

# A Multicenter, Randomized, Equivalence Trial of a New Recombinant Human Chorionic Gonadotropin Preparation versus Ovitrelle® for Ovulation in Women Undergoing Intrauterine Insemination Following Ovarian Stimulation

Abha Majumdar, Rekha Sachan<sup>1</sup>, Yogeshwar S. Nandanwar<sup>2</sup>, Rahul V. Mayekar<sup>2</sup>, Neelu Soni<sup>3</sup>, Manish R. Banker<sup>4</sup>, Rajan S. Vaidya<sup>5</sup>, Manjeet Arora<sup>6</sup>, Girish P. Godbole<sup>7</sup>, Gautam V. Daftary<sup>8</sup>, Ganesh H. Divekar<sup>9</sup>, James John<sup>9</sup>

Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, <sup>6</sup>Department of Obstetrics and Gynaecology, Batra Hospital and Medical Research Centre, New Delhi, <sup>1</sup>Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow, Uttar Pradesh, <sup>2</sup>Department of Obstetrics and Gynaecology, Lokmanya Tilak Municipal Medical College and General Hospital, <sup>3</sup>Department of Obstetrics and Gynaecology, Nowrosjee Wadia Maternity Hospital, Mumbai, <sup>8</sup>Research and Development, <sup>9</sup>Department of Clinical Research and Pharmacovigilance, Bharat Serums and Vaccines Limited, Navi Mumbai, <sup>7</sup>Department of Obstetrics and Gynaecology, Deenanath Mangeshkar Hospital and Research Centre, Pune, Maharashtra, <sup>3</sup>Department of Obstetrics and Gynaecology, Choithram Hospital and Research Centre, Indore, Madhya Pradesh, <sup>4</sup>Nova IVI Fertility, Ahmedabad, Gujarat, India

ABSTRACT

**Context:** A new indigenous recombinant human chorionic gonadotropin (r-hCG) has been developed in India with a comparable pharmacological profile to that of Ovitrelle® (Merck Serono). **Aims:** This study aims to compare the efficacy and safety of the new r-hCG with that of Ovitrelle for induction of ovulation in women undergoing intrauterine insemination (IUI). **Settings and Design:** Randomized (2:1), multicenter, open-label, equivalence clinical trial conducted in India. **Subjects and Methods:** A total of 217 women, aged 20–37 years, undergoing IUI were administered the new r-hCG (test) 250 mcg or Ovitrelle 250 mcg (comparator) after ovarian stimulation with gonadotropins. The ovulation rate was compared as the primary outcome. In addition, pregnancy rates, incidence of adverse events (AEs), and development of immunogenicity were assessed. **Statistical Analysis Used:** The ovulation and pregnancy rates were compared using Chi-squared test with statistical significance at  $P < 0.05$ . **Results:** With 144 women in the test group and 73 in the comparator group, the ovulation rate (85.4% vs. 78.1%;  $P = 0.17$ ) and pregnancy rate (serum  $\beta$  hCG test) (11.8% vs. 12.3%;  $P = 0.91$ ) were similar in both groups. A total of 15 AEs were reported (11 in the test r-hCG group and 4 in the comparator group) in 11 women; none of these were serious, and all were judged to be unrelated to the study drug. No subject developed immunogenic reaction to the test drug. **Conclusions:** The new preparation of r-hCG was equivalent to the conventional preparation of r-hCG in the induction of ovulation in patients undergoing IUI.

**KEYWORDS:** Human chorionic gonadotropin, intrauterine insemination, ovulation induction, recombinant

## INTRODUCTION

Gonadotropins currently used for infertility treatments are considered to have better efficacy, safety, and quality profiles compared to those used in the past. The introduction of recombinant DNA technology in the manufacturing process has been instrumental

**Address for correspondence:** Dr. Rahul V. Mayekar, Department of Obstetrics and Gynaecology, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai - 400 022, Maharashtra, India. E-mail: rvmayekar@gmail.com

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in achieving this.<sup>[1,2]</sup> It started with the commercial availability of recombinant follicle stimulation hormone in 1995.<sup>[2]</sup> The technology makes it possible to avoid the need for human donors and human products thereby decreasing the risk of disease transmission, protein impurities, and batch-to-batch inconsistencies.<sup>[1,2]</sup> Human chorionic gonadotropin (hCG) has been the mainstay for induction of final follicle and oocyte maturation and ovulation by mimicking the endogenous luteinizing hormone (LH) - surge.<sup>[3]</sup> The recombinant version of hCG became commercially available in 2001.<sup>[1]</sup> Although generally, both urinary and recombinant hCG (r-hCG) preparations have been identified to be similar clinically,<sup>[4,5]</sup> certain studies have reported r-hCG to be more efficient in terms of ovulation and pregnancy rates or tolerability as identified by significantly less frequent development of local injection site adverse effects.<sup>[6-9]</sup> For the final follicular maturation and ovulation, as part of various infertility treatments, Ovitrelle® (Merck Serono, Geneva, Switzerland), a preparation of r-hCG, is available in many countries, including India.

Biosimilar medicines, which are highly similar to another already approved biological medicine, are expected to have the same amino acid sequence as the approved preparation, with allowance for small acceptable differences in the microheterogeneity pattern of the molecule.<sup>[10]</sup> These biosimilars can serve to provide increased access to and cost-competitiveness to high-quality biological medicines. Bharat Serums and Vaccines Limited, Mumbai, India has developed the first r-hCG biosimilar in India. This biosimilar has been manufactured using the same technique as used for Ovitrelle, i.e., transfecting Chinese hamster ovary cells with genetic material coding for the  $\alpha$ - and  $\beta$ -subunits of hCG. It has been demonstrated to have similar physicochemical properties and similar biological effects and tolerability in preclinical studies. This study aimed to demonstrate the equivalence of the new r-hCG preparation and the comparator product Ovitrelle in the induction of ovulation before intrauterine insemination (IUI) in infertile women with similar safety profile.

## SUBJECTS AND METHODS

This was a randomized, controlled, open, multicenter, equivalence trial comparing two preparations of r-hCG. The trial was conducted at 11 centers in India. Normogonadotrophic women, aged 20–37 years, undergoing IUI and diagnosed with unexplained infertility, anovulatory infertility, Grade I or II endometriosis or polycystic ovarian syndrome were eligible for the trial. The additional main inclusion criteria were body mass index 18–30 kg/m<sup>2</sup>, presence of a uterus consistent with expected

normal function (e.g., no clinically interfering uterine fibroids) and at least one patent tube, semen parameters of partner/donor compatible with IUI and presence of at least 1 follicle >18 mm poststimulation with gonadotropins. The main exclusion criteria were a premature ovarian failure, hypogonadotropic hypogonadism, poor gonadotropin responder, endometriosis Stage III–IV, more than 3 failed IUIs, history of ovarian hyperstimulation syndrome, abnormal gynecological bleeding, and uncontrolled thyroid or adrenal dysfunction.

A sample size of 210 was selected purely for primary data capture and to have sufficient safety data, such that study group would have 140 individuals, versus 70 in the comparator group (2:1 randomization). All individuals who received the single dose of test r-hCG/Ovitrelle were eligible for efficacy analysis. Women were randomly assigned to either group, through a computer-generated randomization code. The codes were provided to the sites in sealed envelopes. Women randomized to test r-hCG and Ovitrelle groups were administered subcutaneously 6500 IU (250 mcg) of either r-hCG preparation, 24–48 h after completion of ovarian stimulation. An ultrasound examination was performed 36–48 h after administration of r-hCG to check for ovulation and the serum levels of hCG were measured. Those individuals who achieved ovulation underwent IUI. Serum beta hCG levels were measured 16–17 days after IUI to check for biochemical pregnancy (positive beta hCG test). Thirty days after IUI, ultrasound examination was performed to check for gestational sac as a confirmation of clinical pregnancy. In addition, a blood sample was collected before administration of study drug and on days 30 and 90 post-IUI to test for immunogenicity by detecting the presence of anti-drug antibodies. Adverse events (AEs) were recorded from the signing of informed consent till the end-of-trial visit.

The primary endpoints were ovulation 36–48 h postadministration of study drug and serum concentration of hCG measured  $36 \pm 4$  h postadministration of study drug.

Prespecified secondary endpoints included pregnancy rates, the incidence of AEs and incidence of immunogenicity (development of anti-drug antibodies) in the test group.

## Ethics

The trial protocol (code: BSV/r-hCG/10) was approved by the Indian drug regulatory authority and the Institutional Ethics Committees of all the participating centers. The study was registered on Clinical Trials Registry-India (CTRI/CTRI/2014/09/005010). The trial was performed in accordance with the principles of the

Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and local regulatory requirements. All participants provided voluntary, written, informed consent.

### Statistics

The primary efficacy parameter for the study was ovulation 36–48 h postadministration of study drug and concentration of hCG measured 36 ± 4 h postadministration of study drug. The number of individuals who demonstrated ovulation postadministration of study drug were evaluated as percentage of individuals in each treatment group and were compared using Chi-squared test. The evaluation was made with transvaginal sonography and was recorded into the case record form (CRF). The sample size has been calculated on pragmatic basis and justifiable as per central limit theorem.

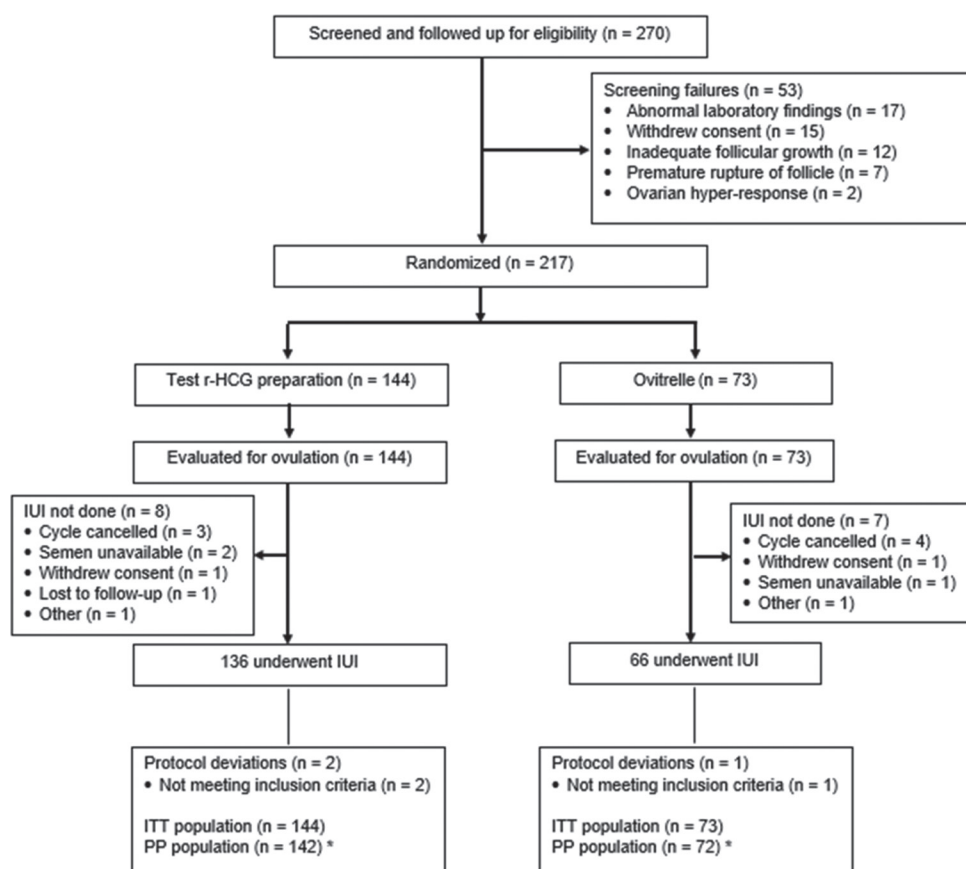
The concentration of hCG 36 ± 4 h postadministration of study drug was another efficacy parameter, which was evaluated by measuring plasma levels of hCG. Due to the lack of uniformity in the collection of sample and measurement among the study sites, this parameter could not be analyzed to demonstrate comparative data between two treatment arms.

Although single measurement of hCG post-hCG administration may not be most appropriate due to variation in peak concentration seen and lack of correlation between hCG concentration and oocyte maturity and ovulation, it provides information of the presence of higher concentration in subject postadministration of hCG.

### RESULTS

The trial was conducted between November 14, 2014, and May 02, 2016. A total of 270 women were screened across 10 sites in India of whom 217 were randomized (144 to test r-hCG and 73 to Ovitrelle) and received one of the study drugs. The trial and participant flow are shown in Figure 1.

Demographics and baseline characteristics were comparable between the two treatment groups [Table 1]. All the individuals belonged to the Asian race. The intention-to-treat (ITT)/safety population included all 217 individuals who received either of the study drugs, and the per protocol (PP) population included 214 (98.6%) individuals. Three individuals were enrolled in the study with age more than specified in inclusion criteria and hence were excluded from the PP population.



**Figure 1:** Trial and participant flow. \*Since the difference between intention-to-treat and per protocol population was minor, only intention-to-treat analysis was performed

Outcome data for the randomized women (ITT population) are displayed in Table 2. The ovulation rate was 85.4% in the test r-hCG group and 78.1% in the Ovitrelle group, with a  $P = 0.17$ . The mean serum level of HCG in the test r-hCG group was 64.3 ( $\pm 40.5$ ) mIU/mL and 101.7 ( $\pm 64.5$ ) mIU/mL in the Ovitrelle group. Due to the lack of uniformity among hospital laboratories and time-point for sample collection, this parameter could not be analyzed to demonstrate comparative data between two treatment arms. The biochemical pregnancy rate was 11.8% in the test r-hCG group and 12.3% in the Ovitrelle group, with a  $P = 0.91$ . Clinical pregnancy was confirmed in 11 individuals from r-hCG group and 5 individuals from Ovitrelle group.

Eight individuals from r-hCG group and three individuals from Ovitrelle group reported 11 and four AEs respectively. Three individuals from r-hCG group and one subject from Ovitrelle group reported more than one AE. The reported AEs and relevant information have been summarized in Table 3. Out of 11 AEs reported in r-hCG group, five were mild and six were moderate in severity. All four AEs reported in Ovitrelle group were mild in severity. All 15 AEs reported in the study were judged to be unrelated to study treatment and resolved without any sequelae/complications. No serious AE was reported during the study in any treatment arm.

### Immunogenicity

None of the individuals in the test r-hCG group developed antibodies to hCG postadministration of the drug.

## DISCUSSION

It is a well-established fact that mid-cycle LH surge is the event which triggers the final oocyte maturation and ovulation. Due to the structural homology and binding to same receptor, the LH-chorionic gonadotropin receptor (LHCGR), hCG mimics the biological action of LH. However, the circulating half-life of hCG is much longer (28–30 h), compared with LH (10–12 h).<sup>[11,12]</sup> The receptor binding affinity at LHCGR is also stronger with hCG and in combination with its longer circulatory half-life makes it 5 times as potent as LH.<sup>[13-15]</sup> In practice, hCG is administered for the final follicular maturation and ovulation. The introduction of a recombinant version of hCG has minimized the concerns associated with u-hCG – risk of infection, risk of immunogenicity, and uneven biological potency.<sup>[16]</sup> This randomized controlled study was performed to compare the efficacy and safety of a new r-hCG preparation with a marketed brand of r-hCG (Ovitrelle).

In this well-matched subject population, the two treatment groups presented no difference in ovulation rates. The

**Table 1: Demographic and baseline characteristics**

Parameter	Test r-hCG	Ovitrelle®	P*
Age (years), mean $\pm$ SD	28.5 $\pm$ 4.0	28.7 $\pm$ 4.1	0.73
Weight (kg), mean $\pm$ SD	56.4 $\pm$ 8.2	55.5 $\pm$ 9.6	0.47
Height (cm), mean $\pm$ SD	155.8 $\pm$ 8.5	156 $\pm$ 7.4	0.86
Infertility duration (months), mean $\pm$ SD	57.3 $\pm$ 38.8	66.5 $\pm$ 46.2	0.12
Reason of infertility, n (%)			
Unexplained	95/144 (66)	48/73 (65.8)	
Male factor	13/144 (9)	8/73 (11)	
Local pathology	5/144 (3.5)	5/73 (6.8)	
Endometriosis	9/144 (6.3)	6/73 (8.2)	
PCOS	12/144 (8.3)	2/73 (2.7)	
Not recorded	10/144 (6.9)	4/73 (5.5)	
Primary: Secondary infertility (n)	137:7	71:2	0.72
Previous treatment cycles, n (%)			
0	73/144 (50.7)	40/73 (54.8)	
1	41/144 (28.5)	15/73 (20.5)	
2	24/144 (16.7)	11/73 (15.1)	
3	4/144 (2.8)	6/73 (8.2)	
6	0/144 (0)	1/73 (1.4)	
8	1/144 (0.7)	0/73 (0)	
Not known	1/144 (0.7)	0/73 (0)	
Antral follicle count, mean $\pm$ SD	9.2 $\pm$ 4.8	9.5 $\pm$ 6.0	0.69
Endometrial thickness (cm), mean $\pm$ SD	8.4 $\pm$ 2.3	9.0 $\pm$ 2.1	0.06

\*Calculated by independent samples *t*-test. PCOS=Polycystic ovarian syndrome; SD=Standard deviation; r-hCG=Recombinant human chorionic gonadotropin

**Table 2: Efficacy data**

Parameter	Test r-hCG (n=144)	Ovitrelle (n=73)	P
Ovulation rate, n (%)	123 (85.4)	57 (78.1)	0.17*
Serum hCG (IU/L), mean $\pm$ SD	64.3 $\pm$ 40.5	101.7 $\pm$ 64.5	- <sup>†</sup>
Biochemical pregnancy rate, n (%)	17 (11.8)	9 (12.3)	0.91*

\*Calculated using Chi-squared test; <sup>†</sup>Not compared due to nonuniformity in measurement across sites. SD=Standard deviation; r-hCG=Recombinant human chorionic gonadotropin; hCG=Human chorionic gonadotropin

percentage of individuals with positive biochemical pregnancy test was also similar for both groups. The serum levels of hCG, 36 h after administration of r-hCG, was much higher in both groups than expected without exogenous addition at the particular stage of the cycle. However, they were not similar in the two groups, possibly due to lack of uniformity among the study sites in the collection time and estimation of hCG levels at the different laboratories. It has been reported that the hCG levels correlate with body mass index and age of the

**Table 3: Safety data**

Group	Age	ADR	Severity	Seriousness	Outcome	Causality*
Test r-hCG	24	Dysuria	Mild	Nonserious	Complete recovery	Unrelated
Test r-hCG	30	Headache	Mild	Nonserious	Complete recovery	Unrelated
Test r-hCG	23	Fever	Mild	Nonserious	Complete recovery	Unrelated
Test r-hCG	30	Weakness	Moderate	Nonserious	Complete recovery	Unrelated
		Loss of appetite	Moderate	Nonserious	Complete recovery	Unrelated
Test r-hCG	34	Headache (1 <sup>st</sup> episode)	Moderate	Nonserious	Complete recovery	Unrelated
		Tingling Numbness	Moderate	Nonserious	Complete recovery	Unrelated
		Headache (2 <sup>nd</sup> episode)	Mild	Nonserious	Complete recovery	Unrelated
Test r-hCG	35	Loose motion	Mild	Nonserious	Complete recovery	Unrelated
Test r-hCG	25	Burning micturition	Moderate	Nonserious	Complete recovery	Unrelated
Test r-hCG	24	Indigestion	Moderate	Nonserious	Complete recovery	Unrelated
Ovitrelle	29	Weakness	Mild	Nonserious	Complete recovery	Unrelated
		Loss of appetite	Mild	Nonserious	Complete recovery	Unrelated
Ovitrelle	28	Vaginal discharge	Mild	Nonserious	Complete recovery	Unrelated
Ovitrelle	30	Low grade fever with cough	Mild	Nonserious	Complete recovery	Unrelated

\*With respect to study drug. ADR=Adverse drug reactions; r-hCG=Recombinant human chorionic gonadotropin

subject.<sup>[16]</sup> This does not have any clinical impact though since it has been identified that there is no correlation between plasma hCG levels and oocyte maturity, ovulation or pregnancy rate.<sup>[17,18]</sup> The biosimilarity between the new r-HCG preparation and Ovitrelle for efficacy parameters was accompanied by a comparable safety profile with none of the individuals in either group reporting a serious AE. The few AEs reported in the study were all judged to be unrelated to the study treatment. In addition, the new r-hCG preparation did not result in immunogenic reactions in any subject.

The Central Drugs Standard Control Organization (CDSCO - national drug regulatory authority of India) approved the new r-hCG preparation on the basis of the results of this study. The similar safety results, coupled with the comparable physicochemical profiles of the two preparations indicate that any possible differences in glycosylation pattern between the two molecules have no clinical consequences. This indigenous preparation of r-hCG was envisioned as a potentially inexpensive option to the comparator brand and can lead to better accessibility to the drug. The presence of multiple brands is expected to usher in competitive pricing and help the infertility experts provide a cost-effective yet clinically equivalent alternative.

## CONCLUSIONS

The demonstrated clinical equivalence of the new r-hCG preparation to the reference comparator Ovitrelle in this clinical trial suggests that the new preparation may serve as a viable alternative to Ovitrelle.

## Financial support and sponsorship

Bharat Serums and Vaccines Limited provided financial and material support to the study.

## Conflicts of interest

Dr. Gautam Daftary is a Managing Director of Bharat Serums and Vaccines Limited. Dr. Ganesh Divekar and Dr. James John are full-time paid employees of Bharat Serums and Vaccines Limited. Bharat Serums and Vaccines funded the entire study.

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