Original Article

A comparative phase III clinical study to evaluate efficacy and safety of TrastuRel™ (biosimilar trastuzumab) and innovator trastuzumab in patients with metastatic human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer

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Abstract

INTRODUCTION: The present study for biosimilar trastuzumab was a multicentric, randomized, two-arm parallel-group, comparative phase III study in patients with metastatic breast cancer. **MATERIALS AND METHODS:** Stage I of the study was conducted among 42 participants with equal distribution in the study and reference arm. After a loading dose of 8 mg/kg trastuzumab was administered intravenously on day 1 of the first cycle; serum samples were obtained at 0, 1.5 (end of IP infusion), 3, 6, 8, 24, 96, 168, and 336 h after the first infusion for the first cycle only. C_{max} and $AUC_{0–336}$ were calculated for a single dose. Stage II enrolled a total of 106 patients across 20 centers who were randomized to receive biosimilar trastuzumab (study trastuzumab) or the reference trastuzumab with paclitaxel. The primary endpoint of the objective response rate (ORR) was analyzed after last the dosed participant had completed 25-week evaluation. The secondary outcome measures included time to tumor progression, progression-free survival and overall survival at week 48, and safety evaluation. **RESULTS:** For reference and study trastuzumab products, mean C_{max} of 229.02 and 210.68 μg/mL and $AUC_{0–336}$ of 24298.29 and 25809.33 (μg × h/mL), respectively, were obtained. The efficacy results demonstrated that study trastuzumab and reference trastuzumab had comparable ORR (48.44% vs. 44.44%). The proportions of participants showing complete response and partial response in each arm were found to be comparable. There were 56 (68.29%) participants in the study arm and 13 (59.09%) participants in the reference arm who had at least one adverse event during the study. Immunogenicity assessment also revealed no participants with positive antibody titer in any of the study arms. **CONCLUSION:** The pharmacokinetics, overall response rate at 25 weeks, and safety of the biosimilar trastuzumab was comparable to the reference trastuzumab.

Key Words: Breast cancer, complete response, human epidermal growth factor receptor 2+, objective response rate, partial response, pharmacokinetics, trastuzumab

Introduction

Human epidermal growth factor receptor 2 (HER2) protein overexpression and/or gene amplification are observed in approximately 20% of breast cancer cases and are associated with a more aggressive natural history compared with HER2-negative counterparts. Trastuzumab was the first targeted therapy approved by the US Food and Drug Administration for HER2-positive breast cancer and has since led to significant improvements in the overall prognosis for patients with HER2-positive metastatic disease. It is a recombinant humanized monoclonal antibody that selectively targets the extracellular domain of the HER2 receptor. Breast cancers with HER2 protein overexpression (3+) and/or gene amplification by immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH), respectively, derive a large benefit from trastuzumab therapy, whereas those with no or weak (0 or 1+) protein expression and nonamplified gene copy are not benefited.[1,2]

Trastuzumab paired with chemotherapy improves survival in women as the first-line treatment for HER2-overexpressing, metastatic breast cancer. Trastuzumab induces HER2 receptor downmodulation, and as a result, inhibits critical signaling pathways (i.e., ras-Raf-MAPK and PI3K/Akt); trastuzumab also inhibits HER2 cleavage, preceding antibody-induced receptor downmodulation, which might contribute to its antitumor activity in some cancers. *In-vivo* trastuzumab inhibits angiogenesis and induces antibody-dependent cellular cytotoxicity [Figure 1].[3]

Preoperative regimens for HER2-positive tumors should, therefore, incorporate trastuzumab. Biosimilar trastuzumab gives substantial opportunities for availability or access and cost saving. Biosimilars of targeted therapies are evaluated based on a stepwise approach of physicochemical and biological characterization, nonclinical toxicology, pharmacokinetics, and pharmacodynamic phase III studies. Globally, trastuzumab biosimilars have been available in the European Union and US. The present study was a phase III confirmatory clinical trial in India that compared the pharmacokinetics, efficacy, safety, and immunogenicity of the proposed biosimilar trastuzumab from Reliance Life Sciences (RLS) with the reference trastuzumab, in combination with a taxane in patients with measurable HER2-positive metastatic breast cancer at various centers across India based on similar design as global studies.[4-6]

Materials and Methods

This study was a phase III (CTRI/2013/04/003549), randomized, two-arm parallel-group study comparing the study trastuzumab with the reference product across 20 sites in India.

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Eligible female patients included in the trial were >18 years of age with histologically or cytologically confirmed adenocarcinoma of the breast with locally advanced or metastatic disease that was HER2-positive confirmed by positive FISH or IHC 3+ score without prior exposure to chemotherapy or trastuzumab in the metastatic setting. The included participants received adjuvant therapy and/or completed no more than 1 regimen of chemotherapy for metastatic disease. Any previous chemotherapy exposure were completed >3 weeks before randomization. Additional eligibility criteria included an Eastern Cooperative Oncology Group Performance Status of 0–2, at least 1 measurable lesion defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Individuals with baseline left ventricular ejection fraction >50% by echocardiography or multiple gate acquisition scan and estimated life expectancy of >6 months were included in the study.

Exclusion criteria included individuals with severe uncontrolled systemic disease, patients with a history of radiation within 4 weeks prior to the first cycle of chemotherapy in the study or planning radiation during the first 3 cycles of the study, previous bone marrow or stem cell transplantation, concurrent second malignancy or leukemia, myeloid aplasia, aplastic anemia, sickle cell disease and/or lymphoma with marrow involvement and/or known brain metastases, and a history of chemotherapy causing delayed myelosuppression. Patients with a history of trastuzumab administration ≤21 days prior to randomization, a history of intolerance (including Grade 3–4 infusion reaction) or hypersensitivity to trastuzumab were excluded.

The study was conducted in two stages.[4] Stage I (depicting pharmacokinetics) recruited 42 participants in a 1:1 ratio (21 individuals in the study arm and 21 individuals in the innovator drug arm). A loading dose of 8 mg/kg trastuzumab for metastatic HER2-overexpressing breast cancer was administered intravenously on day 1 of the first cycle. Serum samples were obtained at 0, 1.5 (end of IP infusion), 3, 6, 8, 24, 96, 168, and 336 h after the first infusion for the first cycle only. Pharmacokinetic parameters (C_{max} and AUC) were calculated for a single dose of the study and reference trastuzumab for these 42 patients during the first cycle. Pharmacokinetic data with available safety/efficacy data from a subset of these patients (those who had completed multiple cycles) was evaluated.

In the second stage (depicting efficacy and safety), a total of 106 individuals were randomized in the study across the centers in two arms (i.e., biosimilar trastuzumab or study arm and innovator trastuzumab or comparator arm in a 4:1 ratio). After randomization, 84 participants were enrolled in the study arm and 22 individuals in the reference arm. A total of 104 individuals were administered at least a single dose of trastuzumab and were included in the safety evaluation (82 individuals in the study arm and 22 individuals in the reference arm). In the study arm, 80 individuals were administered at least a single dose and 53 individuals completed week 25 evaluation. Twenty individuals were administered at least a single dose in the reference arm, and 15 completed week 25 evaluation. These 100 individuals were considered evaluable individuals for efficacy. Out of these 100 evaluable individuals, 68 individuals (53 in study arm and 15 in reference arm) completed week 25 evaluation in the study. A total of 14 individuals (11 in study arm and 03 in reference arm were discontinued from the study before week 25 due to progressive disease (PD). These 14 participants were considered in the primary efficacy analysis with their last assessment or last observation carried forward (LOCF). Hence, for primary efficacy analysis with LOCF for PD, a total of 82 participants (64 in study arm and 18 in reference arm) were considered. The participant disposition is shown in Figure 2.

A loading dose of 8 mg/kg study or reference trastuzumab for metastatic HER2-overexpressing breast cancer was administered intravenously on day 1 of the first cycle only. Subsequent doses of 6 mg/kg were administered intravenously on the first day of each subsequent 3-week cycle for 2–8 cycles. Trastuzumab was administered intravenously

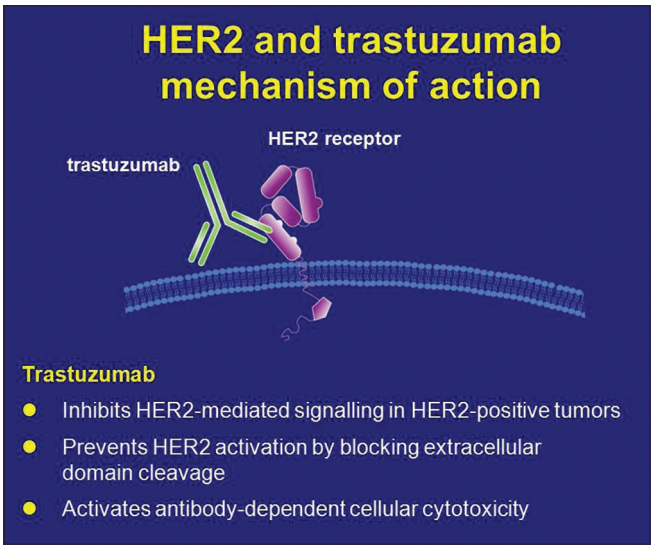

Figure 1: Trastuzumab Mechanism

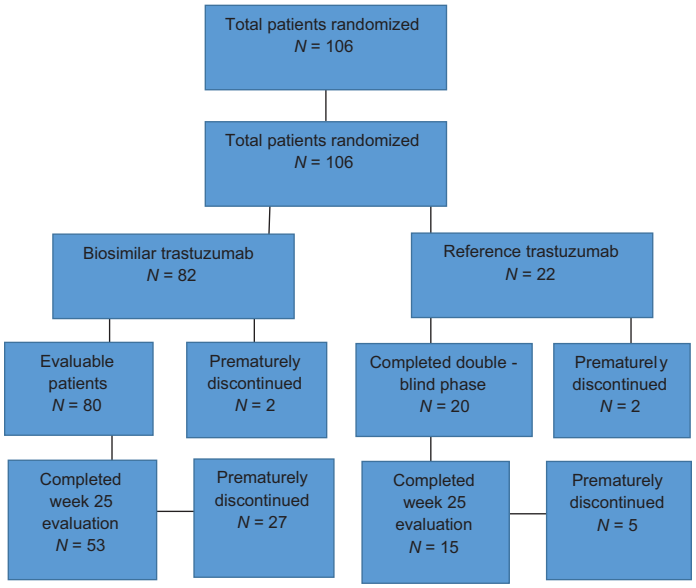

Figure 2: Patient/ Subject disposition

over a 90-min period at all doses. Patients were closely observed for at least 6 h after the start of the first dose of 8 mg/kg of trastuzumab. The first dose 175 mg/m^2 of paclitaxel was given 24 h after the first dose of trastuzumab. Subsequent doses were given at 3-week intervals commencing 30 min after the end of trastuzumab infusion. The respective trastuzumab plus a taxane was administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration.

Evaluations from the end of treatment indicating the onset of a PR or complete response (CR) were followed by a sufficient duration, and evaluation was done at week 25. The primary endpoint of the study was to assess the efficacy as objective response rate (ORR) (CR and partial response [PR]) criteria at week 25. In this study, tumor response was evaluated by CT scan. Based on the size of the lesions, the response of patients to therapy was assessed as per the RECIST 1.1 criteria. As per the protocol and study design, CT scan data were assessed at week 7, week 10, and week 25 for evaluation of response in comparison to the baseline CT scan data for each participant. Lesions were categorized into target lesions, nontarget lesions, and new lesions. An independent assessor verified the assessment of tumor response and his final assessment was considered for evaluating efficacy. Participants who discontinued the study before week 25 due to consent withdrawal or adverse events with their last assessment as PR, CR, stable disease (SD), or no documented PD were excluded from the evaluable population and no LOCF (Last Observation Carry Forward) or any data imputation was done for them.

The randomization schedule was generated by a statistician. Once an individual was found to be eligible for randomization, the site requested a randomization code. Randomization was managed centrally. Participant identification number was a unique number having the site number and patient number.

Assuming an ORR of approximately 17%, a marginal treatment difference of 2%, accrual time of 6 months, treatment period of 24 weeks, randomization ratio of 4:1, and power of more than 80%, a sample size of 105 patients were required including dropouts to show noninferiority.

Results

In Stage I of the study, 42 patients were enrolled and randomized for comparative pharmacokinetic and statistical analysis. For the reference and study products, mean C_{max} of 229.02 and 210.68 μg/mL, $AUC_{0–336}$ of 24298.29 and 25809.33 (μg × h/mL), and $AUC_{0-\infty}$ of 40149.92 and 41681.23 (μg × h/mL), respectively, for trastuzumab. Mean t_{max} was achieved at 2.83 h (median: 1.50 h) and 3.45 h (median: 3.00 h) and t1/2 was 238.96 h and 203.78 h, respectively, for reference and study trastuzumab. Comparison of variability in the pharmacokinetic parameters revealed that variability for lnC_{max} and $lnAUC_{0–336}$ was 25.78 and 41.58, respectively. The observed 90% confidence interval was within the acceptance range of 80.00%–125.00% for Ln-transformed pharmacokinetic parameters C_{max} and $AUC_{0–336}$ for test trastuzumab.

In stage II analysis, comparative analysis (study trastuzumab vs reference innovator product) was performed for primary endpoint data. Intention to treat included all patients who were randomized into the study. A total of 100 participants completed at least one postbaseline efficacy done after any dose of study/reference product and were considered evaluable participants. As shown in Table 1, in total, 82 participants (64 in the study arm and 18 in the reference arm) were included in the efficacy analysis. This population was used for the assessment of primary efficacy endpoint, which included 68 participants with computed tomography (CT) scan evaluation at week 25 and 14 participants with documented PD before week 25. The ORR was observed to be 48.44% in the study arm with 10.94% of the participants showing CR and 37.50% showing PR. The ORR was observed to be 44.44% in the reference trastuzumab arm with 11.11% participants showing CR and 33.33% showing PR. The proportions of participants showing ORR in each arm were compared for statistical significance, and the difference was found to be nonsignificant ($P = 0.764$, $P > 0.05$). The proportions of participants showing CR and PR in each arm were compared for statistical significance, and the difference was found to be nonsignificant ($P > 0.05$).

The percentage of participants showing CR, PR, SD, and PD were comparable in both arms. The proportions of participants showing CR, PR, SD, and PD in each arm were compared for statistical significance, and the difference was found to be nonsignificant ($P > 0.05$) [Table 2].

The proportions of individuals who completed week 25 visits and had efficacy evaluation were comparable in both treatment arms.

The analysis performed to evaluate the response rate in participants with CT evaluation at week 25 without considering any LOCF or data imputation was also comparable in both treatment arms. The overall response rate without considering any LOCF was 58.49% in the study trastuzumab arm with 13.21% participants showing CR and 45.28% showing PR. The overall response rate was observed to be 53.33% in the reference arm with 13.33%

Table 1: Efficacy Evaluation at Week 25 (*N*=82)

Assessed at Week 25	Response	Biosimiar Trastuzumab *N*=64(%)	Innovator Trastuzumab *N*=18(%)	*P*
	CR	07 (10.94)	2 (11.11)	1.00
	PR	24 (37.50)	6 (33.33)	0.742
	ORR	31 (48.44)	8 (44.44)	0.761

Table 2: Summary of overall response (week 25)

Response	Biosimiar Trastuzumab *N*=64(%)	Innovator Trastuzumab *N*=18(%)
CR	07 (10.94)	2 (11.11)
PR	24 (37.50)	6 (33.33)
SD	11 (17.19)	3 (16.67)
PD	21 (32.81)	7 (38.89)
ORR	31 (48.44)	8 (44.44)

participants showing CR and 40.00% showing PR. The proportions of participants showing ORR in each arm were compared for statistical significance and the difference was found to be nonsignificant (P = 0.723).

A total of 104 participants who were dosed were considered for safety analysis. A total of 82 evaluable participants were included from the study arm and 22 from the reference innovator arm. A summary of all adverse events is presented in Table 3.

In the present study, 256 adverse events were reported out of which 196 were reported in the study trastuzumab arm and 60 were reported in the reference arm. There were 68.29% participants in study trastuzumab arm and 59.09% participants in the reference arm who had at least one adverse event in the study.

There were 67.07% participants in the study arm and 59.09% in the reference arm with at least one treatment-emergent adverse event (TEAE) in the study. With respect to at least one TEAE related to study medication, there were 24.39% participants in the study arm and 36.36% in the reference arm.

According to system organ class (SOC) in the study arm, the most commonly reported (incidence ≥5%) TEAEs were related to general disorders and administration site conditions, 25 (30.49%) SOC, followed by nervous system disorders 22 (26.83%), musculoskeletal and connective tissue disorders 17 (20.73%), blood and lymphatic system disorders 15 (18.29%), and gastrointestinal disorders 14 (17.07%).

In the reference arm, the most commonly reported (incidence ≥5%) TEAEs were related to general disorders and administration site conditions 9 (40.91%), followed by nervous system disorders 4 (18.18%), gastrointestinal disorders 4 (18.18%), infections and infestations 4 (18.18%), and musculoskeletal and connective tissue disorders 3 (13.64%). Gastrointestinal disorders mainly included constipation 3 (13.64%), vomiting 3 (13.64%), diarrhea 2 (9.09%), and upper abdominal pain 1 (4.55%).

In this study, 16 serious adverse events (SAEs) were reported. As per the MedDRA coding (Version 16.1, Oracle Corporation, California, USA.), these 16 SAEs were coded into a total of 19 SAE terms (of which 10 were reported in the study arm and 9 in the reference trastuzumab arm). A total of 5 deaths were reported in the study, 3 (3.66%) in the study arm and 2 (9.09%) in the reference arm, with cause of death not ascertained in 4 cases and possibly related to taxane in 1 case from the reference arm. No infusion-related reaction was reported in this study.

Immunogenicity assessment was done using the ELISA technique. A total of 53 participants receiving the study trastuzumab or the reference innovator drug were analyzed for antibody titer. The range of antibody titer was 0.839–1.953 for either arm. During analysis, no sample was found positive for trastuzumab binding antibodies, and no apparent confirmed immunologically mediated safety or efficacy concern was reported in the study.

Discussion

The breast cancer prognosis as well as response to therapy is influenced by different factors including cancer size and stage, histologic type, age, as well as genetic and biological markers. Breast cancer overexpressing the (HER2+ tumors) are very difficult to treat and manage because of the high incidence of metastasis to bone, brain, and liver.[7] Approximately, 20% of breast cancers overexpress HER2, a transmembrane glycoprotein epidermal growth factor receptor with tyrosine kinase activity. Trastuzumab, a humanized monoclonal antibody directed against HER-2 (proto-oncogene), improves the survival and quality of life when given in combination with taxanes as the first-line therapy in women with metastatic breast cancer.[8]

In the present study, biosimilar of trastuzumab for breast cancer over-expressing the (HER2 + tumors), was evaluated for clinical biosimilarity with the reference innovator trastuzumab. Cardiac toxicity continues to limit the use of trastuzumab in metastatic breast cancer patients, specifically in patients with prior anthracycline exposure or other risk factors for cardiomyopathy. As alternatives to anthracyclines, taxanes are more appropriate.[9] The study was conducted in two stages. In the first stage, 42 participants were analyzed for pharmacokinetic similarity, and in the second stage, a total of 106 participants were randomized for the evaluation of efficacy and safety in metastatic breast cancer. The study and reference arm dosages were according to the standard guidelines. Pharmacokinetic parameters were calculated for a single dose of the study and reference product in 42 participants distributed equally in the study and reference arm. Statistically mean C_{max} was comparable in both arms. The AUC_{0-336} was comparable in both arms, but the concentration achieved over this timeframe is on the higher side for the study product compared to the reference. The observed PK results of study trastuzumab have no bearing on the safety and efficacy profile of the biosimilar product.

Table 3: Summary of all adverse events [safety population (*N*=104)

Variable	Biosimilar trastuzumab (*n*=82) *N*,%,E	Innovator molecule (*n*=22) *N*,%,E	*P*
Subject with at least	56 (68.29) 196	13 (59.09) 60	0.431
One adverse event			
At least one treatment	55 (67.07) 193	13 (59.09) 59	0.495
Emergent adverse event			
Death	03 (3.66) 04	02 (9.09) 03	0.285
Subjects discontinued due to	03 (3.66) 10	01 (4.55) 6	1.00
TE adverse event			

This study confirmed that biosimilar trastuzumab improves the overall response rate when combined with chemotherapy for HER2+ breast cancer. The proportions of participants showing CR, PR, SD, and PD in each arm were compared for statistical significance, and the difference was found to be nonsignificant ($P > 0.05$). The effect size was similar to the reference innovator trastuzumab with no significant statistical difference. The safety profile of biosimilar trastuzumab documented in this study was similar to that observed for the reference trastuzumab. The percentage of participants with adverse events in each arm were compared for statistical significance, and the difference was found to be nonsignificant ($P > 0.05$). During analysis, no sample was found to be positive in the study or the reference drug arms for binding antibodies. No new confirmed immunologically mediated major clinical observation related to safety or efficacy were reported in this study. The adverse event profile in the two arms was in line with the known profile of trastuzumab.

Conclusion

Trastuzumab, a humanized monoclonal antibody directed against HER-2, improves the survival and quality of life when given in combination with taxanes as the first-line therapy in women with metastatic breast cancer.[10] The present study was conducted with the intention to establish the clinical biosimilarity of biosimilar trastuzumab to the reference innovator trastuzumab. The combination of TrastuRel™ (biosimilar trastuzumab) with chemotherapy compared to the reference innovator trastuzumab with chemotherapy was found to be noninferior or clinically biosimilar to reference trastuzumab, and can be a suitable treatment equivalent for the medical fraternity in their real-time practice in the management of HER positive breast cancer providing cost benefits.[11]

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Nil.

Conflicts of interest

There are no conflicts of interest.

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