European Journal of Obstetrics & Gynecology and Reproductive Biology 232 (2019) 101–105

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Comparison of the follicular output rate after controlled ovarian stimulation with daily recombinant follicle-stimulating hormone versus corifollitropin alfa

Georg Griesinger[a], Valerie Teal[b], Christine McCrary Sisk[c], Jane Ruman[d,*]

[a] Department of Gynecological Endocrinology and Reproductive Medicine, University Hospital of Schleswig-Holstein, Luebeck, Germany
[b] Department of Late Development Statistics, Merck & Co., Inc., Kenilworth, NJ, USA
[c] Department of Global Scientific and Medical Publications, Merck & Co., Inc., Kenilworth, NJ, USA
[d] Department of Clinical Development, Merck & Co., Inc., Kenilworth, NJ, USA

ARTICLE INFO

Article history:
Received 6 July 2018
Received in revised form 2 November 2018
Accepted 3 November 2018

Keywords:
Ovarian stimulation
Recombinant follicle-stimulating hormone
Corifollitropin alfa
Gonadotropin-releasing hormone antagonist
Follicular output rate

ABSTRACT

Objective: To compare the Follicular Output Rate (FORT) between corifollitropin alfa (CFA) and recombinant follicle-stimulating hormone (rFSH) during controlled ovarian stimulation (COS).
Study design: This retrospective analysis compared FORT between women treated with CFA or rFSH from three clinical trials: ENGAGE (N = 1476; ages 18–36, >60 kg), ENSURE (N = 395; ages 18–36, ≤60 kg), and PURSUE (N = 1388; ages 35–42, ≥50 kg). Women underwent COS in a GnRH antagonist protocol followed by hCG trigger prior to IVF. Antral follicle count (AFC; <11 mm) and pre-ovulatory follicle count (>15 mm) were used for FORT, defined as [pre-ovulatory follicles/AFCx100].
Results: For CFA and rFSH, respectively, mean FORT (adjusted for trial and age) was 85.0 versus 76.8 ($p < 0.001$) in the combined cohort, 86.0 versus 75.0 in ENGAGE ($p < 0.001$), 96.2 versus 79.2 in ENSURE ($p = 0.070$), and 74.1 versus 71.2 in PURSUE ($p = 0.180$); mean oocyte output (oocytes retrieved/AFCx100, adjusted for age) was 121.9 versus 107.3 in ENGAGE ($p = 0.001$), 133.5 versus 102.3 in ENSURE ($p < 0.001$), and 100.6 versus 98.1 in PURSUE ($p = 0.463$). FORT and oocyte output were consistent with the number of metaphase II oocytes retrieved for CFA and rFSH: 10.4 versus 8.8 in ENGAGE ($p < 0.001$), 10.3 versus 7.6 in ENSURE ($p < 0.001$), and 7.5 versus 7.2 in PURSUE ($p = 0.37$). No differences in pregnancy rates based on FORT were observed.
Conclusions: FORT was significantly higher in CFA-stimulated cycles and accurately predicted oocyte output. No association of FORT with pregnancy likelihood was found.

Introduction

The Follicular Output Rate (FORT) is defined as the number of pre-ovulatory follicles in response to follicle-stimulating hormone (FSH) administration, divided by the pre-existing antral follicle count (AFC) [1]. The responsiveness of antral follicles to FSH may predict their reproductive competence, such that patients with a larger proportion of FSH-responsive antral follicles may be more likely to become pregnant after assisted reproductive technologies (ART) [2]. Furthermore, FORT may be a more accurate and immediate measure of the efficacy of ovarian stimulation than oocyte number retrieved [1,2].

Corifollitropin alfa (registered and marketed as Elonva®) is a recombinant protein composed of the carboxy terminal peptide of the human chorionic gonadotropin (hCG) β-subunit fused to the β chain of human FSH [3]. Similar to recombinant FSH (rFSH), corifollitropin alfa interacts only with the FSH receptor and lacks luteinizing hormone (LH) activity but has a ~2-fold longer elimination half-life ($t_{1/2}$) and a ~4-fold longer time interval (t_{max}) to peak serum levels (C_{max}) [4]. Due to its unique pharmacokinetic profile, corifollitropin alfa can function as a sustained follicle stimulant with a similar pharmacodynamic profile as rFSH, but with the ability to initiate and sustain multi-follicular growth during the first 7 days of ovarian stimulation [5]. Consequently, a single dose of corifollitropin alfa can replace the first seven injections of any daily FSH preparation in an ovarian stimulation treatment cycle prior to in vitro fertilization (IVF) [5].

The objective of this analysis was to evaluate whether FORT differs between daily rFSH versus single-dose corifollitropin alfa

* Corresponding author at: Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA.
E-mail address: jruman6129@hotmail.com (J. Ruman).

https://doi.org/10.1016/j.ejogrb.2018.11.002
0301-2115/

during controlled ovarian stimulation in a gonadotropin-releasing hormone (GnRH) antagonist IVF protocol.

Materials and methods

Participants

This was a retrospective analysis of data from women from the three seminal, randomized controlled trials of corifollitropin alfa (Table 1): ENGAGE (NCT00696800) [6], ENSURE (NCT00702845) [7] and PURSUE (NCT01144416) [8]. Complete details of the treatment regimens for each trial have been published elsewhere [6–8]. In ENGAGE, women aged 18–36 years with a body weight >60 kg were randomized to 150 μg corifollitropin alfa (n = 756) or 200 IU rFSH (n = 750) [6]. In ENSURE, women aged 18–36 years with lower body weight (≤60 kg) were randomized to 100 μg corifollitropin alfa (n = 268) or 150 IU rFSH (n = 128) [7]. In PURSUE, older women (aged 35–42 years) with a body weight ≥50 kg were randomized to 150 μg corifollitropin alfa (n = 694) or 300 IU rFSH (n = 696) [8]. All women underwent controlled ovarian stimulation in a GnRH antagonist protocol followed by hCG trigger prior to IVF/intracytoplasmic sperm injection (ICSI) [6–8]. A single subcutaneous injection of corifollitropin alfa or matching placebo was administered on menstrual day 2 or 3. To conceal treatment allocation, daily subcutaneous injections of rFSH or matching placebo began on the same day and continued through the first 7 days of stimulation. From stimulation day 8 onwards, treatment continued in both groups with a daily subcutaneous dose of rFSH up to and including the day of hCG administration. Ganirelix (0.25 mg) was administered subcutaneously once daily starting on stimulation day 5 up to and including the day of hCG administration. Luteal phase support with progesterone (at least 600 mg/day vaginally or at least 50 mg/day intramuscularly) was started on the day of oocyte retrieval and continued for at least 6 weeks or up to menses.

Before the start of ovarian stimulation, ultrasound assessments were performed to measure and count visible follicles. Patients returned to the clinic for ultrasound assessments (days 5 and 8 in ENGAGE; days 1, 3, 5 and 8 in ENSURE; and day 5 in PURSUE), and then daily up to and including the day of hCG administration. Embryo quality was evaluated for all available embryos on day 3 of culture by the local embryologist using a protocol-defined guideline based on the following parameters: number of blastomeres, degree of fragmentation, blastomere size uniformity and presence or absence of multinucleation. Embryos graded as grade 1 (6–10 cells, no fragmentation and equal blastomere size) or grade 2 (allowing up to 20% fragmentation) were qualified as good quality embryos. The quality of embryos continued in culture after day 3 was reassessed on the day of transfer or freezing using grading criteria appropriate for the stage of embryo culture. At embryo transfer, 3 or 5 days after oocyte retrieval, one or two embryos were to be transferred.

All three trials were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate institutional review boards. All procedures performed in human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was provided by all participants before any study procedures were performed.

FORT analysis

The FORT was defined as the number of pre-ovulatory follicles (≥15 mm) in response to ovarian stimulation divided by the pre-treatment AFC (number follicles <11 mm) multiplied by 100. FORT was calculated for each treatment group (corifollitropin alfa and rFSH) by study (Fig. 1). Women were stratified into low (<30%), middle (30%–70%), and high (>70%) FORT groups, and demographic parameters as well as clinical outcome parameters were compared between FORT groups. Next, the mean FORT was compared between treatments (rFSH versus corifollitropin alfa).

Statistical analysis

Subject characteristics were summarized by FORT groups as means and standard deviations, with the p-value for the difference between groups obtained from analysis of variance (ANOVA). For continuous variables, the estimated difference between the two treatment groups and associated p-value were calculated using ANOVA, adjusted for age and center. For the binary outcome of ongoing pregnancy, the treatment groups were compared with a generalized linear model adjusted for age and center. Models were run separately by study and FORT group (low, middle, high).

Results

Baseline demographic characteristics and stimulation data for the patient population in the low, middle, and high FORT groups are shown in Table 2.

FORT was higher with corifollitropin alfa compared with rFSH (Table 3). Increases in FORT and oocyte output with corifollitropin alfa compared with rFSH were observed in the younger cohorts of women from ENGAGE and ENSURE, but not in the older cohort of women from PURSUE (Table 3). FORT and oocyte output were consistent with the number of metaphase II oocytes retrieved in both treatment groups (Table 3).

No significant between-treatment group differences in ongoing pregnancy rates based on FORT were observed in the overall population or within each study. In the total population, the ongoing pregnancy rates were 31.1% in the low FORT group, 31.6% in the middle FORT group, and 31.1% in the high FORT group. The ongoing pregnancy rates (from only fresh embryo transfers) based on FORT group for corifollitropin alfa compared to rFSH for each study are shown in Table 4.

Comment

The ENGAGE, ENSURE and PURSUE randomized, controlled clinical trials conducted in women undergoing controlled ovarian stimulation using a GnRH antagonist protocol demonstrated that a single injection of corifollitropin alfa for the first 7 days of ovarian stimulation was equivalent or non-inferior to daily

Table 1
Randomized controlled trials included in the analysis.

Study	N	Population	CFA single dose (n)	rFSH daily dose (n)
ENGAGE [6]	1476	age 18-36; weight >60 kg	150 μg CFA (n = 741)	200 IU rFSH (n = 735)
ENSURE [7]	395	age 18-36; weight ≤60 kg	100 μg CFA (n = 268)	150 IU rFSH (n = 127)
PURSUE [8]	1388	age 35-42; weight ≥50 kg	150 μg CFA (n = 692)	300 IU rFSH (n = 696)

CFA, corifollitropin alfa; rFSH, recombinant follicle-stimulation hormone.

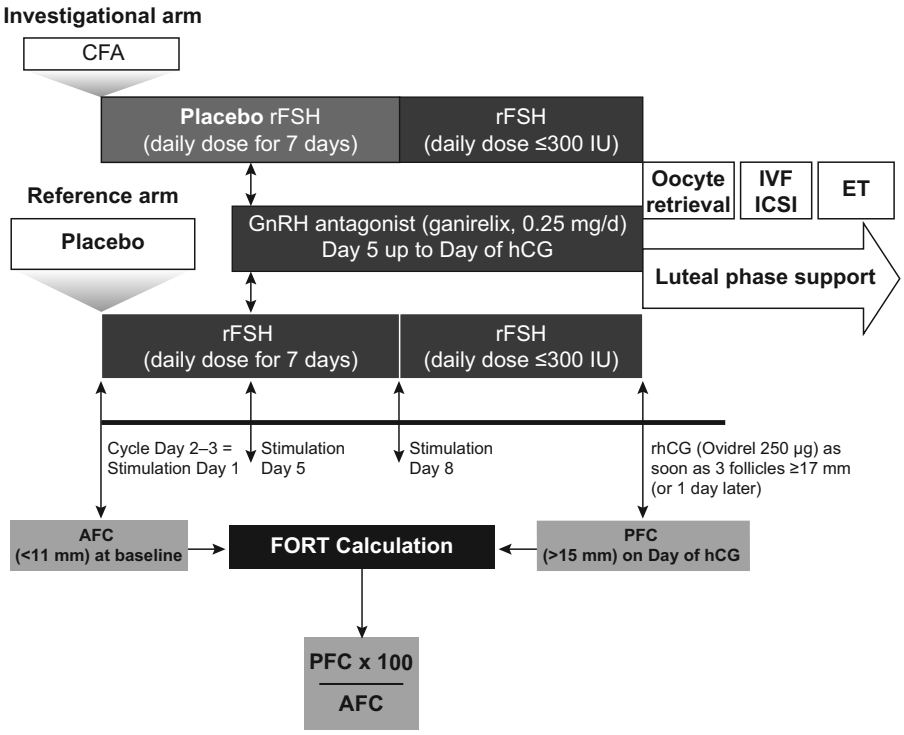

Fig. 1. Study design.
CFA, corifollitropin alfa; rFSH, recombinant follicle-stimulation hormone; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; rhCG, recombinant hCG; AFC, antral follicle count; PFC, pre-ovulatory follicle count.

Table 2
Patient characteristics and controlled ovarian stimulation data in the low, middle and high FORT groups in all treatment groups combined.

	Low FORT (<30%) (n = 899)	Middle FORT (30–70%) (n = 1273)	High FORT (>70%) (n = 976)	p-value
Age, years	34.4 (4.1)	34.3 (4.4)	34.0 (4.4)	0.090
Body mass index at screening	24.3 (3.3)	24.4 (3.4)	24.3 (3.3)	0.646
FSH on Stimulation Day 1, mIU/mL	7.4 (2.4)	6.9 (2.1)	6.6 (1.8)	<.001
Estradiol on Stimulation Day 1, pmol/L	142.4 (56.0)	136.0 (44.0)	133.5 (43.1)	<.001
Estradiol on Day 5, pmol/L	1426.4 (960.5)	1724.2 (1149.0)	1862.6 (1165.4)	<.001
Follicles <11 mm	13.0 (4.2)	12.1 (3.9)	9.8 (4.0)	<.001
Estradiol on Day of hCG, pmol/L	4198.9 (2640.8)	5679.7 (3283.3)	6466.7 (3605.6)	<.001
Progesterone on Day of hCG, nmol/L	3.1 (2.0)	3.4 (1.6)	4.1 (8.8)	<.001
Follicles ≥15 mm	5.2 (2.1)	8.2 (2.9)	11.5 (4.8)	<.001
FORT, n	39.8 (9.8)	68.2 (10.4)	127.2 (63.3)	<.001

FORT, Follicular Output Rate.
*Results for all values are displayed as mean value (± standard deviation [SD]).

injections of rFSH regarding the number of oocytes retrieved, embryo quality, vital pregnancy rates, ongoing pregnancy rates, and live-birth rates [4–6]. The present retrospective analysis used data from these three clinical trials to compare FORT values between corifollitropin alfa and rFSH stimulation and to test if FORT and pregnancy outcome are associated. The results demonstrate that FORT was significantly higher in corifollitropin alfa-stimulated cycles compared to rFSH-stimulated cycles. In addition, FORT accurately predicted oocyte output and the number of metaphase II oocytes. Corifollitropin alfa elicited the growth of more pre-ovulatory follicles from the existing AFC compared with rFSH.

The association between oocyte output and antral follicles that effectively respond to FSH suggests that FORT may be a qualitative indicator of differences in ovarian response and oocyte competence based on the type of gonadotropin used during controlled ovarian stimulation. However, no significant between-treatment group differences in ongoing pregnancy rates based on FORT were observed in any study, despite previously published data [2] that suggest an association between FORT and pregnancy likelihood. This finding may be associated with study design limitations, as only pregnancy outcomes from fresh embryo transfers were analyzed in this study. In addition to analyzing data based on cumulative pregnancy rates allowing for subsequent cycles with frozen embryos, a larger study sample may be necessary to discern clinically meaningful differences in pregnancy outcomes based on FORT. Additional limitations of the present analysis include its retrospective design, and that measurement of antral follicles by transvaginal ultrasound was not standardized across study centers or observers.

In conclusion, FORT was significantly higher in corifollitropin alfa-stimulated cycles compared to rFSH-stimulated cycles and accurately predicted oocyte output and metaphase II oocyte number; however, no association of FORT with pregnancy likelihood could be found. Additional research based on a larger study sample that includes cumulative pregnancy rates may be needed in order to discern clinically meaningful differences in pregnancy outcomes based on FORT.

Table 3
FORT and Oocyte Recovery by Trial and Treatment.

			Treatment Difference	
	CFA	rFSH	CFA-rFSH	Between-treatment p-value
FORT (%)				
Overall	83.8 (2.6)	75.8 (2.7)	8.02	<.0001
ENGAGE	86.5 (4.5)	75.6 (4.4)	10.91	<.0001
ENSURE	93.4 (8.9)	76.9 (11.2)	16.57	0.0033
PURSUE	74.6 (3.1)	71.7 (3.2)	2.98	0.1465
Oocyte Output				
No. of COC recovered/AFC				
Overall	117 (4.1)	105 (4.3)	11.5	<.0001
ENGAGE	123 (7.7)	106 (7.5)	17.52	<.0001
ENSURE	120 (12.8)	90.1 (16)	29.48	0.0003
PURSUE	106 (5)	104 (5)	1.49	0.6467
No. of metaphase I oocytes				
Overall	1 (0.1)	0.87 (0.1)	0.18	0.0045
ENGAGE	1 (0.2)	0.77 (0.2)	0.26	0.0023
ENSURE	0.72 (0.3)	0.64 (0.3)	0.08	0.5888
PURSUE	1.2 (0.2)	1.1 (0.2)	0.14	0.1976
No. of metaphase II oocytes				
Overall	9.1 (0.4)	8 (0.4)	1.07	<.0001
ENGAGE	10.3 (0.6)	8.8 (0.6)	1.56	<.0001
ENSURE	10.3 (1.1)	7.6 (1.3)	2.7	<.0001
PURSUE	7.5 (0.5)	7.2 (0.5)	0.27	0.3846
No. of germinal vesicles stage oocytes				
Overall	1.2 (0.2)	1.4 (0.2)	−0.18	0.0349
ENGAGE	1.3 (0.2)	1.5 (0.2)	−0.18	0.1708
ENSURE	0.83 (0.3)	1.1 (0.4)	−0.26	0.2037
PURSUE	1.3 (0.2)	1.4 (0.2)	−0.16	0.2306

CFA, corifollitropin alfa; rFSH, recombinant follicle-stimulation hormone: FORT, Follicular Output Rate.
No., number; COC, cumulus-oocyte complexes.
Mean (+ 1.96 standard error) adjusted for age for overall, trial-specific planned-age stratum.

Table 4
Ongoing pregnancy rates by trial and FORT group.

						Treatment difference	
Study	**FORT group**[a]	**CFA dose (n)**	**Ongoing pregnancy**	**rFSH dose (n)**	**Ongoing pregnancy**	**CFA - rFSH**	**Between- treatment p-value**
ENGAGE	Low	150 μg (205)	90 (43.9%)	200 IU (213)	74 (34.7%)	9.2	0.055
	Middle	150 μg (281)	107 (38.1%)	200 IU (285)	121 (42.5%)	−4.4	0.288
	High	150 μg (217)	83 (38.2%)	200 IU (214)	80 (37.4%)	0.9	0.853
ENSURE	Low	100 μg (79)	20 (25.3%)	150 IU (36)	13 (36.1%)	−10.8	0.235
	Middle	100 μg (89)	18 (20.2%)	150 IU (50)	17 (34.0%)	−13.8	0.073
	High	100 μg (96)	30 (31.3%)	150 IU (39)	13 (33.3%)	−2.1	0.814
PURSUE	Low	150 μg (165)	38 (23.0%)	300 IU (201)	45 (22.4%)	0.6	0.884
	Middle	150 μg (306)	68 (22.2%)	300 IU (262)	71 (27.1%)	−4.9	0.178
	High	150 μg (202)	47 (23.3%)	300 IU (208)	51 (24.5%)	−1.2	0.766

CFA, corifollitropin alfa; rFSH, recombinant follicle-stimulation hormone.
[a] FORT groups are defined as low <30%, middle 30 to ≤70%, and high >70%.

Conflicts of interest

GG reports paid consultancies for MSD, Merck Serono, Glycotope, Ferring, IBSA, VitroLife, Finox, ReprodWissen GmbH, TEVA, ZIVA, Biosilu, Abbott, NMC Healthcare; and lecture fees from MSD, Merck Serono, IBSA, VitroLife, ReprodWissen GmbH, Abbott, Ferring, and Vitro Life. VT, CMS, and JR are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who may own stock and/or hold stock options in the Company.

Authors' contributions

All authors are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, and interpretation of data in addition to drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data statement

Merck & Co., Inc.'s data sharing policy, including restrictions, is available at http://engagezone.merck.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Funding

Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Acknowledgements

Jennifer Rotonda PhD and Michele McColgan BA, of Merck & Co., Inc., Kenilworth, NJ, provided editorial support.

References

[1] Genro VK, Grynberg M, Scheffer JB, Roux I, Frydman R, Fanchin R. Serum anti-Müllerian hormone levels are negatively related to Follicular Output RaTe (FORT) in normo-cycling women undergoing controlled ovarian hyperstimulation. Hum Reprod 2011;26:671–7.

[2] Gallot V, Berwanger da Silva AL, Genro V, Grynberg M, Frydman N, Fanchin R. Antral follicle responsiveness to follicle-stimulating hormone administration assessed by the Follicular Output RaTe (FORT) may predict in vitro fertilization–embryo transfer outcome. Hum Reprod 2012;27:1066–72.

[3] Fares FA, Suganuma N, Nishimori K, LaPolt PS, Hsueh AJ, Boime I. Design of a long-acting follitropin agonist by fusing the C-terminal sequence of the chorionic gonadotropin beta subunit to the follitropin beta subunit. Proc Natl Acad Sci U S A 1992;89:4304–8.

[4] Fauser BC, Mannaerts BM, Devroey P, Leader A, Boime I, Baird DT. Advances in recombinant DNA technology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. Hum Reprod Update 2009;15:309–21.

[5] de Greef R, Zandvliet AS, de Haan AF, Ijzerman-Boon PC, Marintcheva-Petrova M, Mannaerts BM. Dose selection of corifollitropin alfa by modeling and simulation in controlled ovarian stimulation. Clin Pharmacol Ther 2010;88:79–87.

[6] Devroey P, Boostanfar R, Koper NP, Mannaerts BM, Ijzerman-Boon PC, Fauser BC. A double-blind, non-inferiority RCT comparing corifollitropin alfa and recombinant FSH during the first seven days of ovarian stimulation using a GnRH antagonist protocol. Hum Reprod 2009;24:3063–72 Corrigendum: Hum Reprod 2014;29:1116–1120.

[7] Corifollitropin alfa Ensure Study Group. Corifollitropin alfa for ovarian stimulation in IVF: a randomized trial in lower-body-weight women. Reprod Biomed Online 2010;21:66–76.

[8] Boostanfar R, Shapiro B, Levy M, Rosenwaks Z, Witjes H, Stegmann BJ, et al. A large, comparative, randomized double-blind trial confirming noninferiority of pregnancy rates for corifollitropin alfa compared to rFSH in a GnRH antagonist controlled ovarian stimulation protocol in older IVF patients. Fertil Steril 2015;104:235–40.