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Single-dose pharmacokinetic study comparing the pharmacokinetics of recombinant human chorionic gonadotropin in healthy Japanese and Caucasian women and recombinant human chorionic gonadotropin and urinary human chorionic gonadotropin in healthy Japanese women

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Abstract

Purpose: Recombinant hCG (r-hCG) was approved in Japan in 2016. As a prerequisite for a Phase III study in Japan related to this approval, the pharmacokinetic (PK) profile of r-hCG was investigated.

Methods: An open-label, partly randomized, single-center, single-dose, group-comparison, Phase I PK-bridging study was done that compared a single 250 μg dose of r-hCG with a single 5000 IU dose of urinary hCG (u-hCG) in healthy Japanese women, as well as comparing a single 250 μg dose of r-hCG in Japanese and Caucasian women. The Japanese participants were randomized 1:1 to receive either r-hCG or u-hCG, while the Caucasian participants were weight-matched to the Japanese participants who were receiving r-hCG in a 1:1 fashion. The primary PK parameters were the area under the serum concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$) and the maximum serum concentration (C_{max}).

Results: The mean serum hCG concentration–time profiles of r-hCG in the Japanese and Caucasian participants were a similar shape, but the level of overall exposure was ~20% lower in the Japanese participants. For the Japanese participants, r-hCG resulted in an 11% lower C_{max} but a 19% higher $AUC_{0-\infty}$ compared with u-hCG. No new safety signal was identified.

Conclusion: This study cannot exclude a potential difference in the PK profile of r-hCG between Japanese and Caucasian participants. However, this study does not indicate that there are clinically relevant differences in the serum PK of r-hCG and u-hCG in the Japanese participants.

KEYWORDS

area under curve, human chorionic gonadotropin, Japanese, Ovidrel, pharmacokinetics

1 | INTRODUCTION

Human chorionic gonadotropin (hCG) is used to trigger final follicular maturation and luteinization after the stimulation of follicular growth in women who are undergoing superovulation prior to assisted reproductive technology (ART) techniques, including in vitro fertilization (IVF) and in anovulatory or oligo-ovulatory women after stimulation of follicular growth.[1,2] There are two available preparations of hCG, urinary hCG (u-hCG), which is extracted from the urine of pregnant women,[1] and recombinant hCG (r-hCG), which is produced from Chinese Hamster Ovary cells using recombinant technology.[2] u-hCG is administered via an i.m. injection, while r-hCG is administered s.c.[1,2]

Recombinant hCG was first approved for ART and the induction of ovulation in the USA in September, 2000 (Ovidrel®; EMD Serono, Rockland, MA, USA),[3] in the European Union in February, 2001 (Ovitrelle®; Merck KGaA, Darmstadt, Germany),[4] and in Japan in September, 2016.[5] During the clinical development of r-hCG, its pharmacokinetic (PK) and pharmacodynamic (PD) properties were investigated and compared with those of u-hCG. These studies found that the PK/PD profile of r-hCG was similar to that of u-hCG in healthy male and female participants.[2,6] Furthermore, a meta-analysis of published studies identified that there was no difference in efficacy between r-hCG and u-hCG.[7]

When administered in ethnic groups that are often not routinely included in clinical development programs, for example, Japanese participants, clinically significant differences in efficacy and safety profiles can be observed for some drugs, compared with populations that are well represented in development programs.[8,9] This might be the result of genetic, social, or cultural differences, including diet, exposure to pollution, and differences in medical practice.[9] The dose or regimen that is approved in the original region might therefore not be appropriate for the new ethnic group and bridging PK studies are conducted in order to investigate whether there are any important differences.[8,9]

The International Conference of Harmonisation guideline E5 provides direction on conducting these studies and, in 1998, Japan's Pharmaceutical and Medical Devices Agency (PMDA) adopted these guidelines.[10,11] They state that bridging studies do not have to be conducted in the new region; however, to be eligible, participants from the ethnic group being investigated must meet specific inclusion criteria.[11] For studies including Japanese participants, both of the participant's parents and all of their grandparents must be Japanese, the participant must have been born in Japan, have a valid Japanese passport, not have lived outside of Japan for >5 years, and be consuming a Japanese diet at least once per day.[10]

In order to seek approval, a PK bridging study was conducted as a prerequisite for a single-arm, Phase III study in Japan to assess the efficacy of r-hCG for triggering final follicular maturation and luteinization after stimulation of follicular growth in women who are undergoing superovulation. The aims of this PK bridging study were to compare the area under the serum concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$) and the maximum serum concentration (C_{max}) following a single 250 μg s.c. dose of r-hCG in healthy Japanese and Caucasian women and to compare the $AUC_{0-\infty}$ and C_{max} of a single 250 μg s.c. dose of r-hCG to a single 5000 IU i.m. dose of u-hCG in healthy Japanese women. The study also compared other PK parameters, as well as safety and tolerability between the three treatment arms.

2 | MATERIALS AND METHODS

This was an open-label, partly randomized, single-center, single-dose, group-comparison, Phase I study in healthy female participants (EudraCT: 2010-019105-41). The study was approved by the local ethics committee and was conducted in compliance with the clinical study protocol, the International Council for Harmonisation – Good Clinical Practice, and any additional applicable regulatory requirements. All the participants provided written informed consent prior to any study-related procedure. Participants received compensation for participating in the study.

2.1 | Study participants

Healthy premenopausal Japanese or Caucasian women (aged 20-40 years, inclusive) who had a body weight of 45-65 kg (inclusive), a Body Mass Index (BMI) of 17.0-28.0 kg/m^2 (inclusive), and had a normal menstrual cycle (for the participants aged 25-35 years) or a history of a normal menstrual cycle (combined oral contraceptive pill [OCP] users) were included in this study. To qualify as Japanese, the participants had to meet the specific inclusion criteria, as defined by the PMDA, that were described earlier.[11] As part of the screening process passports were checked, but all the other inclusion criteria specifically for Japanese participants were self-reported.

The exclusion criteria included a contraindication to combined OCPs or gonadotropins; marked changes in body weight in the 3 months before screening; unsuccessful down-regulation (i.e pituitary suppression) with Marvelon® (desogestrel and ethinyl estradiol tablets; Merck Sharp & Dohme, Ltd., Hoddesdon, UK); the use of any prescription or non-prescription medication (excluding Marvelon) within 14 days prior to study drug administration and/or during the course of the study; or the loss or donation of >500 mL of blood within 90 days prior to study entry.

2.2 | Study treatments and interventions

The women were enrolled at a single center in the UK between June, 2010 and March, 2011 and the study design is shown in Fig. 1. Following screening, the eligible participants started taking Marvelon from the morning of the fourth day of a natural bleed or, if they were already on a combined OCP, a withdrawal bleed. The first dose was given in the clinical unit following confirmation of a negative pregnancy status. Marvelon was then taken orally once per day, at the same time each day, and treatment was continued until the follow-up visit. Pituitary down-regulation had to be achieved within a period of 10-25 days. The participants who were not down-regulated within this period were discontinued from the study.

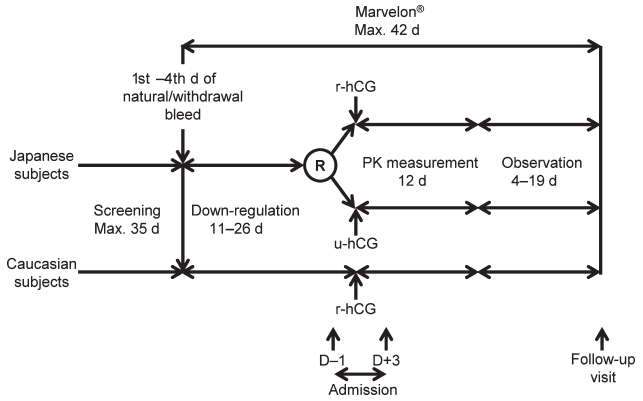

FIGURE 1 Study design. D, day; Max., maximum; PK, pharmacokinetic; R, randomization; r-hCG, recombinant human chorionic gonadotropin; u-hCG, urinary human chorionic gonadotropin

Pituitary down-regulation was confirmed biochemically using hormonal tests (luteinizing hormone [LH] of <2.5 IU/L, follicle-stimulating hormone [FSH] of <4 IU/L, and estradiol of <102 pg/mL) and the absence of mature follicles with a mean diameter of ≥11 mm, determined by transvaginal ultrasound. The down-regulated participants had to have a negative serum pregnancy test on day −1. Japanese participants were then randomized 1:1 to receive either r-hCG or u-hCG, while the Caucasian participants were weight-matched (weights of two matched participants must not differ by >3 kg) to the Japanese participants who were receiving r-hCG in a 1:1 fashion. No Caucasian participant received u-hCG.

A single dose of either 250 μg r-hCG s.c. (Ovitrelle®) or 5000 IU u-hCG i.m. (Pregnyl®; Merck Sharp & Dohme, Ltd., Hoddesdon, UK) was injected in the morning of day 1. The serum samples for PK profiling were collected predose and at 3, 6, 9, 12, 16, 20, 24, 32, 48, 72, 96, 120, 144, 168, 192, 216, 240, and 264 hours postdose. Safety was evaluated throughout the study, up to the final follow-up visit.

2.3 | Study objectives and endpoints

2.3.1 | Pharmacokinetic endpoints

All the PK parameters were calculated and summarized from the serum hCG concentrations and the concentrations of hCG were determined in IU for all treatments. The 250 μg dose of r-hCG was converted to the nominal dose of 6500 IU for the dose-dependent PK parameter evaluation.[2] The primary PK parameters were the $AUC_{0-\infty}$ and C_{max}. The other PK parameters that were investigated were the area under the serum concentration–time curve from time 0 to the last quantifiable time (AUC_{0-t}), the time to reach the maximum serum concentration (t_{max}), the serum terminal half-life ($t_{1/2}$), the apparent volume of distribution (V_z/f), and the apparent total clearance (CL/f).

All the samples were assayed for hCG by using a validated fluoroimmunometric assay (DELFIA® hCG solid-phase, time-resolved fluorimmuno assay kit; PerkinElmer, Waltham, MA, USA). This assay cannot distinguish between recombinant and endogenous hCG and the quantification of hCG using this method is not affected by the presence of LH concentrations of ≤100 IU/mL and FSH concentrations of ≤275 IU/mL. The lower limit of quantification was 2.0 IU/L in serum. The PK parameters for hCG were calculated by using KINETICA™ (ThermoFisher Scientific, Waltham, MA, USA). All the PK parameters were calculated and summarized from the serum hCG concentrations using non-compartmental methods with no baseline adjustment.

2.3.2 | Safety endpoints

The following safety and tolerability endpoints were investigated: incidence and severity of treatment-emergent adverse events (TEAEs; any adverse event occurring after treatment with hCG); vital signs and 12-lead electrocardiogram (ECG); routine hematology, clinical chemistry, and urinalysis; and local tolerability, including the severity of pain, as assessed by the participant using a visual analog scale. Adverse events were categorized according to the Medical Dictionary for Regulatory Activities coding system, tabulated, and listed by treatment and ethnic group and analyzed by their severity and relationship to the drug. The laboratory and vital signs were descriptively summarized and shifts from baseline were calculated.

2.4 | Statistical analysis

This study was designed to estimate the relative bioavailability of hCG in all three treatment arms and to characterize any difference in the PK profile of r-hCG between the Japanese and the Caucasian participants and between r-hCG and u-hCG in the Japanese participants. The required sample size was calculated before the trial was initiated by using coefficient of variation (CV) data from a previous bioequivalence study of r-hCG formulations in Caucasian participants (AUC: 27.7%; C_{max}: 38.7%). The sample size of 12 participants per ethnic group was considered to be appropriate for the comparison of the PK parameters of r-hCG, as this provided 20% precision for $AUC_{0-\infty}$ and 29% for C_{max}. These levels of precision (~20%) are generally appropriate to characterize differences in PK in clinical pharmacology studies. In the Food and Drug Administration's guidance on bioequivalence, for example, 20% is used to define the bioequivalence margins.[12] In addition, 12 Japanese participants received u-hCG in order to provide balanced data across all three groups. The PK analysis was performed on the per-protocol set that included all the participants who received hCG, had no relevant protocol violation or event that was likely to affect comparability of the PK results, had adequate compliance with the trial's medication, and had availability of C_{max} and $AUC_{0-\infty}$ data. Safety and tolerability were analyzed in the safety analysis set that included all the participants who received hCG and had follow-up data.

The continuous measurements were summarized by descriptive statistics (ie the number of observations, mean, standard deviation, CV [%], standard error of the mean, minimum, median, and maximum). Concentration values below the lower limit of quantification were taken as zero for the summary statistics. The PK parameters were also shown as the geometric mean, the geometric CV, and the 95% confidence interval (CI) for the geometric mean. The categorical data

were summarized in frequency tables (ie count and percentages), if not stated otherwise.

An ANOVA model with "ethnic group" as a fixed effect was applied to the log-transformed $AUC_{0-\infty}$ and C_{max} data for the comparison of the Japanese and Caucasian participants following r-hCG treatment. An ANOVA model with "treatment" as a fixed effect was applied to the log-transformed $AUC_{0-\infty}$ and C_{max} data for the comparison of r-hCG and u-hCG treatment in the Japanese participants. Geometric mean group ratios were estimated for each parameter and 90% CIs were calculated. For the t_{max}, the Hodges–Lehmann estimate and the corresponding 90% CIs, according to Moses, were computed. Group ratios were also estimated for the AUC_{0-t} data, as described for the $AUC_{0-\infty}$ and C_{max} data. Adjustments for multiplicity were not performed due to the exploratory nature of the trial.

3 | RESULTS

In total, 61 Japanese participants and 61 Caucasian participants were screened for inclusion in the study. Of these, 30 Japanese participants and 18 Caucasian participants received Marvelon. Subsequent to down-regulation, 24 Japanese participants who fulfilled the down-regulation criteria were randomized (1:1) to receive either r-hCG or u-hCG. Twelve Caucasian participants (weight-matched to the Japanese participants receiving r-hCG) who fulfilled the down-regulation criteria received r-hCG.

3.1 | Baseline characteristics and demographics

The baseline characteristics were comparable between the three treatment groups (Table 1). This confirmed the success of the weight-matching between the Japanese and the Caucasian participants who received r-hCG.

3.2 | Pharmacokinetic evaluation

The mean concentration–time profiles of serum hCG in the Japanese and Caucasian participants who received r-hCG are shown in Fig. 2a. The r-hCG was absorbed rapidly, with mean concentrations increasing steadily during the absorption phase in the participants of both ethnicities. The maximum concentrations occurred between 16 and 32 hours, before declining continuously up to the last sampling time point (264 hours postdose). The mean concentration–time profile for the Japanese participants who received r-hCG was a similar shape, but the hCG concentrations were lower throughout the entire observation period, compared with those of the Caucasian participants. The mean concentration–time profiles of serum hCG in the Japanese participants who received r-hCG or u-hCG are shown in Fig. 2b. The u-hCG also was absorbed rapidly, with maximum concentrations occurring between 16 and 24 hours postdose.

TABLE 1 Baseline characteristics of the participants

Characteristic	Caucasian r-hCG (n = 12)	Japanese r-hCG (n = 12)	Japanese u-hCG (n = 12)
Mean age, years (SD)	30.8 (4.7)	28.5 (4.2)	28.7 (5.2)
Mean weight, kg (SD)	52.0 (4.2)	51.3 (5.2)	54.2 (4.4)
Mean BMI, kg/m^2 (SD)	20.3 (1.5)	20.0 (1.6)	21.5 (2.1)

BMI, Body Mass Index; r-hCG, recombinant human chorionic gonadotropin; SD, standard deviation; u-hCG, urinary human chorionic gonadotropin.

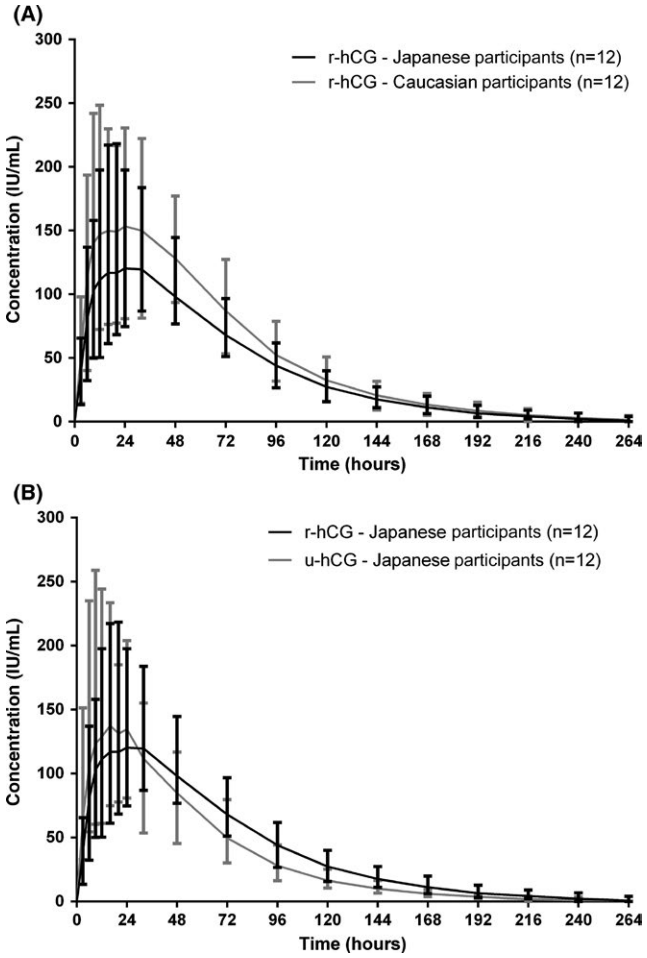

FIGURE 2 Mean concentration–time profiles of human chorionic gonadotropin (hCG) in serum. (A) Recombinant (r)-hCG in the Japanese and Caucasian participants. (B) r-hCG and urinary (u)-hCG in the Japanese participants. The data are shown as the mean ± standard deviation serum concentrations

The serum hCG parameters are shown in Table 2. The mean exposure and mean C_{max} of hCG following a single injection of r-hCG was ~20% lower in the Japanese participants compared with the Caucasian participants. The geometric means of $t_{½}$ were similar for both ethnicities, as was the t_{max}. The CL/f and V_z/f values did not indicate relevant differences between ethnicities.

In the Japanese participants, r-hCG resulted in an 11% lower C_{max}, but a 19% higher AUC, compared with u-hCG. The geometric means

TABLE 2 Serum human chorionic gonadotropin pharmacokinetic parameters

Parameter	r-hCG: Caucasian participants n = 12	r-hCG: Japanese participants n = 12	u-hCG: Japanese participants n = 12
$AUC_{0-\infty}$ (IU/L·hr)	12,946.00 (24.1)	10,278.00 (21.4)	8666.00 (31.6)
C_{max} (IU/L)	158.06 (26.5)	126.26 (31.6)	141.39 (38.4)
AUC_{0-t} (IU/L·hr)	12,787.00 (24.2)	10,130.00 (21.5)	8535.00 (32.1)
t_{max} (hr)[a]	22.0 9.0–48.0	22.0 12.0–48.0	18.0 9.0–24.0
$t_{1/2}$ (hr)	35.70 (11.2)	35.20 (14.8)	34.50 (11.2)
CL/f (L/hr)	0.50 (24.1)	0.63 (21.4)	0.58 (31.6)
V_z/f (L)	25.80 (20.3)	32.20 (24.7)	28.70 (35.6)

Data are shown as the geometric mean (geometric coefficient of variation, %), unless otherwise indicated.

[a]Median and range. $AUC_{0-\infty}$, area under the serum concentration–time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the serum concentration–time curve from time 0 to the last quantifiable time; CL/f, apparent total clearance; C_{max}, maximum serum concentration; r-hCG, recombinant human chorionic gonadotropin; $t_{1/2}$, serum terminal half life; t_{max}, the amount of time to reach the maximum serum concentration; u-hCG, urinary human chorionic gonadotropin; V_z/f, apparent volume of distribution.

of $t_{½}$ were similar for both treatments in the Japanese participants. The t_{max} was slightly higher for the Japanese participants who received r-hCG, compared with the Japanese participants who received u-hCG, but this difference was not considered to be significant. The CL/f and V_z/f values did not indicate relevant differences between treatments.

The results of the ANOVA analysis of the serum PK parameters are shown in Table 3. The ANOVA results show that the $AUC_{0-\infty}$ and C_{max} were ~20% lower in the Japanese participants compared with the Caucasian participants. The results for AUC_{0-t}, t_{max}, CL/f, V_z/f, and $t_{1/2}$ from the ANOVA were in line with the results of the primary analysis. The ANOVA results also do not suggest any relevant difference in the PK profiles of r-hCG and u-hCG in the Japanese participants, as the 90% CIs for the estimated treatment ratios included unity for all of the examined PK parameters. The results for AUC_{0-t}, CL/f, V_z/f, and $t_{1/2}$ from the ANOVA were consistent with the results of the primary analysis. However, the median t_{max} was slightly increased when r-hCG was compared with u-hCG in the Japanese participants.

TABLE 3 ANOVA comparing the serum human chorionic gonadotropin pharmacokinetic parameters between groups

Group	Estimate of the ratio	90% Confidence interval for the estimate	ANOVA coefficient of variation (%)
r-hCG: Japanese *vs* Caucasian			
$AUC_{0-\infty}$ (IU/L·hr)	0.79	0.67–0.95	26.0
C_{max} (IU/Lr)	0.80	0.64–0.99	32.5
AUC_{0-t} (IU/L·hr)	0.79	0.66–0.95	26.3
$t_{1/2}$ (hr)	0.99	0.91–1.08	12.5
t_{max} (hr)	1.50	−4.00–11.00	–
CL/f (L/hr)	1.26	1.06–1.50	26.0
V_z/f (L)	1.24	1.03–1.50	27.5
r-hCG *vs* u-hCG: Japanese participants			
$AUC_{0-\infty}$ (IU/L·hr)	1.19	0.99–1.42	26.0
C_{max} (IU/L)	0.89	0.72–1.11	32.5
AUC_{0-t} (IU/L·hr)	1.19	0.99–1.42	26.3
$t_{1/2}$ (hr)	1.02	0.94–1.11	12.5
t_{max} (hr)	4.00	0.00–12.00	–
CL/f (L/hr)	1.10	0.92–1.31	26.0
V_z/f (L)	1.12	0.93–1.35	27.5

$AUC_{0-\infty}$, area under the serum concentration–time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the serum concentration–time curve from time 0 to the last quantifiable time; CL/f, apparent total clearance; C_{max}, maximum serum concentration; r-hCG, recombinant human chorionic gonadotropin; $t_{1/2}$, serum terminal half life; t_{max}, the amount of time to reach the maximum serum concentration; u-hCG, urinary human chorionic gonadotropin; V_z/f, apparent volume of distribution.

3.3 | Safety evaluation

An overview of the TEAEs is shown in Table 4. There were no deaths, serious TEAEs, or other significant TEAEs, and no participant discontinued due to a TEAE. Overall, 29 out of the 36 participants reported a total of 76 TEAEs, with a similar proportion of participants reporting TEAEs in each group. The TEAEs were reported for 10 (83.3%) participants in both groups receiving r-hCG and nine (75.0%) Japanese participants who received u-hCG. The most commonly reported TEAEs (>10% of participants) were metrorrhagia (n = 10, 27.8%), headache (n = 7, 19.4%), injection site pain (n = 7, 19.4%), and vaginal hemorrhage (n = 4, 11.1%). One severe TEAE of constipation was reported by a Caucasian participant who received r-hCG, but it was not considered to be related to the study's treatment.

Of the 76 TEAEs reported, 15 were reported as drug-related in 11 participants, five who received u-hCG, and three participants in each of the groups receiving r-hCG. All of the drug-related TEAEs that were reported for the participants who received u-hCG were injection site pain, which was also reported for two Japanese participants who received r-hCG. The other drug-related TEAEs that were reported for the participants receiving r-hCG included metrorrhagia (n = 1), headache (n = 1), nausea (n = 1), breast pain (n = 2), diarrhoea (n = 1), and acne (n = 1). No Caucasian participant who received r-hCG reported injection site pain. No significant changes in vital signs, 12-lead ECG, routine hematology, clinical chemistry, or urinalysis were observed.

4 | DISCUSSION

In this study, the mean serum hCG concentration–time profiles of r-hCG in the Japanese and Caucasian participants were similar. The t_{max} was similar in both groups (22 hours); however, the C_{max} was lower in the Japanese participants (126 IU/L), compared with the Caucasian participants (158 IU/L). This resulted in an ~20% lower overall exposure in the Japanese participants and the study therefore cannot exclude a potential difference in the PK of r-hCG between Japanese and Caucasian participants, as the study was not designed to detect differences of a defined magnitude. The reason for this difference in exposure between the two groups is unknown; however, it is possible that a difference in body mass composition between Japanese and Caucasian participants at the low mean weight that was observed in this study might have resulted in a higher volume of distribution in the Japanese participants. It should also be noted that because of weight-matching, the Caucasian population that was recruited for this trial did not represent the Caucasian average.

In the Japanese participants, r-hCG resulted in an 11% lower C_{max}, but a 19% higher $AUC_{0-\infty}$, compared with u-hCG, and the median t_{max} was 18 and 22 hours for u-hCG and r-hCG, respectively. The small, non-significant difference that was observed for the t_{max} might be related to differences in the level of absorption from the administration site (ie i.m. vs s.c.) and, overall, the level of absorption was rapid, with high systemic concentrations reached quickly. In addition, the small, non-significant difference in the C_{max} between r-hCG and u-hCG (126 and 141 IU/L, respectively) would be unlikely to result in any clinical difference. The minimum systemic concentration that is needed to trigger ovulation is undefined; however, 3000 IU of u-hCG has demonstrated efficacy (with lower systemic concentrations). Therefore, this study does not indicate that there are clinically relevant differences in the serum PK of r-hCG and u-hCG in Japanese participants. This is consistent with the results of previous studies that did not find relevant PK differences between r-hCG and u-hCG,[2,6] as well as a clinical trial of r-hCG in Japanese patients.[13]

The adverse events that were observed with single doses of r-hCG and u-hCG were in line with expectations and no new safety signal was identified. However, the local tolerability was observed to be more preferable with r-hCG compared with u-hCG.

Subsequent to the bridging study reported here, a Phase III study with a two-arm, comparative design was undertaken. This open-label, parallel-group, randomized, multicenter, Phase III trial was conducted on 81 Japanese women with anovulation or oligo-ovulation secondary to hypothalamic–pituitary dysfunction or polycystic ovary syndrome who were undergoing ovulation induction with recombinant human FSH.[13] The 250 μg r-hCG dose that was used in this Phase III study was based on the one that had been approved for use in other parts of the world, as the bridging study suggested that there was no clinically relevant PK difference between Caucasian and Japanese women, even though a difference could not be excluded. 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. Ovulation was triggered in all the trial participants and r-hCG was observed to be non-inferior to u-hCG for ovulation induction. Furthermore, the safety profiles of r-hCG and u-hCG were as expected for women receiving fertility treatment. These results suggest that there is no difference in clinical efficacy for Japanese and Caucasian patients who are receiving r-hCG

TABLE 4 Safety results

Side-effect	r-hCG: Caucasian (n = 12)	r-hCG: Japanese (n = 12)	u-hCG: Japanese (n = 12)
Any TEAE	10 (83.3)	10 (83.3)	9 (75.5)
Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
TEAE of severe intensity	1 (8.3)	0 (0.0)	0 (0.0)
Drug-related TEAE	3 (25.0)	3 (25.0)	5 (41.7)
Drug-related TEAE of severe intensity	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs reported in >10% of the participants			
Metrorrhagia	1 (8.3)	6 (50.0)	3 (25.0)
Vaginal hemorrhage	2 (16.7)	2 (16.7)	0 (0.0)
Headache	5 (41.7)	2 (16.7)	0 (0.0)
Pain at the injection site	0 (0.0)	2 (16.7)	5 (41.7)

All the data are presented as n (%). r-hCG, recombinant human chorionic gonadotropin; TEAE, treatment-emergent adverse event; u-hCG, urinary human chorionic gonadotropin.

for ovulation induction for IVF and that therefore there is no need for r-hCG to be given at a different dose in Japanese patients compared with Caucasian patients.

In conclusion, this study could not exclude a potential difference in the serum PK of r-hCG in Japanese and Caucasian participants. The lower exposure to r-hCG in the Japanese participants, compared with the Caucasian participants, is not expected to affect the clinical efficacy or safety of r-hCG in the induction of ovulation or ART in Japanese patients. Moreover, exposure to hCG following a 250 μg r-hCG injection in the Japanese participants was comparable with that observed for 5000 IU u-hCG. Subsequently, no evidence of a difference between r-hCG and u-hCG was observed in a Phase III clinical trial in Japanese participants[13] and the PMDA approved r-hCG to trigger ovulation and luteinization after stimulation of follicular growth in anovulatory or oligo-ovulatory adult women and in women who are undergoing superovulation prior to ART.[5]

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DISCLOSURES

Conflict of interest: Wilhelmina Bagchus is an employee of the Merck Institute for Pharmacometrics, Lausanne, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany. Peter Wolna is an employee of Merck KGaA and Wolfgang Uhl is a former employee of Merck KGaA. *Human and Animal Rights*: The study was approved by the local ethics committee (Welwyn Clinical Pharmacology Ethics Committee, Fulbourn, UK [WCPEC117]). The study was conducted in compliance with the clinical study protocol, the International Council for Harmonization–Good Clinical Practice, and any additional applicable regulatory requirement. All the participants provided written informed consent prior to any study-related procedure. This article does not contain any study with animal participants that were performed by any of the authors.

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