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## ARTICLE

# Pharmacokinetics and follicular dynamics of corifollitropin alfa versus recombinant FSH during ovarian stimulation for IVF

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**Abstract** A single injection of corifollitropin alfa can replace seven daily injections of recombinant FSH (rFSH) using a gonadotrophin-releasing hormone antagonist protocol in ovarian stimulation prior to IVF or intracytoplasmic sperm injection. This double-blind randomized controlled trial assessed the pharmacokinetics and pharmacodynamics of 150 µg corifollitropin alfa versus daily 200 IU rFSH in 1509 patients. Comparative analyses were performed on serum concentrations of FSH immunoreactivity (pharmacokinetics), and the number and size of growing follicles, and inhibin B and oestradiol concentrations as biomarkers of ovarian response (pharmacodynamics). The rate of follicular development was similar in both treatment groups. By stimulation day 8, 33% of patients treated with corifollitropin alfa reached the criterion for human chorionic gonadotrophin (HCG) injection. The number of follicles  $\geq 11$  mm was slightly higher after corifollitropin alfa compared with daily rFSH at stimulation day 8 (difference, 1.2; 95% confidence interval (CI) 0.5–1.8;  $P < 0.01$ ) and on the day of HCG injection (difference, 2.1; 95% CI 1.4–2.8;  $P < 0.01$ ). The rise of inhibin B and oestradiol concentrations was similar in both treatment groups. Although the pharmacokinetics of corifollitropin alfa and rFSH are quite different their pharmacodynamic profiles at the dosages used are similar. [RBM Online](#)

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**KEYWORDS:** corifollitropin alfa, follicular development, inhibin B, oestradiol, sustained follicle stimulant

## Introduction

Corifollitropin alfa is a new recombinant glycoprotein that belongs to the gonadotrophin pharmaceutical class. The compound is designed as a sustained follicle stimulant with the same pharmacodynamic effect as recombinant FSH (rFSH), but with the ability to initiate and sustain multiple follicular growth for an entire week (De Greef et al., 2010; Devroey et al., 2004; Fauser et al., 2009; LaPolt et al., 1992; Loutradis et al., 2009). The  $\alpha$ -subunit of corifollitropin alfa is identical to the common glycoprotein  $\alpha$ -subunit and the FSH  $\beta$ -subunit is extended by a carboxy-terminal peptide (Fares et al., 1992), which, in comparison to rFSH, results in a slower absorption and a longer elimination half-life which are mainly responsible for its sustained activity.

A single subcutaneous (s.c.) injection of the recommended dose of corifollitropin alfa may offer the advantage of replacing the first seven injections of any daily FSH preparation in an ovarian stimulation treatment cycle. Corifollitropin alfa has been studied in the context of gonadotrophin-releasing hormone (GnRH) antagonist co-treatment, a protocol that is simpler and more convenient for patients than conventional long GnRH agonist protocols (Devroey et al., 2009a; Heijnen et al., 2007; Tarlatzis et al., 2006).

The single-dose pharmacokinetic profile of corifollitropin alfa is characterized by a slow absorption resulting in peak concentrations 2 days after injection. Thereafter, serum corifollitropin alfa concentrations decrease steadily, although the FSH activity may be retained above the FSH threshold for 1 week if the administered dose of corifollitropin alfa is sufficiently high (Duijkers et al., 2002). The mean half-life of corifollitropin alfa is approximately 65 h, which is about two-fold higher than rFSH (Balen et al., 2004; Corifollitropin Alfa Dose-Finding Study Group, 2008; Devroey et al., 2004; Duijkers et al., 2002). The dose-normalized

area under the curve (AUC) and dose-normalized maximal concentration ( $C_{max}$ ) are similar across all doses, indicating that the pharmacokinetic parameters of corifollitropin alfa are dose-proportional for doses ranging from 7.5 to 240 µg (Corifollitropin Alfa Dose-Finding Study Group, 2008).

Corifollitropin alfa has the same pharmacodynamic effect as purified FSH preparations because it interacts only with the FSH-receptor and lacks LH activity (LaPolt et al., 1992). In female volunteers with pituitary-suppression of FSH/LH induced by oral contraceptives before treatment, a single injection of 120 µg corifollitropin alfa initiated and sustained multifollicular growth for 7 days (Duijkers et al., 2002). Corifollitropin alfa has been tested in patients undergoing ovarian stimulation for IVF or intracytoplasmic sperm injection (ICSI) using single doses of 60–240 µg (Corifollitropin Alfa Dose-Finding Study Group, 2008; Devroey et al., 2004). Following the dose-finding trial and subsequent pharmacokinetic/pharmacodynamic modelling (De Greef et al., 2010), it was concluded that the recommended dose of corifollitropin alfa was 150 µg for patients with a bodyweight  $>60$  kg and 100 µg for patients with a bodyweight  $\leq 60$  kg.

The aim of the current Engage trial was to establish efficacy and safety of a single injection of 150 µg corifollitropin alfa compared with daily injections of 200 IU rFSH in a GnRH antagonist protocol for ovarian stimulation. The ongoing pregnancy rate in 1509 randomized patients aged 18–36 years and weighing  $>60$  kg was similar in both groups, whereas significantly more oocytes were retrieved with corifollitropin alfa compared with rFSH (Devroey et al., 2009b).

This article discusses the outcome of the Engage trial in terms of the ovarian response by evaluating the number and size of growing follicles as well as serum oestradiol, inhibin B, LH and progesterone after treatment with 150 µg corifollitropin alfa compared with the reference group treated with daily 200 IU rFSH.

## Materials and methods

The design of this trial has been described in detail recently (Devroey et al., 2009b). The study involved 34 centres in North America and Europe and was conducted between June 2006 and January 2008. The study was approved by the independent medical ethics committee or institutional review board for each centre as well as by the responsible health authority and was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines for Good Clinical Practice and local regulatory requirements. Written informed consent was obtained from all participants. An independent data safety monitoring board was appointed to monitor the safety of subjects participating in the trial and written informed consent was provided by all patients. The trial was registered under ClinicalTrials.gov identifier NCT00696800.

### Study population

Women aged 18–36 years with a bodyweight >60 kg, up to and including 90 kg, a body mass index of 18–32 kg/m<sup>2</sup>, a menstrual cycle length of 24–35 days, access to ejaculatory spermatozoa and an indication for ovarian stimulation before IVF or ICSI were eligible to enrol in the study unless they had a history of an endocrine abnormality, clinically relevant abnormal laboratory values or chronic disease or relevant pelvic pathology that could interfere with the ovarian stimulation treatment, embryo implantation or pregnancy. In total 1509 patients were randomized to one of the two treatment groups and 1506 patients started stimulation in either treatment group.

### Study design

The trial was designed as a randomized, double-blind, double-dummy, active-controlled, non-inferiority trial to compare the efficacy of a single injection of corifollitropin alfa with daily injections of rFSH for inducing and sustaining multifollicular growth in an ovarian stimulation regimen for IVF or ICSI.

The primary end-point for this trial on which the sample size calculation was based, was the ongoing pregnancy rate. The predefined non-inferiority margin was –8%, implying that the lower limit of the two-sided 95% confidence interval of the estimated difference in pregnancy rates between the corifollitropin alfa and rFSH group should lie above –8% to claim non-inferiority. Assuming ongoing pregnancy rates of 30% in both treatment groups, at least 1400 subjects (700 per group) were to be included to achieve a power of more than 90% to claim non-inferiority of corifollitropin alfa compared with rFSH.

### Stimulation regimen and assisted reproduction treatments

All patients started treatment after a spontaneous cycle on menstrual day 2 or 3 (Devroey et al., 2009b) with a single s.c. injection of 150 µg (0.5 ml) corifollitropin alfa (Organon, The Netherlands) or matching placebo. To conceal treatment allocation, all patients also started daily s.c. injection of 200 IU rFSH (follitropin beta, Puregon/Follistim AQ Cartridge;

Organon) or matching placebo on the same day (stimulation day 1) using the Puregon/Follistim pen. Daily active or placebo ('dummy') rFSH injections were continued through the first 7 days of stimulation. From stimulation day 8 onward, if needed, treatment in both groups was continued with a daily s.c. dose of (active) rFSH up to and including the day of human chorionic gonadotrophin (HCG) administration. A starting dose of 200 IU recFSH in the reference arm of this trial was selected to meet clinical practice of both European and US sites. The daily dose of 200 IU rFSH could be stepped down from day 6 onwards, but in 82% of the patients treated in the reference group the criteria for HCG were reached without any dose adjustment, indicating the suitability of the selected starting dose for this study population.

To prevent a premature LH surge, the GnRH antagonist ganirelix (0.25 mg, Orgalutran/ganirelix acetate injection; Organon) was administered once daily s.c. starting on stimulation day 5 up to and including the day of HCG injection. Urinary HCG 10,000 IU i.m. was administered to induce final oocyte maturation as soon as at least three follicles ≥17 mm were observed by ultrasound scan. Approximately 34–36 h following HCG administration, a transvaginal ultrasound-guided oocyte retrieval was performed followed by standard IVF or ICSI.

### Assessments

Before the start of ovarian stimulation, baseline testing included an HCG blood test, blood hormone assessments and an ultrasound scan to assess ovarian volume and the number of antral follicles. Patients returned to the clinic to assess the size and number of follicles and hormone concentrations on stimulation days 5 and 8, and then daily up to and including the day of HCG administration. Serum hormones were also collected on the day of embryo transfer and 2 weeks after embryo transfer.

### Pharmacokinetic analysis

Total FSH immunoreactivity concentrations were analysed using a population pharmacokinetic approach. The combined pharmacokinetic data from this trial and two additional phase-2 and phase-3 clinical trials were used to describe the pharmacokinetics of corifollitropin alfa in patients (Corifollitropin Alfa Dose-Finding Study Group, 2008; Corifollitropin Alfa Ensure Study Group, 2010). In this pooled population pharmacokinetic analysis, serum concentrations of corifollitropin alfa and total FSH immunoreactivity were used as measures of drug exposure. Serum corifollitropin alfa concentrations were measured by a solid-phase enzyme-immunoassay, which is specific to corifollitropin alfa and does not crossreact with rFSH or endogenous FSH. Serum FSH immunoreactivity was measured by a fluoroimmunoassay, which is not specific to corifollitropin alfa. The total FSH immunoreactivity of corifollitropin alfa, endogenous FSH and rFSH was determined by this assay. For subjects treated with corifollitropin alfa, prior to the start of treatment with daily rFSH from day 8 onward, total FSH immunoreactivity encompassed exposure to endogenous FSH and to corifollitropin alfa. At baseline, total FSH immunoreactivity was determined only by serum concentrations of endogenous FSH. After injection of corifollitropin alfa,

endogenous FSH was suppressed and FSH immunoreactivity was dominated by exposure to corifollitropin alfa. A pharmacokinetic model was developed to estimate the time profiles of serum concentrations of both endogenous FSH and corifollitropin alfa. This approach allowed description of the time profiles of corifollitropin alfa concentrations (across the entire time range of ovarian stimulation treatment) and total FSH immunoreactivity concentrations (up to the start of rFSH treatment).

### Hormone concentrations

Time profiles of serum concentrations of inhibin B and oestradiol, and follicular development in terms of the number and sizes of follicles were assessed to evaluate the pharmacodynamics of corifollitropin alfa compared with rFSH. The total number of days required to reach the criteria for HCG administration (three follicles  $\geq 17$  mm), as well as the actual duration of stimulation, are indicative of the ovarian response and were therefore also considered as measures of pharmacodynamic response. Pharmacokinetic parameters were derived from a pooled population pharmacokinetic analysis of phase-2 and phase-3 trials, using serum concentrations of total FSH immunoreactivity from this trial.

Validated immunoassays were performed at a central laboratory (Essex Pharma Development, Germany) to measure serum hormone concentrations of FSH, LH, inhibin B, oestradiol and progesterone. Concentrations of FSH, LH, oestradiol and progesterone were determined by time-resolved fluoroimmunoassay (AutoDelfia immunofluorometric assay; PerkinElmer Life and Analytical Sciences, Brussels, Belgium) with a coefficient of variation of  $<10\%$ . Detection limits were 0.25 IU/L, 0.6 IU/L, 49.9 pmol/l and 0.38 ng/ml for FSH, LH, oestradiol and progesterone, respectively. Serum inhibin B concentrations were determined by using a validated

immunoassay (Diagnostic Systems Laboratories, Webster, TX, USA) with a coefficient of variation of  $<10\%$  and a detection limit of 10.0 pg/ml.

Efficacy analyses of all pharmacodynamic parameters were calculated for the all-subjects-treated population (pharmacokinetics and hormonal profiles restricted to subjects with HCG). Thus, patients were grouped according to the treatment they actually received, which resulted in unbiased estimates of the pharmacodynamic effects of corifollitropin alfa versus rFSH.

Descriptive statistics included mean, standard deviation, median, minimum and maximum for continuous variables and frequencies and percentages for counts. Exploratory *P*-values were based on a *t*-test and on a Fisher exact test, respectively.

## Results

### Baseline hormones and ovarian reserve

Both treatment groups were of similar age (mean 31.5 years; range 19–37 years) and bodyweight (68–69 kg). For the majority of patients, this was their first IVF cycle (75% and 74% in the corifollitropin alfa and rFSH groups, respectively). On stimulation day 1, no differences were observed between the treatment groups with regard to antral follicle count, ovarian volume or baseline serum hormone concentrations. Serum FSH concentrations were 6.4 IU/l in each group (Table 1).

### Pharmacokinetics

The calculated pharmacokinetic parameters after corifollitropin alfa treatment are summarized in Table 2. The pharmacokinetic profile of corifollitropin alfa was characterized by

**Table 1** Screening characteristics and baseline characteristics at stimulation day 1 (pre-dose).

	150 $\mu$ g corifollitropin alfa	200 IU recombinant FSH
Characteristic	<i>n</i> = 755 <sup>a</sup>	<i>n</i> = 751 <sup>a</sup>
Age (years)	31.5 $\pm$ 3.3	31.5 $\pm$ 3.2
Weight (kg)	68.8 $\pm$ 7.6	68.4 $\pm$ 7.3
Body mass index (kg/m <sup>2</sup> )	24.8 $\pm$ 2.8	24.8 $\pm$ 2.7
First IVF cycle (%)	75.2	73.6
Duration of infertility (years)	3.3 $\pm$ 2.4	3.2 $\pm$ 2.2
Basal antral follicles ( <i>n</i> )	12.3 $\pm$ 4.6	12.4 $\pm$ 4.4
Total ovarian volume (ml)	13.2 $\pm$ 8.1	13.2 $\pm$ 7.1
Hormone concentrations <sup>b</sup>	<i>n</i> = 732 <sup>c</sup>	<i>n</i> = 742 <sup>c</sup>
Serum FSH (IU/l)	6.39 (1.8–17.7)	6.38 (0.1–15.6)
Serum LH (IU/l)	4.45 (0.9–21.5)	4.39 (1.3–12.2)
Serum oestradiol (pmol/l)	121.48 (25.0–323.0)	119.64 (25.0–347.5)
Serum inhibin B (pg/ml)	49.30 (5.0–188.0)	50.40 (5.0–172.0)
Serum progesterone (nmol/l)	1.70 (0.6–14.2)	1.72 (0.6–21.1)

Values are mean  $\pm$  SD or median (minimum–maximum) unless otherwise indicated.

<sup>a</sup>All-subjects-treated population.

<sup>b</sup>Day 2 or 3 of the menstrual cycle.

<sup>c</sup>All-subjects-treated population, restricted to patients with human chorionic gonadotrophin injection.

**Table 2** Summary of derived pharmacokinetic parameters of corifollitropin alfa ( $n = 731$ ).

Corifollitropin alfa dose	Statistic	$t_{max}$ (h)	$C_{max}$ (ng/ml)	$AUC_{0-\infty}$ (ng h/ml)	$t_{1/2}$ (h)	$k_a$ ( $h^{-1}$ )	$CL/f$ (l/h)	$V/f$ (l)
150 $\mu$ g	Geometric mean	43.8	4.35	668	68.2	0.0432	0.225	22.1
	Coefficient of variance (%)	4.4	24	25	4.4	4.8	25	25

Presented data are Bayesian empirical estimates of all subjects with pharmacokinetic data and were obtained in a population pharmacokinetic analysis. AUC = area under the serum corifollitropin alfa concentration curve;  $C_{max}$  = peak concentration;  $CL/f$  = clearance rate;  $k_a$  = absorption rate constant;  $t_{max}$  = time to peak concentration;  $t_{1/2}$  = half-life;  $V/f$  = volume of distribution.

slow absorption resulting in maximum serum concentrations 44 h after injection and a long elimination half-life of 68 h. Consequently, after administration of corifollitropin alfa, FSH immunoreactivity was maximal on stimulation day 3 (i.e. 2 days post-dose) and gradually declined from day 3 to day 8 of stimulation (**Figure 1A**). Serum FSH immunoreactivity concentrations were higher up to stimulation day 5 for the corifollitropin alfa regimen as compared with the daily rFSH regimen ( $P < 0.01$ ), but were similar from stimulation day 8 onward (**Figures 1A and 2**).

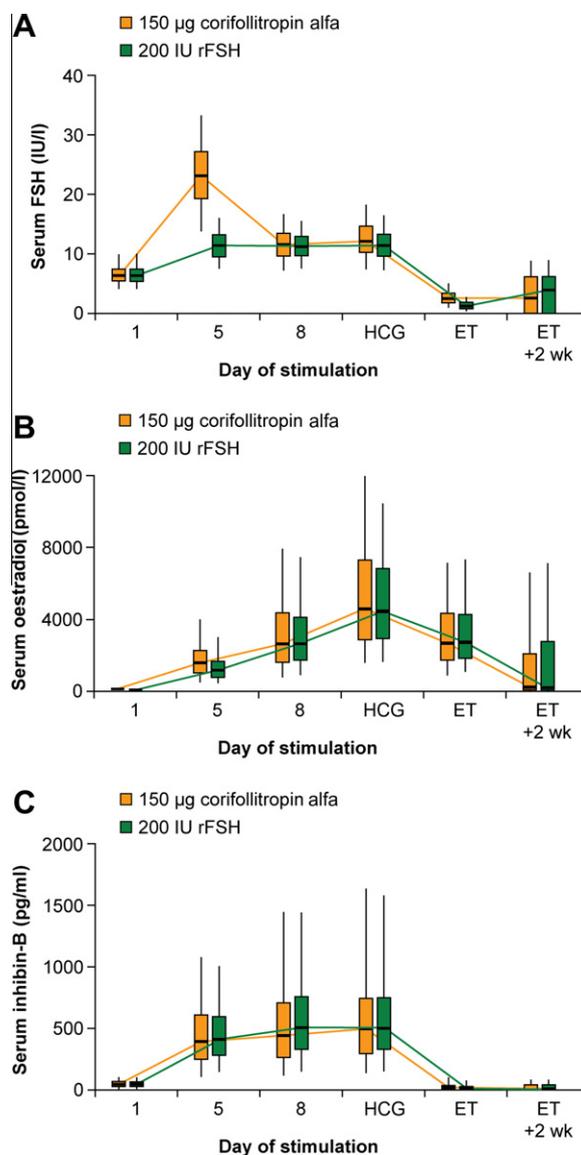
### Duration of stimulation

In total, 33% of the patients (249 of 755) treated with corifollitropin alfa met the criterion for HCG administration prior to or on day 8 of stimulation. The distribution of patients who met the HCG criterion at the different stimulation days was similar between the treatment groups (**Figure 3**). The median duration of stimulation was 9 days in each group and in both groups a median of 400 IU rFSH was administered from stimulation day 8 up to the day of HCG injection. From day 8 onwards, 27.7% in the corifollitropin alfa group and 18.6% in the rFSH group received one or more doses lower than 200 IU rFSH ( $P < 0.01$ ).

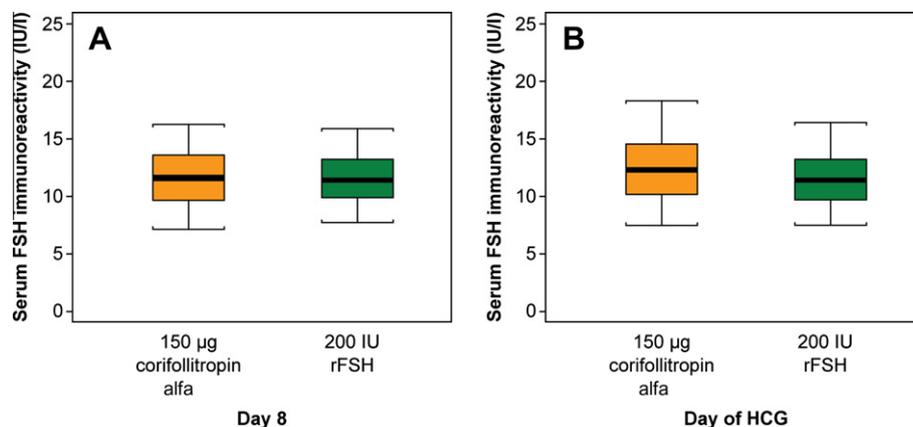
### Hormonal profiles

No differences were noted between the two treatment groups with respect to serum oestradiol and inhibin B concentrations either during stimulation or during the luteal phase (**Figure 1B and C**, respectively). On the day of HCG mean serum oestradiol concentrations were 5497 pmol/l and 5178 pmol/l in the corifollitropin alfa and rFSH group, respectively. Increases of serum inhibin B concentrations were most pronounced during the first 5 days of stimulation, whereas from day 5 to the day of HCG injection, inhibin B concentrations continued to rise, albeit slower, in both treatment groups. On the day of HCG, mean serum inhibin B concentrations were 610 pg/ml and 615 pg/ml in the corifollitropin alfa and rFSH group, respectively.

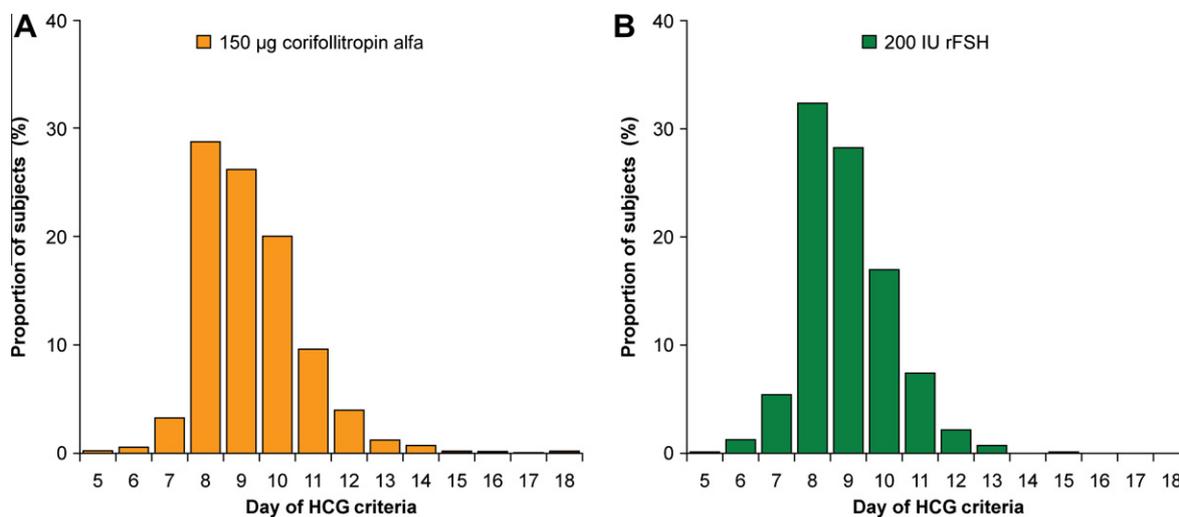
No differences were noted between the two treatment groups with respect to serum LH and progesterone concentrations during stimulation or during the luteal phase (**Figure 4A and B**). Patients treated with corifollitropin alfa showed a large variability in serum LH concentrations at stimulation day 5 just prior to the start of administration of the GnRH antagonist due to the occurrence of premature LH rises (LH value  $\geq 10$  IU/l). The incidence of an LH rise on



**Figure 1** Time profiles of (A) serum recombinant FSH (rFSH) immunoreactivity, (B) serum oestradiol and (C) inhibin B concentrations for the corifollitropin alfa regimen and the daily rFSH regimen. All-subjects-treated population, restricted to subjects with human chorionic gonadotrophin (HCG) injection, from day of stimulation to 2 weeks after embryo transfer (ET). Horizontal black marks represent median values, boxes represent interquartile ranges and whiskers represent 5–95% percentiles.



**Figure 2** Serum FSH immunoreactivity concentrations on (A) stimulation day 8 and (B) the day of human chorionic gonadotrophin (HCG) administration for the corifollitropin alfa regimen and the daily recombinant FSH (rFSH) regimen. Horizontal black marks represent median values, boxes represent interquartile ranges and whiskers represent 5–95% percentiles.



**Figure 3** Proportion of subjects with at least three follicles with a diameter of  $\geq 17$  mm by day the criterion for human chorionic gonadotrophin (HCG) administration was met, for (A) corifollitropin alfa regimen and (B) daily recombinant FSH (rFSH) regimen. All-subjects-treated population.

day 5 was higher in the corifollitropin alfa group than in the rFSH group (7.0% versus 2.1%,  $P < 0.01$ ). The ongoing pregnancy rate in subjects with an LH rise was similar in the two treatment arms (corifollitropin alfa 45.3% (24/53) versus rFSH 31.3% (5/16) per attempt). The percentage of subjects with a LH rise on stimulation day 8 or on the day of HCG was below 1% in each treatment group.

### Multifollicular development

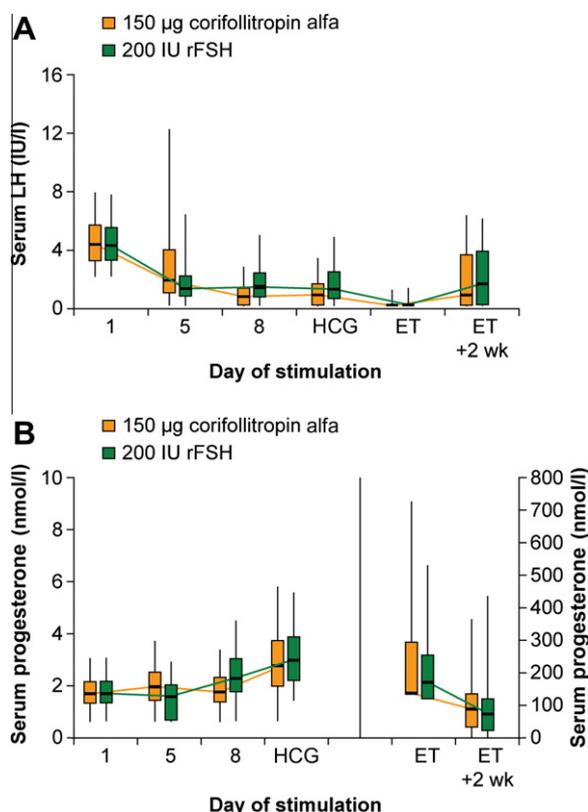
The growth rate and the number of recruited follicles  $\geq 11$  mm were similar in both treatment groups (Figure 5). The mean number of follicles  $\geq 11$  mm was also similar on stimulation day 5 in both treatment groups, whereas at stimulation day 8 and on the day of HCG injection, slightly more follicles between 11 mm and 16 mm were observed in the corifollitropin alfa group (Figure 6).

On stimulation day 8, the mean  $\pm$  SD number of follicles  $\geq 11$  mm was slightly higher after treatment with 150 µg corifollitropin alfa compared with daily 200 IU rFSH, i.e.

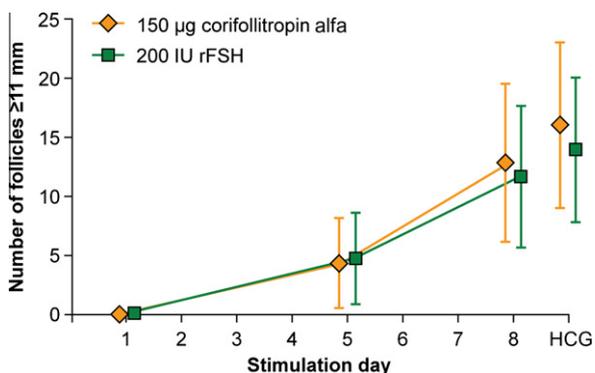
12.8  $\pm$  6.7 versus 11.6  $\pm$  6.0 and the 95% confidence interval (CI) of the difference was 0.5–1.8 ( $P < 0.01$ ). On the day of HCG, the mean  $\pm$  SD number of follicles  $\geq 11$  mm was 16.0  $\pm$  7.0 for the corifollitropin alfa treatment group versus 13.9  $\pm$  6.1 for the rFSH group and the 95% CI of the difference was 1.4–2.8 ( $P < 0.01$ ). The slightly higher follicular response with corifollitropin alfa resulted in a higher mean  $\pm$  SD number of cumulus–oocyte–complexes compared with rFSH (13.7  $\pm$  8.2 versus 12.5  $\pm$  6.8,  $P < 0.01$ , respectively), with an equal recovery rate in the two groups.

### Discussion

This report analysed the pharmacokinetic and pharmacodynamic data from the Engage trial, a phase-3, randomized, double blind, active-controlled, non-inferiority clinical trial that investigated the efficacy and safety of a single injection of corifollitropin alfa to induce multifollicular development for ovarian stimulation, using daily rFSH as a reference, in



**Figure 4** Time profiles of concentrations of (A) serum LH and (B) progesterone for the corifollitropin alfa regimen and the daily recombinant FSH (rFSH) regimen. All-subjects-treated population, restricted to subjects with human chorionic gonadotrophin (HCG) injection, from day of stimulation to 2 weeks after embryo transfer (ET). Horizontal black marks represent median values, boxes represent interquartile ranges and whiskers represent 5–95% percentiles.



**Figure 5** Mean  $\pm$  SD follicles  $\geq 11$  mm during stimulation and on the day of human chorionic gonadotrophin (HCG) administration for the corifollitropin alfa regimen and the daily recombinant follicle-stimulating hormone (rFSH) regimen. All-subjects-treated population.

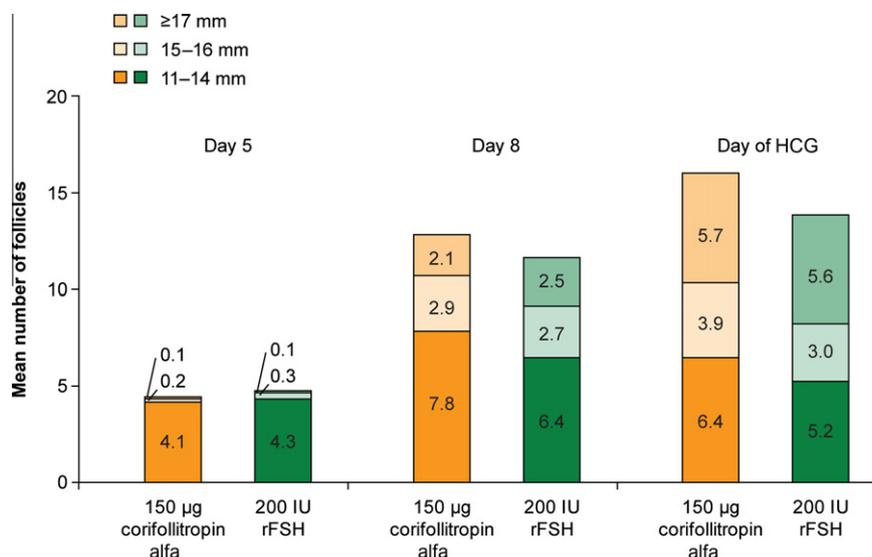
1506 women with a bodyweight 60–90 kg (Devroey et al., 2009b). The primary end-point of this trial, ongoing pregnancy rate, was reported recently as being 38.9% in the cori-

follitropin alfa group and 38.1% in the rFSH group (Devroey et al., 2009b).

In this large phase-3 trial, additional sparse pharmacokinetic sampling was performed. Although the number of samples per patient was limited, the number of patients evaluable for pharmacokinetics was larger than in any previous study of corifollitropin alfa. The pharmacokinetic findings for corifollitropin alfa in this trial were comparable to those previously reported in pituitary-suppressed female volunteers (Duijkers et al., 2002) and IVF patients (Corifollitropin Alfa Dose-Finding Study Group, 2008; Devroey et al., 2004). These findings confirm that with the slow absorption after subcutaneous administration and the long elimination half-life of corifollitropin alfa, a single 150 µg dose is sufficient to extend the FSH threshold window for an entire week, thus supporting multiple follicular growth (Fauser et al., 2009; Macklon et al., 2006). Previous studies have described the inverse relationship between exposure and bodyweight (De Greef et al., 2010). In order to cover a broad bodyweight range and to prevent overexposure, two strengths of corifollitropin alfa (100 µg for subjects  $\leq 60$  kg (Corifollitropin Alfa Ensure Study Group, 2010) and 150 µg for subjects  $> 60$  kg (Devroey et al., 2009b) were selected that would finally result in similar exposure and, therefore, similar ovarian response. The current report describes the exposure and pharmacodynamic response due to a single injection of 150 µg in subjects weighing more than 60 kg.

Despite the different pharmacokinetic profiles of corifollitropin alfa and rFSH in the present study, the pharmacodynamic properties were comparable. The growth rate of recruited follicles produced by a single injection of corifollitropin alfa appeared to be comparable to that of 7 days of rFSH, as documented by the similar duration of stimulation for which the criterion for HCG injection was reached. Compared with patients receiving daily rFSH, patients in the corifollitropin alfa group had a slightly higher number of medium-sized follicles (11–16 mm), but the number of larger follicles ( $\geq 17$  mm) required as a criterion for HCG administration was comparable between the treatment groups. The difference in the follicular response between the two regimens may be explained by higher FSH immunoreactivity concentrations up to stimulation day 5 after treatment with a single dose of corifollitropin as compared with the daily rFSH regimen. The slightly higher follicular response was observed along with a similar profile of serum inhibin B and oestradiol concentrations over time. The observed difference in follicular response was small though significant due to the large numbers of patients included in the trial. In addition, the differences were observed in the number of follicles  $< 17$  mm, which contribute less to the serum concentrations of oestradiol (Bomsel-Helmreich et al., 1979; van Dessel et al., 1996). However follicles  $< 11$  mm contribute more to circulating concentrations of inhibin B (Hohmann et al., 2005; Wen et al., 2006).

Whereas data on follicular development are presented per started cycle, serum hormone concentrations during the follicular phase are presented for subjects who received HCG. This allowed a comparative evaluation of the hormone profiles during the whole treatment cycle for subjects without cycle cancellation during ovarian stimulation. The number of subjects who discontinued treatment prior to HCG injection was small ( $n = 23$  in the corifollitropin alfa group



**Figure 6** Mean number and size distribution of follicles  $\geq 11$  mm for the corifollitropin alfa regimen and the daily recombinant follicle-stimulating hormone (rFSH) regimen. All-subjects-treated population.

and  $n = 9$  in the rFSH group) and reasons for cancellation varied from insufficient ovarian response to a too high ovarian response. Accordingly, time profiles of serum hormone concentrations largely differed between subjects who discontinued treatment prior to HCG injection, but their exclusion did not impact the average hormone profile or the comparison between the two treatment regimens.

The significantly higher number of follicles  $\geq 11$  mm in the corifollitropin alfa regimen compared with the rFSH regimen (difference of 2.1 on the day of HCG injection; 95% CI 1.4–2.8;  $P < 0.01$ ) is in keeping with the differences observed in the larger overall cohort of follicles and the treatment difference in the number of cumulus–oocyte–complexes retrieved (difference of 1.2; 95% CI 0.5–1.9;  $P < 0.01$  in favour of corifollitropin alfa) (Devroey et al., 2009b). While the higher mean ovarian response may require prudence in potential high responders, it may be considered a benefit in the older patient to obtain the optimal number of oocytes to enhance the chance of pregnancy (Broekmans et al., 2006). The study population in this trial included potential normal responders with regular menstrual cycles and with a basal antral follicle count  $< 20$ . Over three-quarters of the patients in the study were undergoing their first IVF cycle and so their ovarian response to treatment was unknown.

Previous clinical trials of the GnRH antagonist ganirelix have indicated that premature LH rises ( $> 10$  IU/l) prior to the start of the GnRH antagonist at stimulation day 6 occur more frequently in high responder patients and when a higher starting dose of rFSH is applied in the same patient population (The European Orgalutran study group, 2000; The North American ganirelix trial, 2001). Accordingly, compared with the rFSH reference group, the higher FSH activity during the first days of stimulation in patients treated with corifollitropin alfa may explain the higher incidence of early LH rises at stimulation day 5. The clinical outcome data revealed that there was no relevant difference in ongoing pregnancy rates in the subjects with

a premature LH rise as compared with the overall ongoing pregnancy rate. Therefore, the clinical impact of the slightly higher incidence of premature LH rises is considered negligible.

In summary, the differences in the pharmacokinetics of corifollitropin alfa and daily rFSH are quite distinct, but the induced pharmacodynamic effects are similar. A single dose of 150 µg corifollitropin alfa resulted in a similar growth rate of follicles, a similar rise in serum inhibin B and oestradiol concentrations and a slightly higher number of follicles as compared with daily 200 IU rFSH. The favourable findings of this study, combined with the potential for a simpler approach to ovarian stimulation by reducing the number of injections, should prove to be a more patient-friendly approach to treatment.

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