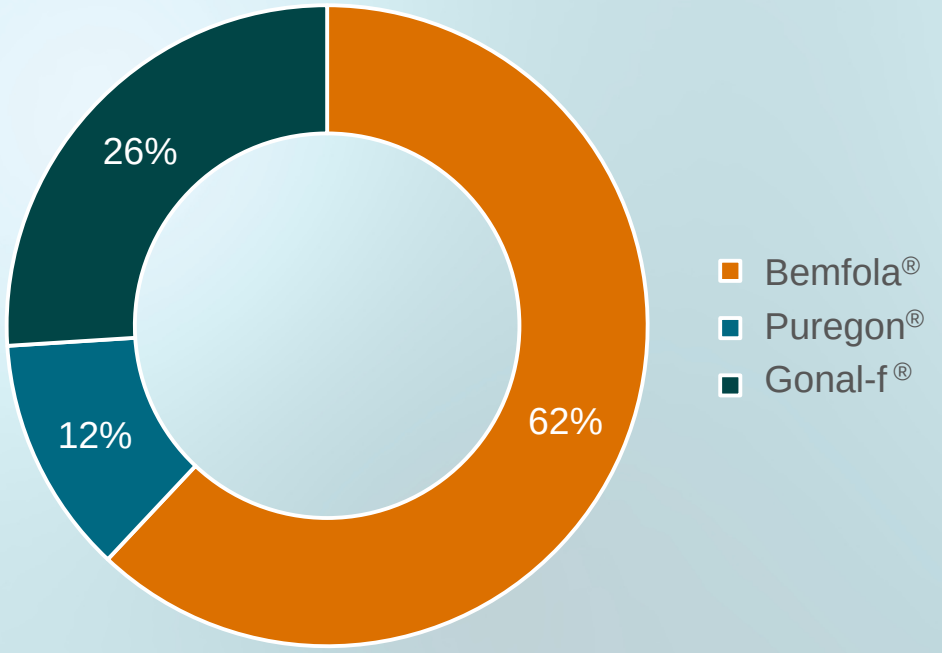
In UK and Switzerland, treatment-naïve patients preferred Bemfola® pen compared to on-market alternatives[1]

The Bemfola® pen showed a superior ranking for:

- Pen size
- Learning of use
- Injection preparation
- Injection handling

Proportion of overall 'best' ranking (n=65 women)



Adapted from Imthurn et al. 2014.

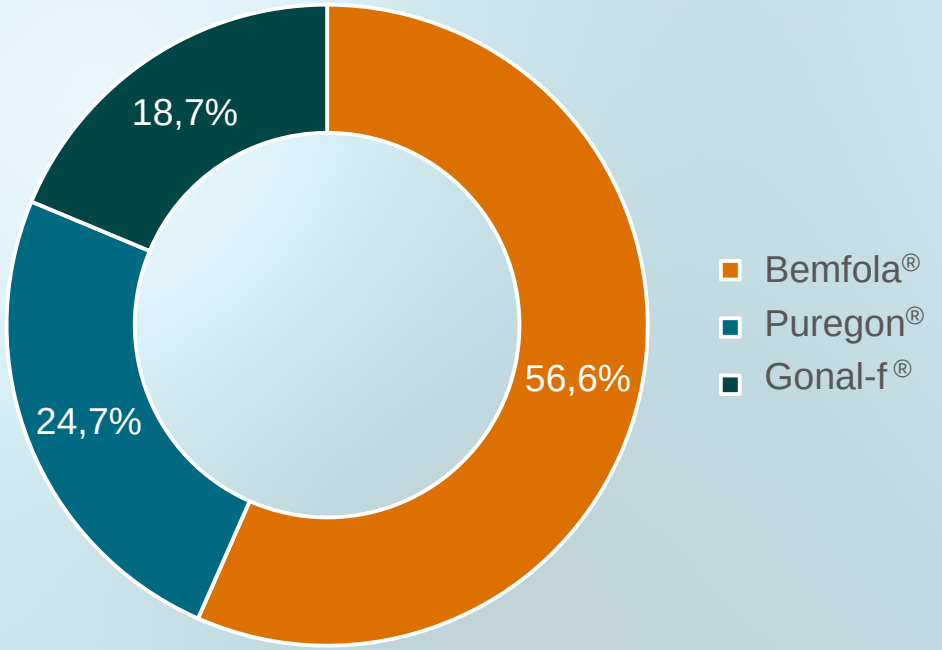
1. Imthurn B, et al. *Expert Opin Drug Deliv.* 2014;11:1859–1864.

GEDEON RICHTER

In Spain, following demonstration of 3 rFSH pens, women were asked:

“Of the three pens, what would be your preferred option for your treatment?”[1]

n=438/458 women who expressed an opinion[1]



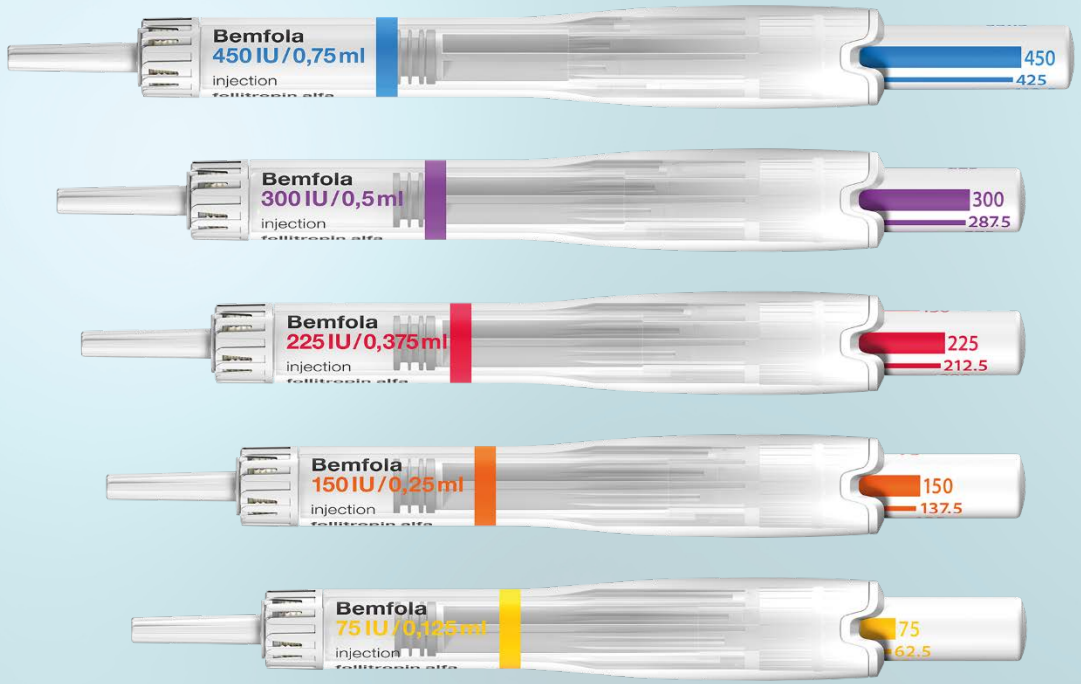
Adapted from Quintero et al. 2016.

1. Quintero LA, et al. *Rev Iberoam Fert Rep Hum*. 2016;33(3):42–51.

GEDEON RICHTER

A human factor interactions study showed that the Bemfola® pen is easy to teach and to use[1]

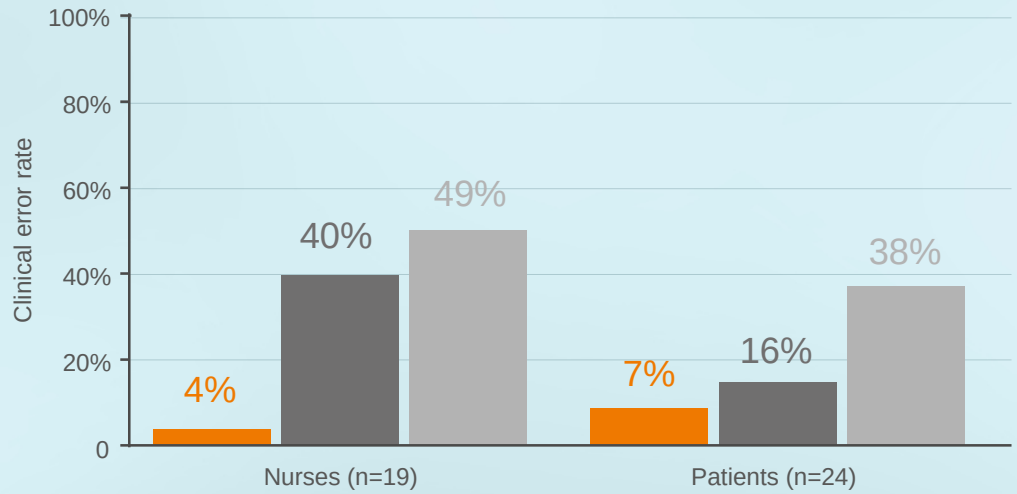
- In total, 18 infertile patients and 19 infertility nurses were recruited across 6 European countries: Germany, Netherlands, Spain, Sweden, Denmark and UK
- Extensive testing, including both nurse–patient pairings and in-depth interviews, showed that the Bemfola® pen is easy to learn, use, teach and change dose, as well as being easy to adapt in diverse possible scenarios that a patient could encounter in standard clinical practice

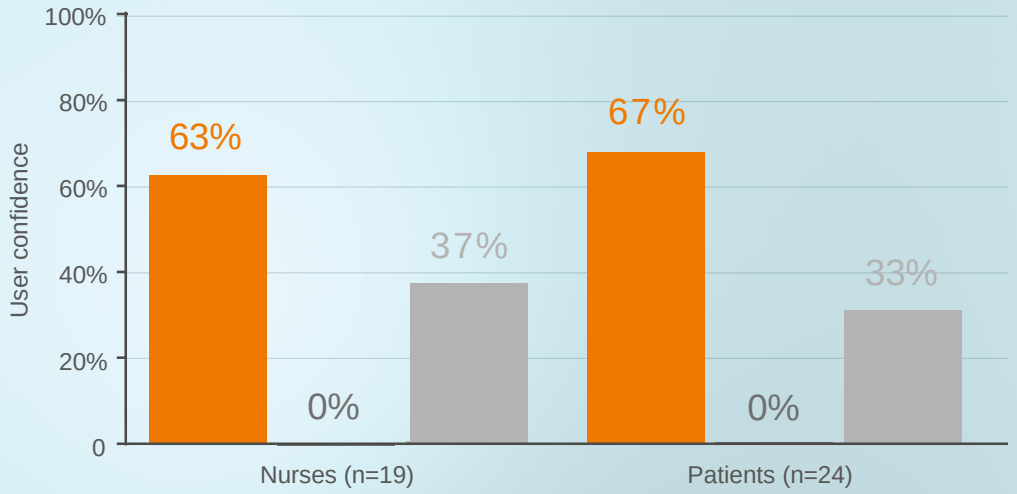


1. Saunders H, et al. *Expert Opin Drug Deliv.* 2018;15(6):549–558.

GEDEON RICHTER

Patients and nurses are more confident administering Bemfola® than market alternatives[1]





Bemfola® Ovaleap® Gonal-f®

Adapted from Saunders et al. 2020.

In a user experience study with nurses and patients, the Bemfola® pen was superior to Gonal-f® and Ovaleap®:[1]

- Fewer steps to prepare and administer an injection
- Lower clinical error rate
- Higher user confidence

Nurses performed a mock 150 IU injection with each pen and patients performed a 150 IU injection after training, followed by a further 225 IU injection.[1]

1. Saunders H, et al. *Expert Opin Drug Deliv.* 2020; doi: 10.1080/17425247.2021.1863944.

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Does Bemfola® result in more or less drug wastage than currently used gonadotrophins?

- If less than the full amount in the pen is administered, a single-use Bemfola® pen will waste some of the drug
- A multidose pen will waste any drug left in the final pen used
- Also a dilemma exists with multidose pens – if the full amount in the other pens is not used, should the patient receive two injections or waste the residual drug in each pen?

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Bemfola® pen has the potential to reduce wastage compared to current practice[1]

Real-world study

- Study in five UK infertility clinics in 2014

4,724 treatment cycles

- 4,078 Gonal-f®
- 646 Menopur®

Example of one of the centres using four different starting doses for 623 IVF cycles

Comparison of drug wastage for each daily dose (IUs)		
Starting dose (IU)	Current gonadotropin wastage	Bemfola® wastage
150	23,775	0
200	24,350	36,750
225	58,275	0
300	47,175	0
Total	**153,575**	**36,750**

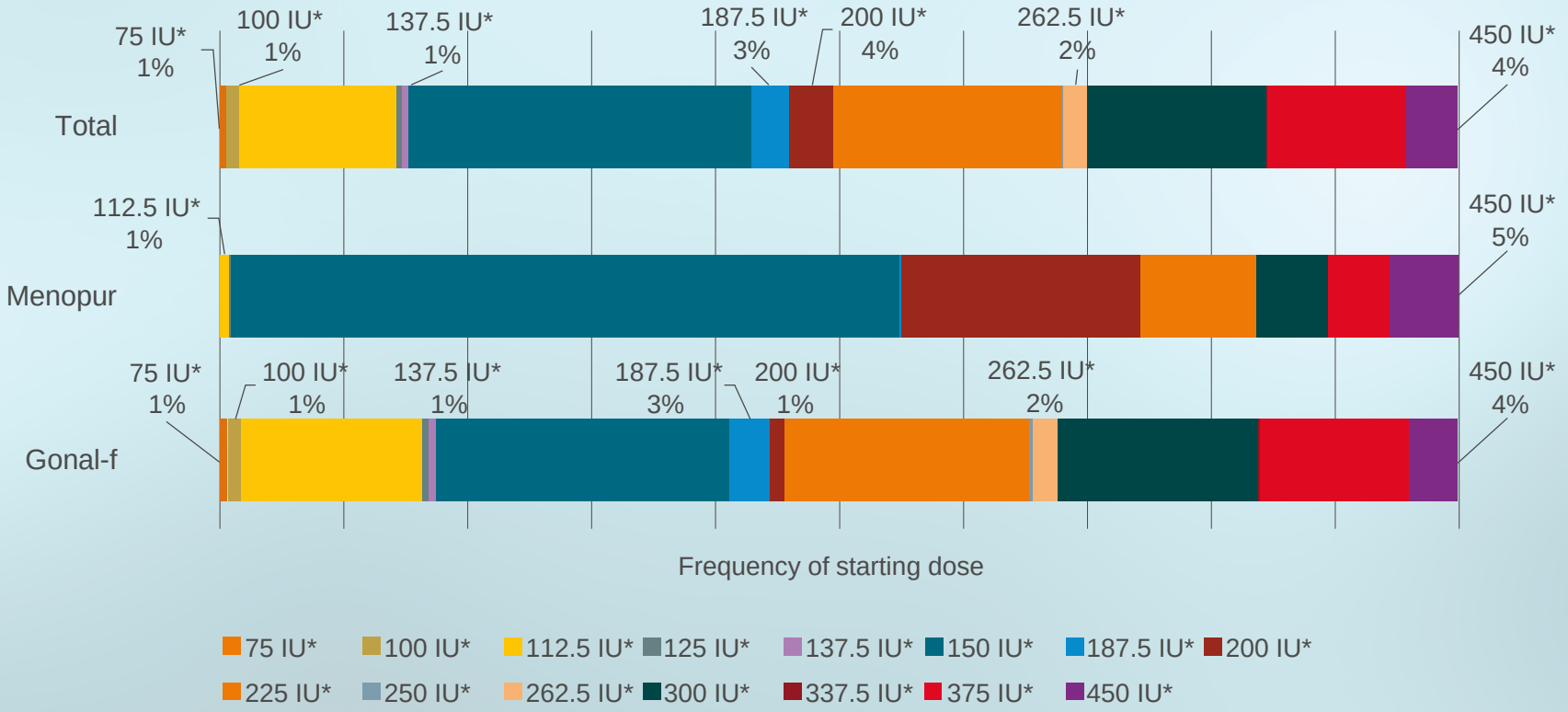
Adapted from Foxon et al. 2018.

1. Foxon G, et al. *Hum Fertil (Camb).* 2018;21:275–228.

GEDEON RICHTER

150 IU is the most common Gonal-f® and Menopur® starting dose[1]

Frequency of starting dose used across Gonal-f® and Menopur® treatment cycles in five UK fertility clinics[1]



Adapted from Foxon et al. 2018.

The most common starting doses:

1. 150 IU: 28%
2. 225 IU: 18%
3. 300 IU: 15%

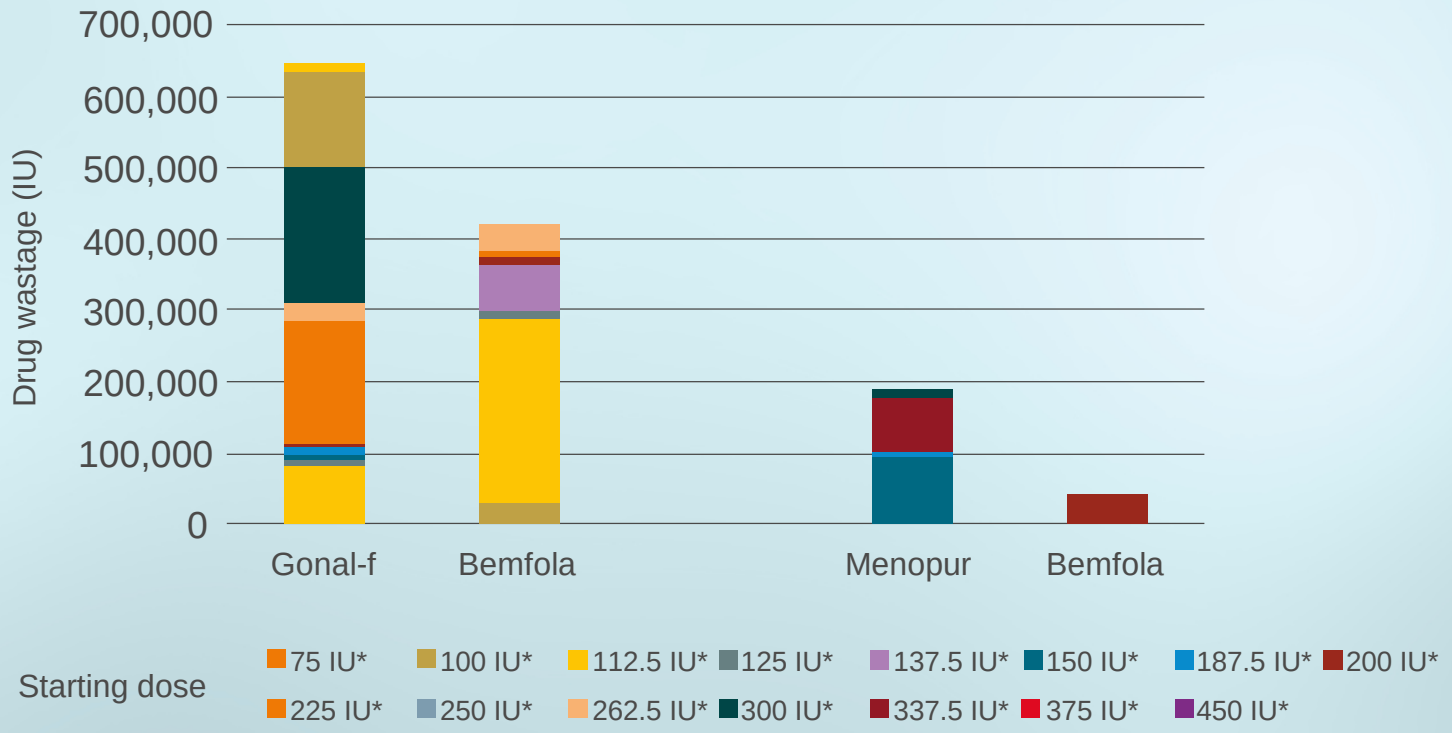
- The average treatment cycle was 9–12 days

*Starting doses that are not prescribed for Menopur® cycles.

1. Foxon G, et al. *Hum Fertil (Camb).* 2018;21:275–228.

GEDEON RICHTER

Use of Bemfola® instead of either Gonal-f® or Menopur® could reduce drug wastage[1]



Drug wastage incurred more frequently during Gonal-f® or Menopur® treatment cycles compared with drug wastage if Bemfola® was used during the same cycles[1]

Adapted from Foxon et al. 2018.

*Starting doses that are not prescribed for Menopur® cycles.

1. Foxon G, et al. *Hum Fertil (Camb).* 2018;21:275–228.

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Further potential reduction of wastage

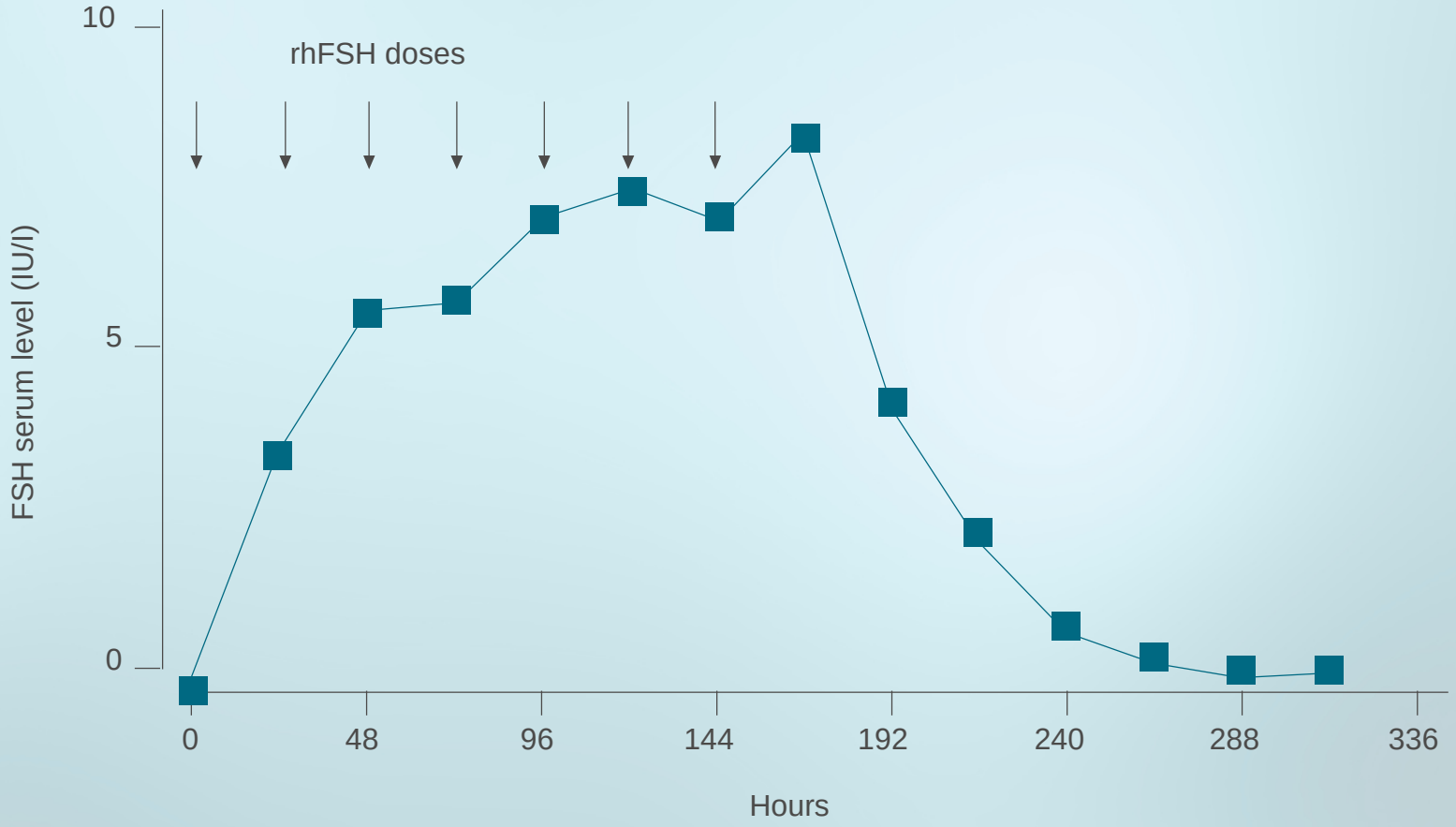
The Foxon 2018 study looked at wastage based on real-world evidence of multiple starting doses and alteration of dose during treatment.[1]

Wastage was decreased if there was no dose alteration and the optimal dose was used from the outset.

- Is there an advantage to altering the FSH dose during stimulation?
- How important is the initial FSH dose?

1. Foxon G, et al. *Hum Fertil (Camb).* 2018;21:275–228.

Maximal pharmacokinetic effect of rhFSH was not reached until 4 days of repeated daily subcutaneous administration[1]

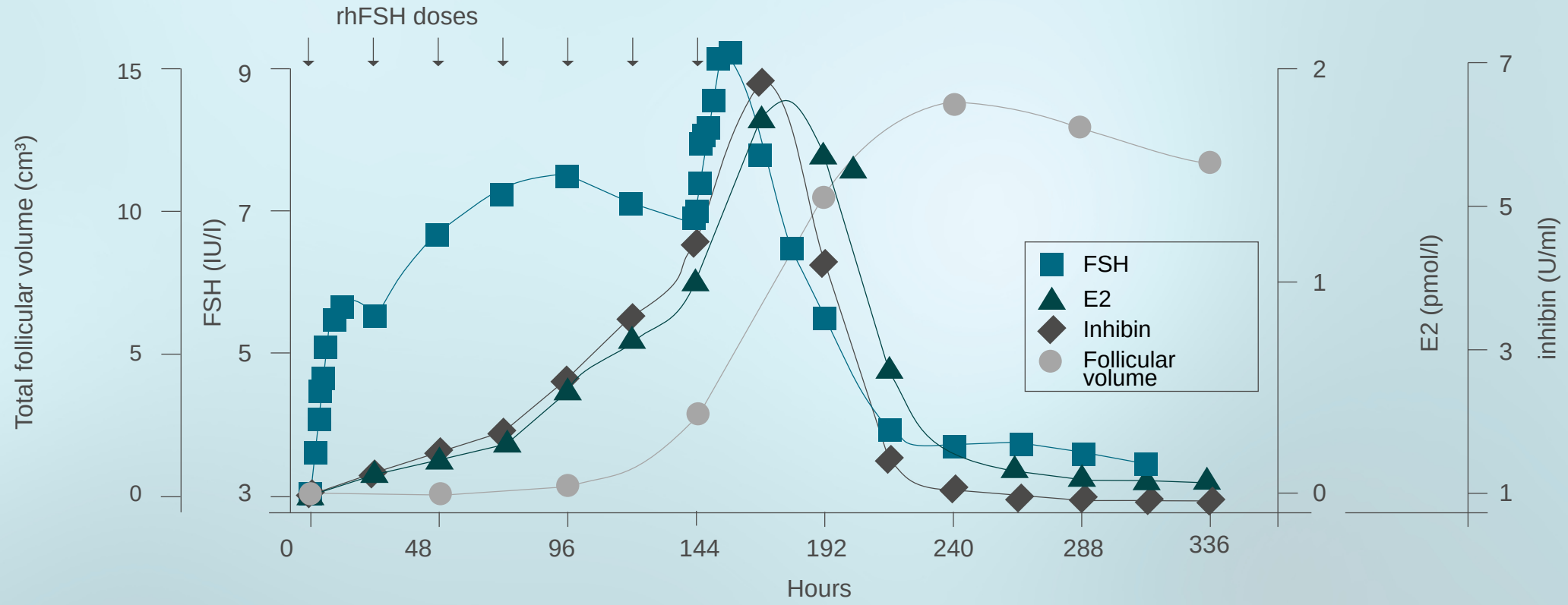


Adapted from Le Contonnec et al. 1994.

rhFSH, recombinant human follicle stimulating hormone.

1. Le Contonnec JY, et al. *Fertil Steril.* 1994;61:679–686.

Further lag from peak FSH of ≈4 days to pharmacodynamic response (E2, inhibin and follicular diameter)[1]



Adapted from Le Contonnec et al. 1998.

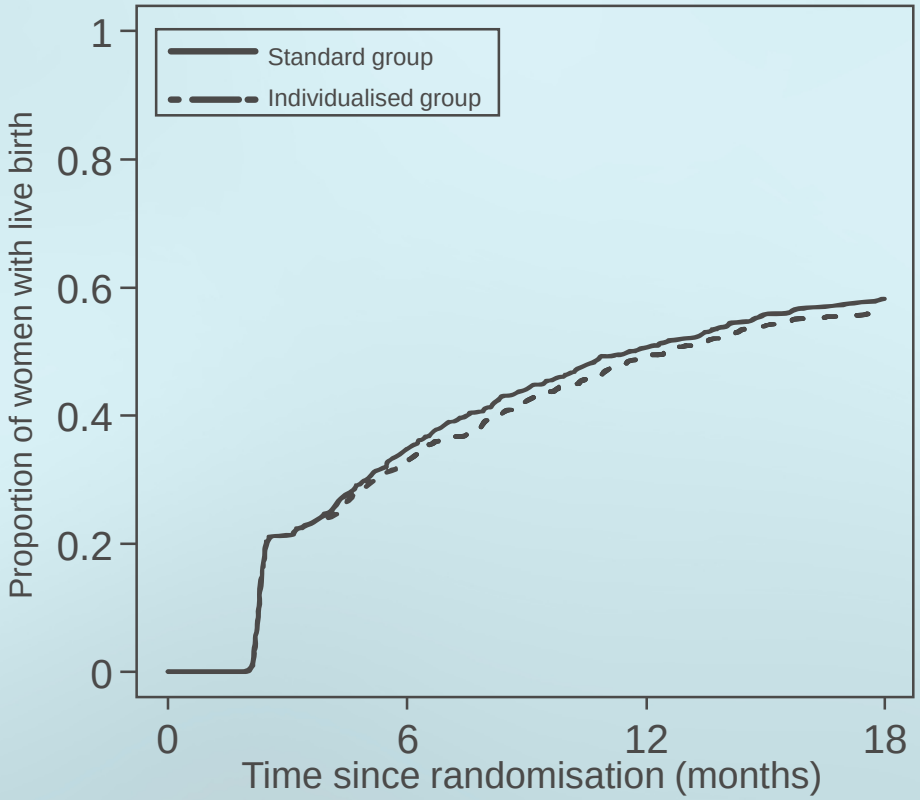
1. Le Contonnec JY, et al. *Fertil Steril.* 1998;69(2):201–209.

Is there benefit to altering rFSH dose during ovarian stimulation?

- There is a delay of 3–4 days to achieve a steady state of FSH[1]
- Once a steady state of FSH is achieved, there is a further delay of about 4 days before an effect on follicular development occurs[1]
- This is a problem for potential high responders, as they may continue to develop multiple small follicles[1]
- This may also be a problem for poor responders, as they experience a long lag compared to other study groups, possibly because those follicles that are growing have commandeered the blood supply[1]
- In summary, altering rFSH dose is appropriate for ovulation induction but not for ovarian stimulation prior to IVF

1. Le Contonnec JY, et al. *Fertil Steril.* 1994;61:679–686.

Although individualising FSH starting dose is common, perhaps this is not as critical as once thought?



Adapted from van Tilborg et al. 2017.

OPTIMIST study, looking at 1,515 women undergoing first IVF/ICSI cycle, found no benefit on live-birth rate using individualised FSH dosing compared to a standard FSH dosage.[1]

Although individualised dosing led to a reduction of the rate of mild and moderate OHSS, no effects on the occurrence of severe OHSS could be demonstrated.[1]

ICSI, intracytoplasmic sperm injection; OHSS, ovarian hyperstimulation syndrome.

1. van Tilborg TC, et al. *Hum Reprod*, 2017;32(12):2485–2495.

Is there benefit to incorporating a freeze-all option in routine ovarian stimulation strategy?

In high responders a freeze-all provides an effective method allowing for continuation on the same dose of FSH, enabling them to maintain a high-pregnancy rate without an excess risk of OHSS[1]

In most poor responders the outlook is not good irrespective of approach other than donor oocytes. However, there are several treatment options that can be discussed with patients:

- Continuing on the same dose of FSH until oocyte retrieval and embryo transfer
- Cancelling IVF cycle and starting again on a higher FSH dose
- Possibly continuing onto oocyte retrieval, freezing all embryos and then continuing on a higher FSH dose until a further oocyte retrieval and freeze all for later pooled preimplantation genetic screening and blastocyst transfer[2]

OHSS, ovarian hyperstimulation syndrome.

1. Roque M, et al. *Hum Reprod Update.* 2019;25:2–14; 2. Milán M, et al. *Reprod Biomed Online*. 2010;21:649–657.

ESHRE guidelines: ovarian stimulation for IVF/ICSI[1]

Recommendation		
A freeze-all strategy is recommended to fully eliminate the risk of late-onset OHSS	Strong	⨁⨁⨁◯
Prior to start of ovarian stimulation, a risk assessment for high response is advised	GPP	⨁⨁⨁◯
Adjustment (increase or decrease) of the gonadotrophin dose in the mid-stimulation phase during ovarian stimulation is probably not recommended	Conditional	⨁⨁⨁◯

ESHRE, European Society of Human Reproduction and Embryology; GPP, good practice point; ICSI, intracytoplasmic sperm injection; OHSS, ovarian hyperstimulation syndrome.

1. ESHRE. Guideline on Ovarian Stimulation for IVF/ICSI. Available at https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI. Accessed April 2021.

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ESPART study: poor responders data suggests fewer oocytes with LH and no benefit in pregnancy rates[1]

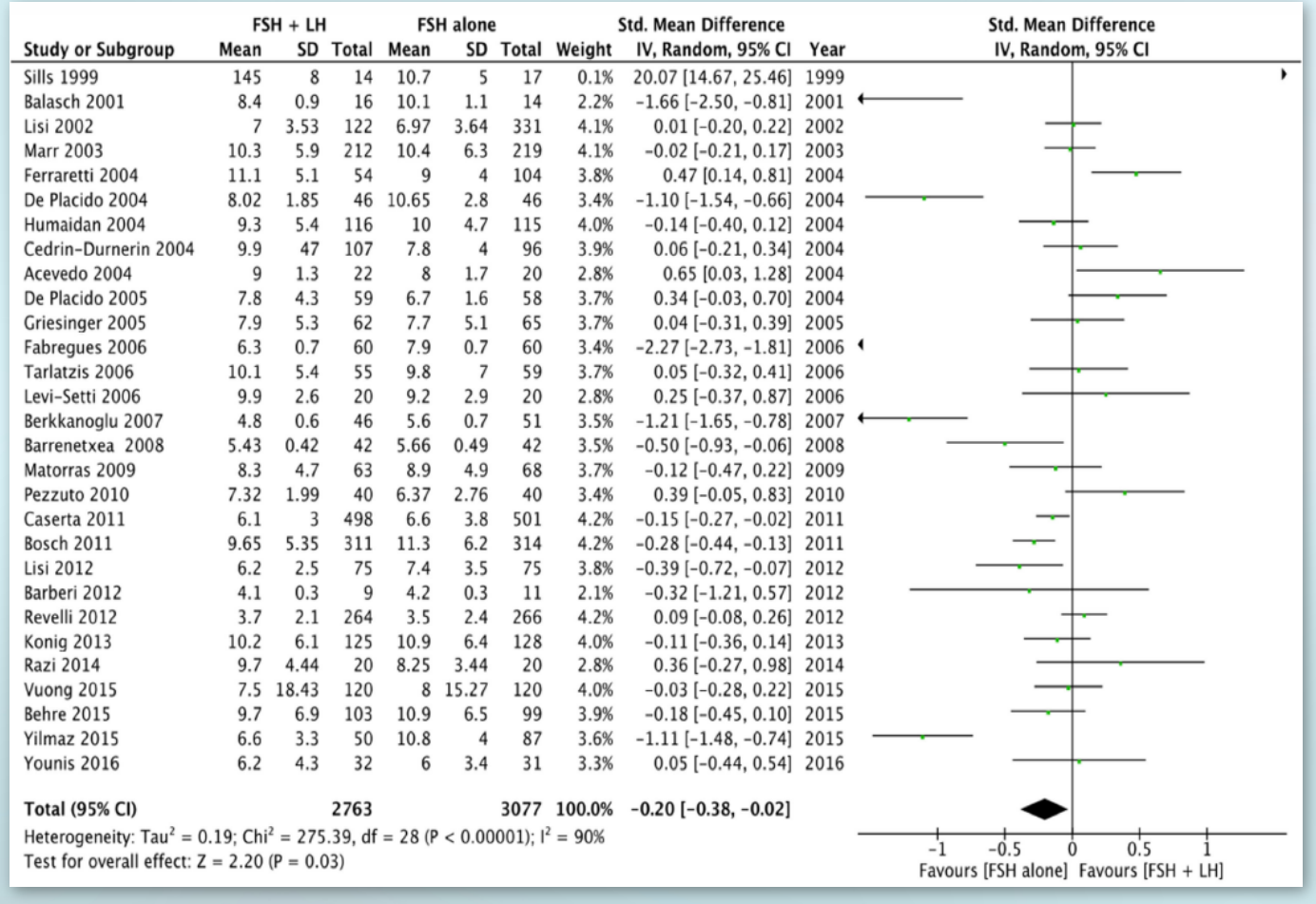
ITT analysis set	rFSH + rLH	rFSH
Number of participants	462	477
Oocytes – mean (SD)	**3.3** (2.71)	**3.6** (2.82)*
Ongoing pregnancy rate	11.0	12.4
Live birth rate	10.6	11.7
Embryo implantation rate	14.7	15.6
Clinical pregnancy rate	14.1	16.8
Biochemical pregnancy rate	17.3	23.9

Adapted from van Tilborg et al. 2017.

LH activity impacts steroidogenesis and excess LH inhibits follicular growth[2,3]

*p=0.054. Mean difference (net) −0.235, 2-sided CI 95% −0.4741 to 0.003.
CI, confidence interval; ITT, intention-to-treat; LH, luteinising hormone; rLH, recombinant luteinising hormone.
1. ClinicalTrials.gov. NCT02047227. Available at https://clinicaltrials.gov/ct2/show/NCT02047227. Accessed April 2021; 2. Hillier SG. *Hum Reprod.* 1994;9(2):188–191; 3. Loumaye E, et al. *Hum Reprod.* 2003;18(12):2719–2720.

Meta-analysis of 5,840 patients in 29 studies confirmed LH reduced number of oocytes when added to FSH



Study or Subgroup	FSH + LH Mean	SD	Total	FSH alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Sills 1999	145	8	14	10.7	5	17	0.1%	20.07 [14.67, 25.46]	1999
Balasch 2001	8.4	0.9	16	10.1	1.1	14	2.2%	-1.66 [-2.50, -0.81]	2001
Lisi 2002	7	3.53	122	6.97	3.64	331	4.1%	0.01 [-0.20, 0.22]	2002
Marr 2003	10.3	5.9	212	10.4	6.3	219	4.1%	-0.02 [-0.21, 0.17]	2003
Ferraretti 2004	11.1	5.1	54	9	4	104	3.8%	0.47 [0.14, 0.81]	2004
De Placido 2004	8.02	1.85	46	10.65	2.8	46	3.4%	-1.10 [-1.54, -0.66]	2004
Humaidan 2004	9.3	5.4	116	10	4.7	115	4.0%	-0.14 [-0.40, 0.12]	2004
Cedrin-Durnerin 2004	9.9	47	107	7.8	4	96	3.9%	0.06 [-0.21, 0.34]	2004
Acevedo 2004	9	1.3	22	8	1.7	20	2.8%	0.65 [0.03, 1.28]	2004
De Placido 2005	7.8	4.3	59	6.7	1.6	58	3.7%	0.34 [-0.03, 0.70]	2004
Griesinger 2005	7.9	5.3	62	7.7	5.1	65	3.7%	0.04 [-0.31, 0.39]	2005
Fabregues 2006	6.3	0.7	60	7.9	0.7	60	3.4%	-2.27 [-2.73, -1.81]	2006
Tarlatzis 2006	10.1	5.4	55	9.8	7	59	3.7%	0.05 [-0.32, 0.41]	2006
Levi-Setti 2006	9.9	2.6	20	9.2	2.9	20	2.8%	0.25 [-0.37, 0.87]	2006
Berkkanoglu 2007	4.8	0.6	46	5.6	0.7	51	3.5%	-1.21 [-1.65, -0.78]	2007
Barrenetxea 2008	5.43	0.42	42	5.66	0.49	42	3.5%	-0.50 [-0.93, -0.06]	2008
Matorras 2009	8.3	4.7	63	8.9	4.9	68	3.7%	-0.12 [-0.47, 0.22]	2009
Pezzuto 2010	7.32	1.99	40	6.37	2.76	40	3.4%	0.39 [-0.05, 0.83]	2010
Caserta 2011	6.1	3	498	6.6	3.8	501	4.2%	-0.15 [-0.27, -0.02]	2011
Bosch 2011	9.65	5.35	311	11.3	6.2	314	4.2%	-0.28 [-0.44, -0.13]	2011
Lisi 2012	6.2	2.5	75	7.4	3.5	75	3.8%	-0.39 [-0.72, -0.07]	2012
Barberi 2012	4.1	0.3	9	4.2	0.3	11	2.1%	-0.32 [-1.21, 0.57]	2012
Revelli 2012	3.7	2.1	264	3.5	2.4	266	4.2%	0.09 [-0.08, 0.26]	2012
Konig 2013	10.2	6.1	125	10.9	6.4	128	4.0%	-0.11 [-0.36, 0.14]	2013
Razi 2014	9.7	4.44	20	8.25	3.44	20	2.8%	0.36 [-0.27, 0.98]	2014
Vuong 2015	7.5	18.43	120	8	15.27	120	4.0%	-0.03 [-0.28, 0.22]	2015
Behre 2015	9.7	6.9	103	10.9	6.5	99	3.9%	-0.18 [-0.45, 0.10]	2015
Yilmaz 2015	6.6	3.3	50	10.8	4	87	3.6%	-1.11 [-1.48, -0.74]	2015
Younis 2016	6.2	4.3	32	6	3.4	31	3.3%	0.05 [-0.44, 0.54]	2016
Total (95% CI)			**2763**			**3077**	**100.0%**	**-0.20 [-0.38, -0.02]**	

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 275.39$, df = 28 ($P < 0.00001$); $I^2 = 90\%$

Test for overall effect: Z = 2.20 (P = 0.03)

Studies using FSH + LH retrieved a significantly lower number of oocytes compared to FSH alone (p=0.010)[1]

CI, confidence interval; LH, luteinising hormone.

1. Santi D, et al. *Front Endocrinol (Lausanne).* 2017;8:114.

MEGASET study: rFSH produced more oocytes and hMG did not improve embryo quality[1]

	hMG (n=374) Mean ± SD	rFSH (n=375) Mean ± SD	*p* value
Quantity measures			
Oocytes retrieved	9.1±5.2	10.7±5.8	<0.001
Day 3 no. of embryos available	4.0±3.0	4.8±3.7	0.005
Day 5 no. of blastocysts	2.7±2.5	3.1±3.0	0.125
Quality measures			
Of oocytes retrieved – % metaphase II	77±23%	78±19%	0.798
Of oocytes retrieved – fertilisation rate	75±23%	76±22%	0.969
Of fertilised oocytes – % top embryos	31±30%	31±28%	0.546
Blastocyst quality	No difference in multiple comparisons		0.232–0.958

Adapted from Devroey et al. 2012.

hMG, human menopausal gonadotropin.

1. Devroey P, et al. *Fertil Steril.* 2012;97:561–571.

BIRTH study: oocyte retrieval tended to be lower with combination therapy in a real-world evaluation[1]

Population*	Number of oocytes retrieved ± SD	
	rFSH	rFSH+LH
All patients	15.1±9.4 (n=681)	11.2±8.5 (n=488)
Normal responders	13.6±7.6 (n=234)	10.1±6.1 (n=144)
Suboptimal responders	9.9±7.2 (n=89)	7.9±5.2 (n=185)
Poor responders	3.7±2.6 (n=40)	4.6±2.7 (n=48)
Oocyte donors	19.1±9.5 (n=318)	20.8±9.4 (n=111)

Adapted from Ferrando et al. 2020.

BIRTH: a non-interventional, real-world study of 1,222 women treated in 26 centres across Spain[1]

*Poor responders were defined as (≥2 of the following): ≥40 years old (or any other risk for poor ovarian response); ≤3 oocytes with a conventional stimulation protocol; AFC <5 to 7 follicles or AMH <0.5–1.1 ng/ml. Suboptimal responders were defined as: either, <38 years old with ≤3 oocytes with a conventional stimulation protocol or AFC <5 follicles or AMH <0.5 ng/ml; or, >37 years old without previous features and stimulated with >225 IU FSH in combination with LH activity from HMG or rLH. Normal responders were defined as: either, <38 years old with AMH <1.5 ng/ml and no risk factors of poor ovarian response (endometriosis grade I–II, previous poor ovarian response); or, women with high ovarian reserve.

AFC, antral follicle count; AMH, anti-Müllerian hormone; HMG, human menopausal hormone; LH, luteinising hormone; rLH, recombinant luteinising hormone.

1. Ferrando M, et al. *Fertil Res Pract*. 2020;6:13.

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ESHRE guidelines: ovarian stimulation for IVF/ICSI[1]

Recommendation

The use of rFSH and hMG for ovarian stimulation is equally recommended	Strong	⨁⨁⨁◯

Although there are no recommendations on rLH, the guidelines state:

- rLH and rFSH have similar live-birth rates compared to rFSH alone
- Probably not recommended for the general population
- Useful specific patient groups WHO-I anovulatory patients

Note: no beneficial effect

- In poor responders
- In advanced age

ESHRE, European Society of Human Reproduction and Embryology; hMG, human menopausal gonadotropin; ICSI, intracytoplasmic sperm injection; rLH, recombinant luteinising hormone; WHO, World Health Organization.

1. ESHRE. Guideline on Ovarian Stimulation for IVF/ICSI. Available at https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI. Accessed April 2021.

Conclusions

- Following 8 years of development, the EMA was satisfied that biosimilarity of Bemfola® to Gonal-f® was demonstrated[1–4]
- Bemfola® pregnancy rates in the real-world setting are consistent with alternatives and adverse reaction rates are low[4]
- Compared to alternative rFSH pens, patients preferred the award-winning Bemfola® pen, which has been shown to be very easy to teach, learn and use[5]
- Bemfola® has the potential to reduce drug wastage and fits perfectly with new directions in ovarian stimulation, including freeze-all IVF cycles[6]
- ESHRE 2019 guidelines on ovarian stimulation advise against dose alteration during stimulation and do not identify a benefit to adding LH activity to FSH stimulation[7]

EMA, European Medicines Agency; ESHRE, European Society of Human Reproduction and Embryology; LH, luteinising hormone.

1. Polymun (2012) Comparability Exercise Bemfola® vs. Gonal-f® Ver.3; 2. Determination of the biological activity of FSH following subcutaneous administration to rats; LPT Report No. 22564/279; July 2012; 3. Wolzt M, et al. *Eur J Drug Metab Pharmacokinet*. 2016;41(3):259–265; 4. Rettenbacher M, et al. *Reprod Biomed Online.* 2015;30(5):504–513; 5. Saunders H, et al. *Expert Opin Drug Deliv.* 2018;15(6):549–558; 6. Foxon G, et al. *Hum Fertil (Camb).* 2018;21:275–228; 7. ESHRE. Guideline on Ovarian Stimulation for IVF/ICSI. Available at https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI. Accessed April 2021.

GEDEON RICHTER

Abbreviated Prescribing Information

Bemfola pre-filled pens containing follitropin alfa 75 IU, 150 IU, 225 IU, 300 IU, 450 IU

ATC code: G03GA05

Indications: Anovulation (including polycystic ovarian syndrome, PCOS) in adult women who have been unresponsive to treatment with clomiphene citrate; stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT); in association with luteinising hormone preparation for the stimulation of follicular development in women with severe LH (< 1.2 IU/L) and FSH deficiency; stimulation of spermatogenesis in adult men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

Treatment should be initiated under the supervision of a physician experienced in the treatment of fertility disorders.

Administration: Bemfola is given by subcutaneous injection.

Posology: *Women with anovulation (including PCOS)* – Daily injections, starting by Day 7 of the cycle. Treatment typically commences at 75-150 IU FSH daily and is increased preferably by 37.5 or 75 IU at 7 or preferably 14-day intervals if necessary. Maximum daily dose is usually not higher than 225 IU FSH. *Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other assisted reproductive technologies* – A commonly used regimen for superovulation involves the administration of 150-225 IU of Bemfola daily, commencing on day 2 or 3 of the cycle. Maximum daily dose is usually not higher than 450 IU daily. *Women with anovulation resulting from severe LH and FSH deficiency* – Bemfola should be given as a course of daily injections simultaneously with lutropin alfa. Treatment can start at any time and may commence at 75 IU of lutropin alfa daily with 75-150 IU FSH. If appropriate, the FSH dose should be adapted after 7-14 day intervals by 37.5 IU-75 IU increments for up to 5 weeks. *Men with hypogonadotropic hypogonadism* – 150 IU Bemfola should be given three times a week, concomitantly with hCG, for a minimum of 4 months.

Contraindications: Hypersensitivity to any of the active substance or to any of the excipients; tumours of the hypothalamus or pituitary gland; ovarian enlargement or ovarian cyst not due to PCOS; gynaecological haemorrhages of unknown aetiology; ovarian, uterine or mammary carcinoma. Bemfola must not be used when an effective response cannot be obtained e.g. primary ovarian failure, malformations of sexual organs incompatible with pregnancy, fibroid tumours of the uterus incompatible with pregnancy, primary testicular insufficiency.

Warnings: Treatment in women: Ovarian hyperstimulation should be avoided by ultrasonic control of follicular development and regular assessment of serum oestradiol levels. In case of threatening unwanted hyperstimulation, the dose of Bemfola should be reduced, or in case of an excessive response, administration must be stopped and hCG withheld. Symptoms of mild and moderate hyperstimulation syndrome are abdominal pain, nausea, diarrhoea, and moderate enlargement of ovaries and ovarian cysts. Symptoms of severe hyperstimulation syndrome are large ovarian cysts, abdominal distension, dyspnoea, weight gain and in rare cases arteriothromboembolic processes.

Interactions: Concomitant use of Bemfola with other medicinal products used to stimulate ovulation (e.g. hCG, clomiphene citrate) may potentiate the follicular response, whereas concurrent use of GnRH agonist or antagonist may need an increased dose of Bemfola.

Undesirable effects: In women: headache, ovarian cysts, injection site reactions, ovarian hyperstimulation syndrome (OHSS), hypersensitivity reactions; in men: injection site reactions, acne, gynecomastia, varicocele, weight gain.

Please read all of this leaflet before using!

Marketing Authorisation Holder: Gedeon Richter Plc, Gyömrői út 19-21, 1103 Budapest, Hungary. Phone number and email address for adverse events: +36 1 505 7032; drugsafety@richter.hu. Marketing Authorisation Number: EU/1/13/909/001-15.

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GEDEON RICHTER