

# 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

**P. Devroey<sup>1</sup>, R. Boostanfar<sup>2</sup>, N.P. Koper<sup>3</sup>, B.M.J.L. Mannaerts<sup>4,7</sup>, P.J.M. Verweij<sup>4</sup>, B.J. Stegmann<sup>5,8</sup>, P.C. IJzerman-Boon<sup>4</sup>, and B.C.J.M. Fauser<sup>6</sup> on behalf of the ENGAGE Investigators**

<sup>1</sup>Center for Reproductive Medicine, UZ Brussel, Brussels, Belgium <sup>2</sup>Huntington Reproductive Center, Encino, CA, USA <sup>3</sup>Synthon BV, Nijmegen, The Netherlands <sup>4</sup>MSD, Oss, The Netherlands <sup>5</sup>Merck & Co. Inc., Whitehouse Station, NJ, USA <sup>6</sup>Department of Reproductive Medicine and Gynecology, University Medical Center, Utrecht, The Netherlands

<sup>8</sup>Correspondence address. E-mail: barbara.stegmann@merck.com

*Hum Reprod.* 2009;**24**:3063–3072

This corrigendum describes adjustments made to the ENGAGE study database following data quality review, resulting in minor changes to the published study results. The impacted parameters from Tables I, II, III, Figure 3 and Supplemental Tables II and III of the original publication are summarized in the data displays below.

In 2011, an audit of one of the ENGAGE study sites revealed inconsistencies in the way oocytes were counted in this study. Specifically, it was discovered that some sites included atretic oocytes and cumulus oocyte complexes without an oocyte present (“empty shells”) in the count for number of oocytes retrieved, while others excluded them from the count. In response to these findings, a uniform criterion was developed so that atretic oocytes and “empty shells” were always included in the total oocyte counts. The records from all of the sites were then reexamined and this new criterion was applied. This resulted in corrections to the number of oocytes retrieved in 55 out of 1506 subjects and, in most of these cases, the use of the new criterion increased the total number of oocytes by 1 or 2. At the same time, a separate review of pregnancy and infant follow-up data revealed a single, previously unreported, pregnancy in the corifollitropin alfa treatment group (ultrasound data were not available 10 weeks after embryo transfer and follow-up information could not initially be obtained, so by protocol the patient was considered to be “not pregnant”). This information was corrected after receiving confirmation of a live birth. The corrected results for ongoing pregnancies and number of oocytes retrieved are noted in bold font in Table II.

In Table IV of the original publication, clinical efficacy outcomes per started cycle (intent-to-treat population), the numbers (%) of subjects with an ongoing pregnancy and a multiple pregnancy in the corifollitropin alfa group should be 295 (39.0%) and 84 (28.5%), respectively, rather than the originally reported numbers of 294 (38.9%) and 83 (28.2%), respectively. The resulting p-values for the between-treatment group differences in the ongoing pregnancy and multiple pregnancy rates are  $p = 0.67$  and  $0.16$ , respectively, rather than the originally reported values of  $p = 0.71$  and  $0.18$ , respectively. A corrected version of Figure 3, ‘Ongoing pregnancy rates stratified for fertilization procedure, number of embryos transferred and the day of transfer’, is available upon request.

In addition, four previously unreported serious adverse events (SAEs) were identified. One patient had a SAE of pleurisy prior to receiving study drug. Three other SAEs, which occurred in the intervention portion of the study, were reported during the pregnancy and infant follow-up studies. Of these 3 SAEs, two occurred in the recombinant FSH (rFSH) group (i.e., one subject with a possibly drug-related report of ovarian cyst and one subject with an unlikely drug-related report of hyperemesis gravidarum), and one occurred in the corifollitropin alfa group (i.e., one subject with a non-drug-related report of antepartum haemorrhage). None of the SAEs in this study resulted in discontinuations. The number of subjects with SAEs in the corifollitropin alfa and rFSH groups shown in the safety section of the published paper should be 38 and 39, respectively, rather than the originally reported numbers of 37 for both treatment groups.

In summary, the re-analysis of the oocyte data, the additional pregnancy and SAE reports resulted in relatively minor changes to the

<sup>7</sup>Current Affiliation: Ferring Pharmaceuticals A/S, Copenhagen, Denmark

**Table 1** Demographics, fertility characteristics and baseline (stimulation day 1) ultrasound scan (USS) and serum hormone levels per treatment group (intent-to-treat population)

	Previously Published Results		Corrected Results	
	Corifollitropin alfa (n = 756)	rFSH (n = 750)	Corifollitropin alfa (n = 756)	rFSH (n = 750)
Demographics				
Age (years)	31.5 (3.3)	31.5 (3.2)	31.5 (3.3)	31.5 (3.2)
Body weight (kg)	68.8 (7.6)	68.4 (7.3)	68.8 (7.6)	68.4 (7.3)
BMI (kg/m <sup>2</sup> )	24.8 (2.8)	24.8 (2.7)	24.8 (2.8)	24.8 (2.7)
Race, n (%)				
Asian	21 (2.8)	21 (2.8)	<b>22 (2.9)</b>	<b>22 (2.9)</b>
Black	33 (4.4)	28 (3.7)	33 (4.4)	28 (3.7)
Caucasian	643 (85.1)	650 (86.7)	643 (85.1)	<b>649 (86.5)</b>
Other	59 (7.8)	51 (6.8)	<b>58 (7.7)</b>	51 (6.8)
Fertility characteristics				
Primary infertility, n(%)	403 (53.3)	393 (52.4)	403 (53.3)	393 (52.4)
Duration of infertility (years)	3.3 (2.4)	3.2 (2.2)	3.3 (2.4)	3.2 (2.2)
Cause of infertility <sup>a)</sup> , n (%)				
Male factor	388 (51.3)	347 (46.3)	388 (51.3)	347 (46.3)
Tubal factor	198 (26.2)	191 (25.5)	198 (26.2)	191 (25.5)
Endometriosis	109 (14.4)	115 (15.3)	109 (14.4)	115 (15.3)
Other/unexplained	246 (32.5)	262 (34.9)	246 (32.5)	262 (34.9)
First IVF cycle, n (%)	569 (75.3)	552 (73.6)	569 (75.3)	552 (73.6)
Stimulation day 1				
Total ovarian volume(mL) <sup>b)</sup>	13.2 (8.1)	13.2 (7.1)	13.2 (8.1)	13.2 (7.1)
Basal AFC (< 11 mm)	12.3 (4.6)	12.4 (4.4)	<b>12.3 (4.5)</b>	12.4 (4.4)
FSH (IU/L)	6.7 (2.1)	6.6 (1.9)	6.7 (2.1)	6.6 (1.9)
LH (IU/L)	4.8 (2.0)	4.7 (1.8)	4.8 (2.0)	4.7 (1.8)
E2 (pmol/L)	126.1 (39.3)	124.8 (37.4)	<b>126.1 (39.2)</b>	<b>124.8 (37.1)</b>
Progesterone (nmol/L)	1.8 (1.3)	1.8 (1.4)	1.8 (1.3)	1.8 (1.4)

AFC: antral follicle count, E2: estradiol, rFSH: recombinant FSH.

Numbers are mean (SD) unless otherwise indicated.

<sup>a)</sup>A patient can have multiple causes of infertility.

<sup>b)</sup>According to the formula for a prolate ellipsoid: 0.523 x longitudinal x antero-posterior x transverse diameters as measured per transvaginal ultrasound.

previously published data. The overall conclusions of the ENGAGE study : Other changes in the data relative to the original paper are noted by  
 remain unchanged. : bold font in the tables adapted from the original publication.

**Table II** Primary end-points of the ENGAGE trial: ongoing pregnancy rate (assessed at least 10 weeks after embryo transfer) and the mean (SD) number of cumulus-oocyte-complexes retrieved (intent-to-treat population)

	Previously Published Results				Corrected Results			
	Corifollitropin alfa (n = 756)	rFSH (n = 750)	Estimated difference <sup>a)</sup> [95% CI]	P-value	Corifollitropin alfa (n = 756)	rFSH (n = 750)	Estimated difference <sup>a)</sup> [95% CI]	P-value
Ongoing pregnancies (n)	294	286			<b>295</b>	286		
Per started cycle	38.9%	38.1%	0.9 [-3.9; 5.7]	0.71	<b>39.0%</b>	38.1%	<b>1.1 [-3.8; 5.9]</b>	<b>0.67</b>
Per embryo transfer	43.8%	40.6%	3.1 [-2.0; 8.2]	0.24	<b>43.9%</b>	40.6%	<b>3.3 [-1.9; 8.4]</b>	<b>0.21</b>
Cumulus-oocyte-complexes retrieved								
Per started cycle	13.7 (8.2)	12.5 (6.7)	1.2 [0.5; 1.9]	0.001	<b>13.8 (8.3)</b>	<b>12.6 (6.8)</b>	1.2 [0.5; 1.9]	0.001
Per oocyte retrieval	14.1 (7.9)	12.7 (6.7)	1.6 [0.8; 2.3]	<0.001	<b>14.2 (8.0)</b>	<b>12.7 (6.2)</b>	1.6 [0.8; 2.3]	<0.001

P-value corresponds to the test whether the treatment difference equals zero.

<sup>a)</sup>Estimated treatment difference (corifollitropin alfa - rFSH) adjusted for covariates.

**Table III Clinical parameters from stimulation phase up to embryo transfer (intent-to-treat population)**

	Previously Published Results		Corrected Results	
	Corifollitropin alfa (n = 756)	rFSH (n = 750)	Corifollitropin alfa (n = 756)	rFSH (n = 750)
Stimulation characteristics <sup>a)</sup>				
Total dose of rFSH (IU)	400 (0–2000)	1800 (400–2800)	400 (0–2000)	1800 (400–2800)
Total dose of rFSH from day 8 onwards (IU)	400 (0–2000)	400 (0–1400)	400 (0–2000)	400 (0–1400)
Total duration of stimulation (days) <sup>b)</sup>	9 (6–18)	9 (6–15)	9 (6–18)	9 (6–15)
Follicles, day of hCG <sup>a)</sup>				
≥ 11 mm	16.0 (7.0)	13.9 (6.1)	16.0 (7.0)	13.9 (6.1)
≥ 15 mm	9.6 (4.8)	8.7 (4.0)	9.6 (4.8)	8.7 (4.0)
≥ 17 mm	5.7 (3.2)	5.6 (2.9)	5.7 (3.2)	5.6 (2.9)
Serum parameters, day of hCG <sup>a)</sup>				
FSH (IU/L)	12.5 (3.3)	11.6 (2.8)	12.5 (3.3)	11.6 (2.8)
LH (IU/L)	1.4 (1.8)	1.9 (1.6)	1.4 (1.8)	1.9 (1.6)
E2 (pmol/L)	5508.8 (3469.8)	5165.3 (435.6)	<b>5486.7 (3461.9)</b>	<b>5154.9 (2999.5)</b>
Inhibin-B (pg/mL)	610.3 (492.3)	614.8 (435.6)	610.3 (492.3)	614.8 (435.6)
Progesterone (nmol/L)	3.0 (2.1)	3.2 (1.5)	<b>3.2 (4.9)</b>	3.2 (1.5)
Clinical outcome per started cycle				
Oocytes retrieved, ICSI only	13.8 (7.6)	12.1 (6.3)	13.8 ( <b>7.7</b> )	<b>12.2 (6.4)</b>
Metaphase II oocytes (ICSI only)	10.8 (6.5)	9.2 (5.1)	10.8 (6.5)	9.2 (5.1)
% of total	78.9 (18.9)	77.4 (18.1)	<b>78.9 (18.7)</b>	<b>77.2 (18.1)</b>
Fertilization rate (%) <sup>c,d)</sup>	66.0 (23.4)	67.6 (22.9)	66.0 ( <b>23.5</b> )	67.6 (22.9)
Total number of embryos obtained (day 3) <sup>c)</sup>	8.3 (5.6)	7.4 (4.8)	<b>8.4 (5.5)</b>	<b>7.5 (4.8)</b>
Excellent (top) quality embryos (grade 1) <sup>c)</sup>	2.6 (3.4)	2.5 (3.4)	2.6 (3.4)	2.5 (3.4)
Good quality embryos (grade 1 + 2) <sup>c)</sup>	4.6 (4.3)	4.4 (3.9)	<b>4.7 (4.3)</b>	<b>4.5 (3.9)</b>
Single embryo transfer (%) <sup>d)</sup>	25.7	27.0	25.7	27.0
Embryos transferred <sup>e)</sup>	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)
Embryos cryopreserved <sup>f)</sup>	4.3 (3.6)	3.9 (2.7)	<b>4.3 (3.5)</b>	3.9 (2.7)

Numbers are mean (SD) unless otherwise indicated.

<sup>a)</sup>Restricted to patients with hCG injection.

<sup>b)</sup>Number of days up to and including the day of hCG administration.

<sup>c)</sup>Restricted to patients with IVF and/or ICSI.

<sup>d)</sup>Defined as 100 times the number of mature oocytes (with two pronuclei) obtained divided by the number of oocytes used for fertilization.

<sup>e)</sup>Restricted to patients with embryo transfer.

<sup>f)</sup>Restricted to patients with cryopreserved embryos.

Subgroup	Previously Published Results			Corrected Results				
	Treatment	n	N	%	Treatment	n	N	%
IVF	CFA	88	241	36.5%	CFA	88	<b>242</b>	<b>36.4%</b>
	rFSH	85	240	35.4%	rFSH	85	240	35.4%
ICSI	CFA	164	413	39.7%	CFA	<b>165</b>	<b>410</b>	<b>40.2%</b>
	rFSH	168	417	40.3%	rFSH	168	417	40.3%
Single	CFA	60	173	34.7%	CFA	<b>61</b>	173	<b>35.3%</b>
	rFSH	55	190	28.9%	rFSH	55	190	28.9%
Double	CFA	234	499	46.9%	CFA	234	499	46.9%
	rFSH	231	514	44.9%	rFSH	231	514	44.9%
Day 3	CFA	169	405	41.7%	CFA	169	405	41.7%
	rFSH	156	445	35.1%	rFSH	156	445	35.1%
Day 5	CFA	121	257	47.1%	CFA	<b>122</b>	257	47.5%
	rFSH	126	249	50.6%	rFSH	126	249	50.6%

n=subjects with ongoing pregnancy; N=number of subjects  
CFA=Corifollitropin alfa (150 µg); rFSH=rFSH (200 IU/day)  
Subset with double embryo transfer includes three patients with three embryos transferred.

**Figure 3** Data are displayed here in tabular format rather than as a figure per the original publication. Ongoing pregnancy rates stratified for fertilization procedure, number of embryos transferred and day of transfer.