

Phase III trial comparing the efficacy and safety of recombinant- or urine-derived human chorionic gonadotropin for ovulation triggering in Japanese women diagnosed with anovulation or oligo-ovulation and undergoing ovulation induction with follitropin-alfa

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Abstract

Aim: Outside of Japan, recombinant-human chorionic gonadotropin (r-hCG) is widely used for the induction of final follicular maturation and early luteinization in women undergoing ovulation induction; whereas in Japan, urine-derived hCG (u-hCG) is predominantly used. The primary objective of this study was to demonstrate the non-inferiority of r-hCG to u-hCG for ovulation induction, as assessed by the ovulation rate.

Methods: This was an open-label, parallel-group, randomized, multicenter, phase III trial in Japanese women with anovulation or oligo-ovulation secondary to hypothalamic-pituitary dysfunction or polycystic ovary syndrome, undergoing ovulation induction with recombinant-human follicle-stimulating hormone. The women were randomized (2:1) to receive either a single 250 µg s.c. dose of r-hCG or a single 5000 IU i.m. dose of u-hCG for ovulation triggering.

Results: Eighty-one women were randomized to either r-hCG (n=54) or u-hCG (n=27). Ovulation occurred in 100% of the participants and treatment with r-hCG was observed to be non-inferior to u-hCG for ovulation induction. Overall, the type and severity of adverse events were as expected for women receiving fertility treatment.

Conclusion: This study demonstrated that r-hCG was non-inferior to u-hCG for inducing ovulation. Furthermore, r-hCG demonstrated an expected safety profile, with no new safety concerns identified.

KEYWORDS

assisted reproductive techniques, human chorionic gonadotropin, oocyte retrieval, ovulation, ovulation induction

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1 | INTRODUCTION

Human chorionic gonadotropin (hCG) is widely used as a surrogate for luteinizing hormone to induce final oocyte maturation in women who are undergoing ovulation induction.¹ Globally, both recombinant-hCG (r-hCG) and urine-derived hCG (u-hCG) are used for this purpose, with r-hCG typically used at a dose of 250 µg and u-hCG used at a dose of 5000–10 000 IU.¹ Outside of Japan, comparative clinical trials have demonstrated that administration of 250 µg of r-hCG is as effective as 5000 IU and 10 000 IU of u-hCG for the induction of final follicular maturation and early luteinization in assisted reproductive techniques and as effective as 5000 IU of u-hCG for ovulation induction.^{2–4} A meta-analysis of nine of these trials observed a mean (95% confidence interval [CI]) difference of -0.04 (-0.69 – 0.62) oocytes retrieved with r-hCG, compared with u-hCG, and no statistically significant difference ($P=.28$) between the preparations for the ongoing pregnancy or live birth rates.⁵ However, a lower risk of adverse events (AEs) has been observed with r-hCG compared with u-hCG (odds ratio [95% CI] 0.39 [0.25–0.61]).⁵ These AEs include injection site reactions, such as pain, inflammation, itching, and bruising, which have been observed in clinical trials to occur in fewer women who receive r-hCG, compared with those who receive u-hCG.^{2,6}

Furthermore, u-hCG has a number of disadvantages, compared with r-hCG, including batch-to-batch inconsistency, which has been observed to affect the treatment response and the potential for adverse immunologic reactions that are caused by the presence of non-hCG proteins.^{6–9} Outside of Japan, r-hCG is, therefore, widely used for the induction of final follicular maturation and early luteinization in women who are undergoing ovulation induction, whereas in Japan u-hCG is still predominantly used.

A phase III trial was conducted to investigate whether a single 250 µg s.c. dose of r-hCG was non-inferior to a single 5000 IU i.m. dose of u-hCG for inducing ovulation in Japanese women who had been diagnosed with anovulation or oligo-ovulation secondary to hypothalamic–pituitary dysfunction or polycystic ovary syndrome (PCOS) and who were undergoing ovulation induction with recombinant-human follicle-stimulating hormone (r-hFSH).

2 | MATERIALS AND METHODS

This was an open-label, parallel-group, randomized, multicenter, phase III trial (ClinicalTrials.gov. identifier: NCT01653743) in Japanese

women who were undergoing ovulation induction with r-hFSH. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation–Good Clinical Practice guidelines, and all applicable regulatory requirements, with all the participants providing written informed consent prior to entry into the trial.

2.1 | Study participants

Healthy premenopausal Japanese women (aged 20–39 years, inclusive) who wished to conceive, had a body mass index (BMI) of 17.0–29.0 kg/m² (inclusive), and who were diagnosed with anovulation or oligo-ovulation secondary to hypothalamic–pituitary dysfunction (Grade 1 amenorrhea, oligomenorrhea, or anovulatory cycles) or PCOS were included if they met the following criteria: spontaneous menstruation (at least twice per year) or a positive response to progestin, as shown by menstruation; no known defect of the fallopian tubes that precluded ovulation induction; a normal uterine cavity on screening transvaginal ultrasound; a male partner with a normal semen analysis, as defined by World Health Organization standards, within 12 months prior to informed consent; and normal cervical smear results within 12 months prior to informed consent.

The exclusion criteria included infertility due to causes other than hypothalamic–pituitary dysfunction or PCOS, a history of severe ovarian hyperstimulation syndrome (OHSS; classified according to the Japan Reproductive/Endocrine Working Group guidelines¹⁰), active thromboembolic disorders, the presence of, or suspected, gonadotropin- or estrogen-dependent malignancy, a history of allergic reaction or hypersensitivity to hCG- or gonadotropin-containing product(s) and/or their excipients, or a contraindication to pregnancy.

2.2 | Study treatments and interventions

Women were enrolled at 15 centers in Japan and the trial was conducted between September 2012 and December 2014. The study design is shown in Figure 1. Women underwent ovulation induction therapy with single, daily injections of r-hFSH (follitropin alfa; Merck KGaA, Darmstadt, Germany) according to a low-dose, step-up protocol for a maximum of 28 days, unless a rise in estradiol levels was recorded suggesting imminent follicular maturation. The starting dose of r-hFSH was 75 IU s.c. per day, unless there was an indication of increased risk of OHSS or in cases in which a starting dose of <75 IU was recommended by the principal investigator. Dose increment changes of 37.5 IU every 7 days were permitted based on the ovarian response.

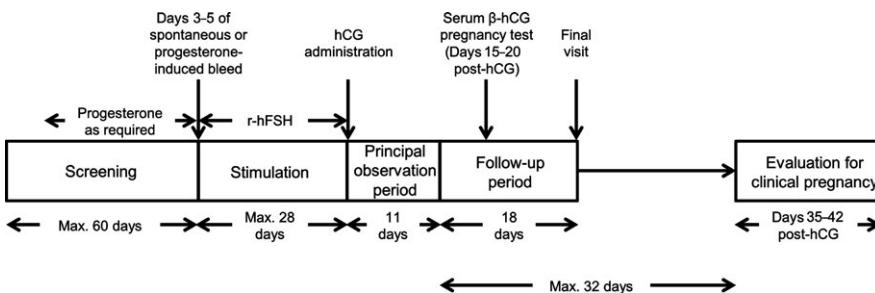
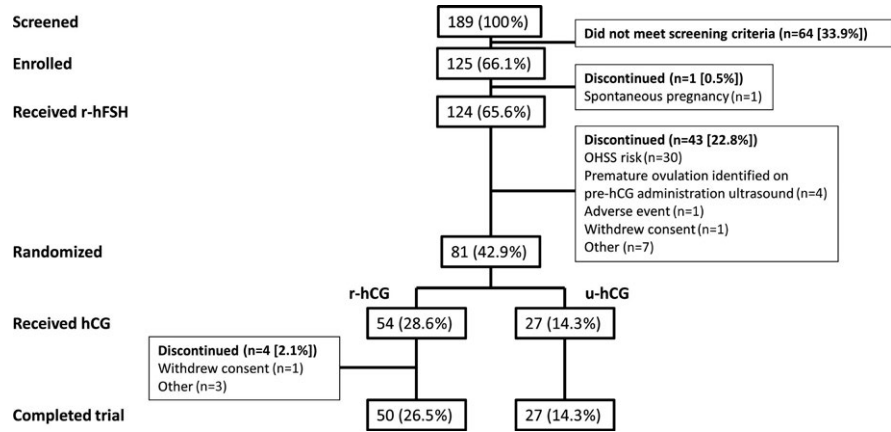


FIGURE 1 Study design. hCG, human chorionic gonadotropin; Max., maximum; r-hFSH, recombinant-human follicle-stimulating hormone

FIGURE 2 Subject disposition. hCG, human chorionic gonadotropin; OHSS, ovarian hyperstimulation syndrome; r-hCG, recombinant-human chorionic gonadotropin; r-hFSH, recombinant-human follicle-stimulating hormone; u-hCG, urine-derived human chorionic gonadotropin



After stimulation with r-hFSH was completed, patients were randomized (2:1) to receive either a single 250 µg s.c. dose of r-hCG (Merck KGaA, Darmstadt, Germany) or a single 5000 IU i.m. dose of u-hCG (Mochida Pharmaceutical Company, Ltd, Tokyo, Japan) once all of the following criteria were met: the mean diameter of the dominant follicle was ≥ 18 mm; there were no more than three follicles with a mean diameter ≥ 16 mm; and the serum estradiol level was within an acceptable range for the number of follicles present and was ≤ 2000 pg/mL.

Women were randomized according to a predefined computer-generated list in random permuted blocks that were stratified by site. Randomization was coordinated centrally via an interactive Voice and Web response system. Following hCG administration, fertilization was attempted through either intercourse within 48 hours of hCG administration or by intrauterine insemination, depending on the participant's preference. Intrauterine insemination was performed according to the normal procedures of the trial site. Luteal phase support was not provided during the trial.

2.3 | Study objectives and end points

The primary objective of this study was to determine whether a single 250 µg s.c. dose of r-hCG was non-inferior to a single 5000 IU i.m. dose of u-hCG for ovulation induction in Japanese women who had been diagnosed with anovulation or oligo-ovulation secondary to hypothalamic-pituitary dysfunction or PCOS and who were undergoing ovulation induction with r-hFSH. The non-inferiority margin was -20%.

The primary efficacy end point was the ovulation rate, where ovulation was defined as a mid-luteal serum progesterone level ≥ 5 ng/mL, in all the participants who received hCG and had a serum progesterone level < 5 ng/mL prior to hCG administration. The higher of the values taken on the visit on either days 5-7 or days 8-10 post-hCG administration was taken as the final value for this determination. If clinical pregnancy was achieved, this was counted as successful ovulation, regardless of the mid-luteal serum progesterone levels.

The secondary efficacy end points included the ovulation rate, where ovulation was defined as a mid-luteal serum progesterone level ≥ 9.4 ng/mL. Other secondary efficacy end points were mid-luteal endometrial thickness and biochemical and clinical pregnancy rates. Biochemical pregnancy was defined as any miscarriage without

evidence of a fetal sac on transvaginal ultrasound on the day 35-42 post-hCG visit, but with a positive serum β -hCG pregnancy test (β -hCG > 10 IU/L) on the day 15-20 post-hCG administration visit. Clinical pregnancy was defined as the presence of a fetal sac on transvaginal ultrasound on the day 35-42 post-hCG administration visit.

Safety and tolerability, including the incidence and severity of AEs, incidence of OHSS, and local tolerability were also investigated. AEs were classified by their severity and causal relationship to the study treatment. AEs with an onset date occurring on or after hCG use were classed as "treatment-emergent AEs" (TEAEs).

2.4 | Statistical analysis

The ovulation rate following a single 5000 IU dose of u-hCG as part of an ovulation induction cycle using r-hFSH in a low-dose, step-up protocol was assumed to be 95%, based on observations from two Japanese trials of r-hFSH for ovulation induction.¹¹ An ovulation rate of 95% also was observed in a global phase III trial that investigated a single 250 µg dose of r-hCG as part of an ovulation induction cycle using r-hFSH with a similar low-dose, step-up protocol.²

Assuming that the ovulation rate would be 95% in both arms, 72 evaluable participants (48 treated with r-hCG and 24 with u-hCG) were required to demonstrate that the lower limit of the two-sided 95% CI of the difference in the ovulation rate (r-hCG minus u-hCG) was above the non-inferiority margin of -20%, with at least 90% power. Allowing for a 15% cycle cancellation rate (based on the data from the trials that were used in the previous calculation¹¹), a total of 87 participants needed to be enrolled in order that 72 might be evaluable.

The primary efficacy end point was investigated in the modified intention-to-treat (ITT) population, which included all the participants who were randomized to receive either r-hCG or u-hCG and who completed the primary efficacy assessment. The exact two-sided 95% CI of the difference (Chang and Zhang method¹²) in ovulation rates was calculated and if the lower bound of the 95% CI was above -20% then non-inferiority was assumed. The secondary efficacy end points were also investigated in the modified ITT population and were reported as percentages with corresponding CIs. The safety analysis was conducted using the safety population, which included all participants who received either r-hCG or u-hCG.

3 | RESULTS

A total of 189 women were screened for inclusion in the trial, of whom 125 were enrolled (Figure 2). Of these women, 124 started controlled ovarian stimulation with r-hFSH and one woman discontinued prior to ovulation stimulation because of a spontaneous pregnancy. Forty-three women discontinued during controlled ovarian stimulation, with the main reason for discontinuation being the risk of OHSS ($n=30$). Following controlled ovarian stimulation, 81 women were randomized to receive either r-hCG ($n=54$) or u-hCG ($n=27$) to trigger ovulation, and this represented both the modified ITT and safety populations. Subsequent to ovulation triggering, four women discontinued in the r-hCG arm (due to inadequate compliance with trial medication [$n=1$], withdrawal of consent [$n=1$], the investigator's judgment [$n=1$], and the use of prohibited drugs [$n=1$]) and did not complete the trial.

3.1 | Baseline characteristics and demographics

Demographics, baseline characteristics, and infertility history were comparable between the two treatment groups (Table 1). The median age was 31.5 years, the median weight was 52.8 kg, and the median BMI was 20.8 kg/m². The majority of the women had primary infertility, with all the participants having female infertility only. The main cause of female infertility was ovulatory dysfunction, mostly as a result of oligo-ovulation. The median duration of infertility was longer in the group that received r-hCG, compared with the group that received u-hCG (2.0 years and 1.0 year, respectively).

3.2 | Efficacy evaluation

For the primary efficacy evaluation, ovulation, defined as a mid-luteal progesterone level ≥ 5 ng/mL, was reported in all the participants in the modified ITT population (Table 2) and the lower limit of the two-sided 95% CI of the difference between ovulation rates was -7.8% , which was above the non-inferiority margin of -20% . Therefore, treatment with r-hCG was non-inferior to u-hCG for ovulation induction. Furthermore, for the secondary efficacy evaluation, ovulation, defined as mid-luteal progesterone ≥ 9.4 ng/mL, was reported in 52 (96.3%) women who received r-hCG and 24 (88.9%) women who received u-hCG (Table 2). The lower limit of the two-sided 95% CI of the difference between ovulation rates was -5.2% , which was above the non-inferiority margin of -20% , also demonstrating non-inferiority for this outcome.

The median mid-luteal phase endometrial thickness 5-7 days following hCG administration was comparable between the treatment groups: 11.0 mm and 12.0 mm in the r-hCG and u-hCG treatment groups, respectively. A similar proportion of women had a positive β -hCG pregnancy test 15-20 days following hCG administration: 35.2% of the women who had received r-hCG and 37.0% of the women who had received u-hCG. Biochemical pregnancy was reported in the same proportion of patients in both treatment arms (3.7% in both arms; Table 2). The clinical pregnancy rate was also

TABLE 1 Baseline characteristics and demographics (modified intention-to-treat population)

	r-hCG (n=54)	u-hCG (n=27)	Overall (n=81)
Age (years), median	33.30	30.00	31.50
Weight (kg), median	51.55	54.50	52.80
BMI (kg/m ²), median	20.60	21.00	20.80
Infertility, N (%)			
Primary	38 (70.4)	20 (74.1)	58 (71.6)
Secondary	16 (29.6)	7 (25.9)	23 (28.4)
Duration of infertility (years), median	2.0	1.0	2.0
Type of infertility, N (%)			
Female infertility only	54 (100.0)	27 (100.0)	81 (100.0)
Cause(s) of female infertility, N (%)			
Endometriosis	1 (1.9)	0 (0.0)	1 (1.2)
Ovulatory dysfunction	54 (100.0)	27 (100.0)	81 (100.0)
Anovulation	5 (9.3)	2 (7.4)	7 (8.6)
Oligo-ovulation	49 (90.7)	25 (92.6)	74 (91.4)
Causes of ovulatory dysfunction, N (%)			
Grade 1 amenorrhea	7 (13.0)	5 (18.5)	12 (14.8)
Oligomenorrhea	34 (63.0)	14 (51.9)	48 (59.3)
Polycystic ovary syndrome	13 (24.1)	8 (29.6)	21 (25.9)
Type of menstruation, N (%)			
Oligo-amenorrhea (<6 periods/year)	17 (31.5)	13 (48.1)	30 (37.0)
Oligo-amenorrhea (≥ 6 periods/year)	33 (61.1)	12 (44.4)	45 (55.6)
Secondary amenorrhea	4 (7.4)	1 (3.7)	5 (6.2)
Menstrual irregularity	0 (0.0)	1 (3.7)	1 (1.2)

BMI, body mass index; r-hCG, recombinant-human chorionic gonadotropin; u-hCG, urine-derived human chorionic gonadotropin.

comparable in both groups (29.6% and 33.3% with r-hCG and u-hCG, respectively; Table 2).

3.3 | Safety evaluation

The incidence of AEs and hCG-related TEAEs was higher in the group that received r-hCG, compared with the group that received u-hCG (Table 3). At least one AE was experienced pre-hCG administration by 27.8% and 11.1% of the women who received r-hCG and u-hCG, respectively. At least one hCG-related TEAE was experienced by 38.9% of the women who received r-hCG and 29.6% of the women who received u-hCG. The type and frequency of TEAEs did not represent any new safety concerns, compared with the known safety profile of r-hCG.⁵

The most commonly reported TEAEs were OHSS, ovarian cyst, and injection site erythema and pain. Mild, moderate, and severe OHSS were reported by 7.4%, 3.7%, and 3.7% of the patients who were treated with r-hCG and 7.4%, 7.4%, and 0.0% of those who were treated with u-hCG. In one participant from the r-hCG group, OHSS

TABLE 2 Efficacy end points (modified intention-to-treat population)

	r-hCG (n=54)	u-hCG (n=27)
Primary endpoint		
Ovulation rate, defined as a mid-luteal progesterone level ≥ 5 ng/mL		
Participants with a serum progesterone level, N (%)		
<5 ng/mL on day 0 post-hCG visit	54 (100.0)	27 (100.0)
≥ 5 ng/mL on day 5-7 post-hCG visit	52 (96.3)	26 (96.3)
≥ 5 ng/mL on day 8-10 post-hCG visit	48 (88.9)	25 (92.6)
Participants with a mid-luteal serum progesterone level ≥ 5 ng/mL, N (%)	54 (100.0)	27 (100.0)
Participants with successful ovulation, N (%)	54 (100.0)	27 (100.0)
Difference in the ovulation rate, % (95% CI)	0.0 (-7.8-12.8)	
Secondary endpoints		
Ovulation rate, defined as a mid-luteal progesterone level ≥ 9.4 ng/mL		
Participants with a mid-luteal serum progesterone level ≥ 9.4 ng/mL, N (%)	51 (94.4)	24 (88.9)
Ovulation rate defined by a progesterone level ≥ 9.4 ng/mL or clinical pregnancy, N (%)	52 (96.3)	24 (88.9)
Difference in the ovulation rate, % (95% CI)	7.4 (-5.2-25.6)	
Mid-luteal endometrial thickness		
Median endometrial thickness, mm	11.0	12.0
Biochemical and clinical pregnancy rates		
Positive β -hCG pregnancy test, ^a N (%)	19 (35.2)	10 (37.0)
Biochemical pregnancy ^b rate, % (95% CI)	3.7 (0.5-12.7)	3.7 (0.1-19.0)
Clinical pregnancy ^c rate, % (95% CI)	29.6 (18.0-43.6)	33.3 (16.5-54.0)

CI, confidence interval; r-hCG, recombinant-human chorionic gonadotropin; u-hCG, urine-derived human chorionic gonadotropin.

^a β -hCG (β -human chorionic gonadotropin) pregnancy test was performed at the day 15-20 post-hCG administration visit (serum β -hCG >10 IU/L).

^bBiochemical pregnancy was defined as any miscarriage without any evidence of a fetal sac on transvaginal ultrasound on the visit 35-42 days following hCG administration despite a positive β -hCG pregnancy test 15-20 days post-hCG.

^cClinical pregnancy was defined as the presence of at least one fetal sac on transvaginal ultrasound at the visit 35-42 days following hCG administration.

TABLE 3 Summary of adverse events (AEs) (safety population)

	r-hCG (n=54) N (%)	u-hCG (n=27) N (%)
At least one AE pre-hCG administration	15 (27.8)	3 (11.1)
At least one TEAE	33 (61.1)	11 (40.7)
At least one hCG-related TEAE	21 (38.9)	8 (29.6)
At least one serious AE	1 (1.9)	0 (0.0)
At least one serious hCG-related TEAE	1 (1.9)	0 (0.0)
Death	0 (0.0)	0 (0.0)

hCG, human chorionic gonadotropin; r-hCG, recombinant-human chorionic gonadotropin; TEAE, treatment-emergent adverse event; u-hCG, urine-derived human chorionic gonadotropin.

was considered to be a serious TEAE in one participant who received r-hCG. The incidence of ovarian cyst was identical with r-hCG and u-hCG, occurring in 11.1% of participants in both groups. Injection site erythema was reported by 9.3% and 7.4% of the women who received r-hCG and u-hCG, respectively, and injection site pain was reported by 3.7% and 11.1% of women, respectively. All the injection site AEs were mild in intensity.

4 | DISCUSSION

This open-label, randomized controlled trial, in 81 women who were undergoing controlled ovarian stimulation, demonstrated that r-hCG was non-inferior to u-hCG for inducing ovulation in Japanese women who had been diagnosed with anovulation or oligo-ovulation secondary to hypothalamic-pituitary dysfunction or PCOS and who were undergoing ovulation induction with r-hFSH. Similar proportions of women who received r-hCG and u-hCG had positive β -hCG pregnancy tests and the mid-luteal phase endometrial thickness was comparable in both groups. The clinical pregnancy rate was also similar in women who received r-hCG or u-hCG.

A higher proportion of women experienced TEAEs with r-hCG, compared with those who received u-hCG (38.9% vs 29.6%, respectively). This result is different from those that have been reported previously by trials comparing r-hCG with u-hCG, which report significantly fewer AEs with r-hCG.^{2,4-6,13,14} It should be noted that the incidence of AEs pre-hCG administration was also higher in the group that received r-hCG compared with the group that received u-hCG. Furthermore, the overall incidence of OHSS that was observed in this study (14.8% in both arms) was higher than that reported in

the literature or previous trials.^{2,6,14} This higher incidence might be because most studies only report moderate and severe OHSS, rather than all OHSS, and if the incidence of mild OHSS is removed, the hCG-related OHSS rates are comparable with other studies (moderate or severe OHSS: 7.4% in both the r-hCG and the u-hCG treatment groups).

Overall, the type and severity of AEs that were observed were as expected for women receiving fertility treatment.^{2,5,6} These results highlight that r-hCG for ovulation triggering is similarly effective and has a similar safety profile compared with u-hCG in this population. Local tolerability was similar in both groups, except for pain, which was lower with r-hCG compared with u-hCG. This might potentially increase patient acceptability,¹³ making home injection more suitable with r-hCG.

A potential limitation of this study was its open-label design; however, owing to the mechanism of action of hCG and the similarity of the results to those from global studies, it is unlikely that this would have affected the outcomes.^{2,5,6} In addition, some causes of ovulatory dysfunction (eg, infertility due to causes other than hypothalamic-pituitary dysfunction or PCOS) were listed in the exclusion criteria and therefore not the entire population of patients with ovulatory dysfunction is reflected in this trial.

In conclusion, this phase III study demonstrated that the efficacy of a single 250 µg s.c. dose of r-hCG was non-inferior to a single 5000 IU i.m. dose of u-hCG in inducing ovulation in Japanese women who had been diagnosed with anovulation or oligo-ovulation secondary to hypothalamic-pituitary dysfunction or PCOS and who were undergoing ovulation induction with r-hFSH. A 100% ovulation rate was observed with both r-hCG and u-hCG. Furthermore, r-hCG demonstrated an expected safety profile in women receiving fertility treatment, with no new safety concerns identified.

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DISCLOSURE

Conflicts of interest: Daniela Rogoff is a former employee of EMD Serono Research & Development Institute, Inc., a business of Merck KGaA, Darmstadt, Germany. Shin Shimizu is an employee of Merck Serono Company, Ltd, an affiliate of Merck KGaA, Darmstadt, Germany. Hideyuki Ikenaga, Yudai Tanaka, Masahide Shiotani, and

Osamu Ishihara declare that they have no relevant conflict of interest. *Human rights statement and informed consent:* All the procedures that were followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study. *Animal studies:* This article does not contain any studies with animals performed by any of the authors.

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