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Effect of a Proposed Trastuzumab Biosimilar Compared With Trastuzumab on Overall Response Rate in Patients With ERBB2 (HER2)–Positive Metastatic Breast Cancer
A Randomized Clinical Trial

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IMPORTANCE Treatment with the anti-ERBB2 humanized monoclonal antibody trastuzumab and chemotherapy significantly improves outcome in patients with ERBB2 (HER2)–positive metastatic breast cancer; a clinically effective biosimilar may help increase access to this therapy.

OBJECTIVE To compare the overall response rate and assess the safety of a proposed trastuzumab biosimilar plus a taxane or trastuzumab plus a taxane in patients without prior treatment for ERBB2-positive metastatic breast cancer.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, double-blind, randomized, parallel-group, phase 3 equivalence study in patients with metastatic breast cancer. From December 2012 to August 2015, 500 patients were randomized 1:1 to receive a proposed biosimilar or trastuzumab plus a taxane. Chemotherapy was administered for at least 24 weeks followed by antibody alone until unacceptable toxic effects or disease progression occurred.

INTERVENTIONS Proposed biosimilar (n = 230) or trastuzumab (n = 228) with a taxane.

MAIN OUTCOMES AND MEASURES The primary outcome was week 24 overall response rate (ORR) defined as complete or partial response. Equivalence boundaries were 0.81 to 1.24 with a 90% CI for ORR ratio (proposed biosimilar/trastuzumab) and −15% to 15% with a 95% CI for ORR difference. Secondary outcome measures included time to tumor progression, progression-free and overall survival at week 48, and adverse events.

RESULTS Among 500 women randomized, the intention-to-treat population included 458 women (mean [SD] age, 53.6 [11.11] years) and the safety population included 493 women. The ORR was 69.6% (95% CI, 63.62%-75.51%) for the proposed biosimilar vs 64.0% (95% CI, 57.81%-70.26%) for trastuzumab. The ORR ratio (1.09; 90% CI, 0.974-1.211) and ORR difference (5.53; 95% CI, −3.08 to 14.04) were within the equivalence boundaries. At week 48, there was no statistically significant difference with the proposed biosimilar vs trastuzumab for time to tumor progression (41.3% vs 43.0%; −1.7%; 95% CI, −11.1% to 6.9%), progression-free survival (44.3% vs 44.7%; −0.4%; 95% CI, −9.4% to 8.7%), or overall survival (89.1% vs 85.1%; 4.0%; 95% CI, −2.1% to 10.3%). In the proposed biosimilar and trastuzumab groups, 239 (98.6%) and 233 (94.7%) had at least 1 adverse event, the most common including neutropenia (57.5% vs 53.3%), peripheral neuropathy (23.1% vs 24.8%), and diarrhea (20.6% vs 20.7%).

CONCLUSIONS AND RELEVANCE Among women with ERBB2-positive metastatic breast cancer receiving taxanes, the use of a proposed trastuzumab biosimilar compared with trastuzumab resulted in an equivalent overall response rate at 24 weeks. Further study is needed to assess safety and long-term clinical outcome.

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Editorial

Supplemental content

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Group Information: A complete list of the Heritage Study Investigators is provided in the eAppendix in Supplement 1.

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Biological agents, including monoclonal antibodies, have increased the treatment options and greatly improved outcomes for a number of cancers.[1,2] However, patient access to these biologics is limited in many countries.[3-5] With impending patent expiration of some biological agents, development of biosimilars has become a high priority for drug developers and health authorities throughout the world to provide access to high-quality alternatives.[6]

Trastuzumab combined with chemotherapy has markedly improved response, progression-free survival (PFS), and overall survival for ERBB2 (formerly human epidermal growth factor receptor 2 [HER2] or HER2/neu)-positive metastatic breast cancer and improved survival in early-stage ERBB2-positive breast cancer[7-9] and metastatic ERBB2-positive gastric cancer compared with chemotherapy alone.[10] The efficacy and safety of the proposed trastuzumab biosimilar were evaluated based on a stepwise approach of physicochemical and biological characterization, nonclinical, pharmacokinetic, and pharmacodynamic studies.[11] This phase 3 confirmatory clinical study (Heritage Study) compared the efficacy, safety, and immunogenicity of the proposed biosimilar in combination with a taxane vs the reference drug trastuzumab in combination with a taxane in patients with measurable ERBB2-positive metastatic breast cancer.

Key Points

Question Are the effects of a proposed trastuzumab biosimilar equivalent to those of trastuzumab in the treatment of ERBB2 (formerly HER2 or HER2/neu)–positive metastatic breast cancer?

Findings In this randomized clinical trial that included 458 women, the overall response rate to the proposed biosimilar plus a taxane at 24 weeks was 69.6% (95% CI, 63.62%-75.51%) compared with 64.0% (95% CI, 57.81%-70.26%) for trastuzumab plus a taxane, which was within predefined equivalence boundaries.

Meaning Although further assessment is needed to establish long-term clinical outcomes and safety, the availability of a clinically effective biosimilar treatment option for trastuzumab may lead to broader access to this therapy for patients with breast cancer.

Methods

Heritage Study Design and Objectives

This was a multicenter, international, double-blind, randomized, parallel-group, phase 3 study comparing the efficacy and safety of a proposed trastuzumab biosimilar plus a taxane (docetaxel or paclitaxel by physician choice) vs trastuzumab plus a taxane in patients with ERBB2-positive metastatic breast cancer (part 1) (**Figure**), with continuation of either the proposed biosimilar or trastuzumab for participants who had at least stable disease to evaluate continued safety and immunogenicity (part 2). In part 1, patients were randomized in a 1:1 ratio to the 2 treatment groups within 3 days prior to cycle 1 (day 1). After completing a minimum of 8 cycles (24 weeks), participants with at least stable disease (based on radiographic tumor assessments and clinical evaluation) were eligible for part 2. In part 2, patients continued to receive their originally allocated treatment until the occurrence of disease progression, unacceptable toxic effects, or death. The results of part 1 of this 24-week study are presented together with time to tumor progression (TTP), PFS, and overall survival for patients with 48 weeks of follow-up. The complete results from part 2 will be presented in a future publication.

This study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use tripartite guideline on the ethical principles of good clinical practice (guideline E6) and applicable regulatory requirements including the archiving of essential documents. All study patients provided written informed consent, and patients with breast cancer treated at study sites had the opportunity to decline participation. The full trial protocol (available in Supplement 2), the patient information and consent form, and other relevant study documentation were approved by the institutional review board or ethics committee at each study center before initiation of the study. Informed consent was obtained in writing from all study participants prior to enrollment. Race and ethnicity were reported as part of standard patient demographic data and were classified by the investigator using predefined options, including Asian, black/African American, Caucasian, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native, and other.

Eligibility

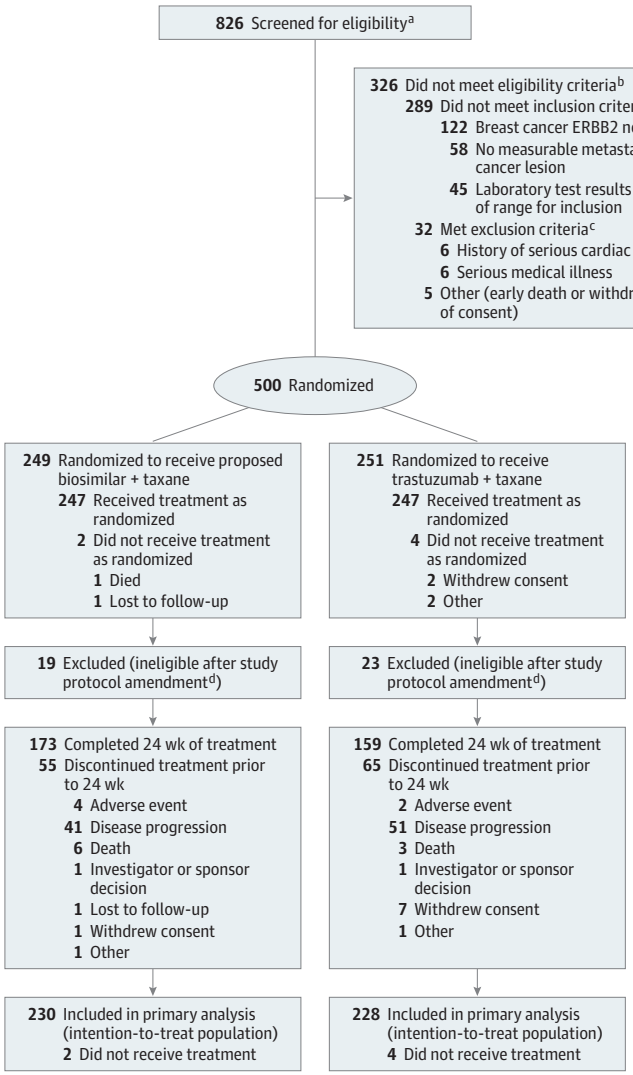
Eligible patients were male or female with breast cancer that was measurably ERBB2 positive (defined as central laboratory documentation of ERBB2-positive overexpression by immunohistochemistry [IHC], ie, IHC3+, or IHC2+ with fluorescent in situ hybridization confirmation [ratio >2]) without prior exposure to chemotherapy or trastuzumab in the metastatic setting. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2, left ventricular ejection fraction (LVEF) within institutional range of normal, and at least 1 year since adjuvant therapy with trastuzumab. Patients with newly detected central nervous system metastases had to have stable disease following treatment (eg, radiotherapy, stereotactic radiosurgery). Hormonal agents had to be discontinued before beginning study therapy. The full inclusion and exclusion criteria are listed in the trial protocol in Supplement 2.

Exclusion criteria included a history of unstable angina, heart failure, myocardial infarction less than 1 year from randomization, or other clinically significant cardiac disease, grade 2 or higher peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, a history of any other cancer within 5 years prior to screening with the exception of in situ cancers or nonmelanomatous skin cancers, or significant medical illness that would increase the risk of treatment or impede evaluation of response in the judgment of the treatment physician.

Treatment

Patients were randomized in a 1:1 ratio to the proposed biosimilar plus a taxane or to trastuzumab plus a taxane. A centralized randomization procedure was used with preallocated blocks.

Figure. Flow of Patients Through the Trial



[a] Nine patients were rescreened (only counted once in the total number of patients screened).

[b] All reasons for screening failures were not reported by all study sites.

[c] Exclusion criteria included a history of unstable angina, heart failure, myocardial infarction less than 1 year from randomization, or other clinically significant cardiac disease, grade 2 or higher peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, a history of any other cancer within 5 years prior to screening with the exception of in situ cancers or nonmelanomatous skin cancers, or serious medical illness that would increase the risk of treatment or impede evaluation of response in the judgment of the treatment physician.

[d] Protocol amendment changed eligibility criteria to exclude patients who had already received first-line therapy. This allowed performance of the primary efficacy analyses in a homogeneous patient population.

A blocking size of 8 was used in the treatment assignment. Patients were stratified at randomization based on 3 factors, including tumor progression to metastatic phase in 2 or fewer years or more than 2 years after primary diagnosis, centrally determined estrogen receptor and progesterone receptor status (≥1 positive or both negative), and type of taxane; each factor consisted of 2 levels, resulting in a total of 8 stratification combinations. Treatment allocation was blinded using an interactive voice response or interactive web response system.

Trastuzumab (Herceptin; Roche Pharma AG) or the proposed biosimilar (MYL-1401O; Mylan) was administered as an intravenous infusion every 3 weeks. An initial 8-mg/kg loading dose was administered over 90 minutes, followed by dosing every 3 weeks of 6 mg/kg over 30 minutes.

The choice of taxane (docetaxel or paclitaxel) was by investigator decision at each study site and was applied to all patients enrolled at that site. Docetaxel was administered at 75 mg/m^2 every 3 weeks and paclitaxel at 80 mg/m^2 weekly. Paclitaxel could be omitted by investigator choice for 1 week every 4 weeks.

The proposed biosimilar plus a taxane or trastuzumab plus a taxane was administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration) unless the participant experienced unacceptable adverse effects, had disease progression, or was prematurely withdrawn from treatment. In patients with responding or stable disease, chemotherapy could be discontinued after 8 treatment cycles; trastuzumab was continued every 3 weeks until disease progression occurred.

Tumor assessments were conducted every 6 weeks. Computed tomography or magnetic resonance imaging of the chest and upper abdomen and, if clinically indicated, bone and/or brain imaging were performed to quantify disease burden. Images were sent electronically to Parexel

Table 1. Patient Demographic Characteristics, Disease History, and Baseline Characteristics in the Intention-to-Treat Population

Characteristic	Proposed Biosimilar + Taxane (n = 230)	Trastuzumab + Taxane (n = 228)
Age		
Mean (SD), y	54.3 (10.97)	52.9 (11.22)
Median (range), y	55.0 (26-79)	54.0 (26-82)
<50 y, No. (%)	74 (32.2)	86 (37.7)
≥50 y, No. (%)	156 (67.8)	142 (62.3)
Race, No. (%)		
Asian	70 (30.4)	72 (31.6)
Black or African American	1 (0.4)	2 (0.9)
White	159 (69.1)	154 (67.5)
Previous treatment, No. (%)		
Trastuzumab	22 (9.6)	16 (7.0)
Taxane	46 (20.0)	42 (18.4)
Assigned taxane, No. (%)		
Docetaxel	193 (83.9)	192 (84.2)
Paclitaxel	35 (15.2)	32 (14.0)
No treatment	2 (0.9)	4 (1.8)
Tumor endocrine status, No. (%)		
ER and PR negative	128 (55.7)	127 (55.7)
ER and/or PR positive	102 (44.3)	101 (44.3)
ECOG Performance Status, No. (%)[a]	(n = 247)	(n = 246)
0	127 (51.4)	107 (43.5)
1	115 (46.6)	132 (53.7)
2	5 (2.0)	6 (2.4)
Missing	0	1 (0.4)
LVEF, %[a]	(n = 246)	(n = 244)
Mean (SD)	64.0 (5.79)	64.1 (5.71)
Median (range)	64.0 (51-82)	63.0 (51-84)
ADA, No. (%)[a]	(n = 247)	(n = 246)
Positive	14 (5.7)	22 (8.9)
Negative	233 (94.3)	224 (91.1)
Antibody titer[b]		
Mean (95% CI)	2.8 (1.7-3.9)	2.5 (1.8-3.2)
Median (range)	2.2 (1-7.1)	2.3 (1-6.9)
ERBB2 ECD, No. (%)		
<15 ng/mL	60 (26.1)	46 (20.2)
≥15 ng/mL	162 (70.4)	172 (75.4)
Missing	8 (3.5)	10 (4.4)
Time from initial diagnosis to metastatic disease, No. (%)		
<2 y	146 (63.5)	153 (67.1)
≥2 y	75 (32.6)	71 (31.1)
Missing	9 (3.9)	4 (1.8)
No. of metastatic sites, No. (%)		
1	58 (25.2)	61 (26.8)
2	87 (37.8)	67 (29.4)
3	44 (19.1)	57 (25.0)
≥4	41 (17.8)	43 (18.9)
Presence of visceral metastases, No. (%)		
Yes	172 (74.8)	185 (81.1)
No	58 (25.2)	43 (18.9)
CNS as first site of metastasis, No. (%)		
Yes	1 (0.4)	2 (0.9)
No	229 (99.6)	226 (99.1)

(continued)

Table 1. Patient Demographic Characteristics, Disease History, and Baseline Characteristics in the Intention-to-Treat Population (continued)

Abbreviations: ADA, antidrug antibody; CNS, central nervous system; ECD, extracellular domain; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; LVEF, left ventricular ejection fraction; PR, progesterone receptor.

[a] Sample sizes are the numbers of patients with available data within the treatment group.

[b] The titer value corresponds to the highest dilution of a sample that yields a positive result in the assay.

Informatics, and tumor measurements were performed by blinded reviewers using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. Responses were confirmed with a second tumor assessment at least 4 weeks after the first response.

End Points

The primary end point was to compare the objective overall response rate (ORR), defined as complete or partial response by RECIST version 1.1 criteria[12] at week 24.

Secondary end points analyzed at week 48 included TTP, defined as the time from randomization to the date of first documentation of objective progression; PFS, defined as the time from randomization to first documentation of objective progression or to death due to any cause; and overall survival, defined as the time from randomization to the date of death due to any cause. Analyses of these secondary end points were not adjusted for multiplicity and should therefore be interpreted as exploratory.

Other end points evaluated at both 24 and 48 weeks included adverse events, laboratory assessments, LVEF, and immunogenicity. Population pharmacokinetic end points included area under the curve, maximum drug concentration, and minimum drug concentration. All end point assessments were blinded to group assignment.

The investigator was responsible for the detection and documentation of events meeting the criteria and definition of an adverse event. At each visit the participant was asked to report any issues, and the investigator evaluated and monitored any reported event. Clinically relevant observations made by the investigator during the visit were also considered to be an adverse event. Treatment-emergent adverse events, defined as events that began or worsened at or after treatment with the investigational drug and on or within 28 days following the last dose of investigational drug, were the adverse events of interest in this study.

Statistical Analysis

The primary efficacy analysis was conducted in the intention-to-treat (ITT) population (all patients randomized after the amendment as defined in the Figure). Patients with missing data or who were lost to follow-up were categorized based on best response at 24 weeks or at the time of the last tumor assessment. If no response data were available, patients were included as nonresponders. The safety population included all participants who received at least 1 dose of study drug in any amount.

The pharmacokinetic population included all randomized patients who received at least 1 complete dose of study drug and who provided at least 1 postdose sample for pharmacokinetic analysis. The population pharmacokinetic analysis was based on the pharmacokinetic population. A population pharmacokinetic model was developed using a 2-compartment linear model including assessment of covariate effects on the interindividual variability in pharmacokinetic parameters. The effect of ERBB2 extracellular domain on trastuzumab pharmacokinetic levels was evaluated as part of the primary covariate analysis. Observed minimum drug concentration values at the end of cycle 1 and cycle 6 were used to assess the similarity of the proposed biosimilar vs trastuzumab using the 2 one-sided *t* tests statistical approach for bioequivalence.

SAS version 9.3 statistical software (SAS Institute Inc) was used to analyze the data from this study. The statistical analysis plan is provided in Supplement 3.

Primary Efficacy Analysis

The primary efficacy end point was ORR based on central imaging evaluation. Per US Food and Drug Administration (FDA) recommendation (internal written communication with FDA, April 25, 2012), the equivalence analysis was based on the ratio of ORRs with a 90% confidence interval. To compare the primary efficacy end point for the 2 treatment groups, the ratio of the ORRs at week 24 was assessed for statistical significance.

A 2-sided 90% confidence interval for the ratio of ORRs at week 24 was calculated based on the method of logarithmic transformation with no adjustment for covariates. The 2-sided 90% confidence interval was equivalent to 2 one-sided tests at the 5% level. Equivalence was declared if the confidence interval was completely within the equivalence range of 0.81 to 1.24. A 2-sided 95% confidence interval was also calculated for exploratory purposes.

The European Medicines Agency (EMA) requested that the difference in ORRs be used as the primary efficacy analysis, using a 95% confidence interval (internal written communication with EMA, March 15, 2013). A 2-sided 95% confidence interval for the difference of the ORRs at week 24 was calculated. Equivalence was declared if the confidence interval was completely within the equivalence range of −15% to 15%.

The equivalence margins for ORR were derived based on meta-analysis of ORR from previous randomized trials.[13-15] The final clinical justification was determined by relating ORR with PFS using the weighted least squares regression model. Through the weighted least squares regression model, the boundaries of the equivalence margins correspond to a deviation of 1.9 months or less from a median PFS of 12 months, which was not considered to be clinically meaningful.

Secondary Efficacy Analysis

Secondary end points included TTP, PFS (centrally confirmed), and overall survival (investigator assessed) at week 48. Kaplan-Meier plots by treatment and the unadjusted log-rank test for any covariates were performed. Cox proportional hazards model was used to analyze for treatment effects, adjusting for subgroup. Univariate analysis and multivariate analysis with forward selection were performed. Hazard ratios and 95% confidence intervals were calculated.

Sample Size Calculation

Per FDA recommendation, the equivalence analysis was based on the ratio of ORRs using historical randomized trastuzumab trials[13-15] with a fixed-effects meta-analysis (statistical analysis plan in Supplement 3) to estimate the treatment effect of trastuzumab plus chemotherapy vs chemotherapy alone.

Sample sizes of 410 patients for the FDA-recommended end point and 400 patients for the EMA-recommended end point were required to provide at least 80% power to declare the proposed biosimilar equivalent to trastuzumab in the analysis of ORR at week 24. These sample sizes assumed that both treatment groups would exhibit an ORR of 69% at week 24,[16] that the ratio of ORR for the proposed biosimilar to trastuzumab would be analyzed with a 2-sided 90% confidence interval, and that the difference between the 2 groups would be analyzed with a 2-sided 95% confidence interval. Therefore, a sample size of 410 patients was chosen to satisfy the recommendations of both regulatory agencies for equivalence analysis. To arrive at the planned number of patients, the required sample size of 410 was increased to 456 to reflect an estimated 10% attrition rate.

Additional Analysis

A description of the secondary efficacy analysis, including TTP, PFS, overall survival, immunogenicity, population pharmacokinetics, and safety, is provided in the statistical analysis plan (Supplement 3). Sensitivity and exploratory analyses are also described in the statistical analysis plan (Supplement 3).

To evaluate site-specific effects, an unplanned mixed-effect analysis was performed. Specifically, the generalized linear mixed model (Proc GLIMMIX in SAS) was fit with ORR as the response variable, site as random effect, and the other factors or covariates (treatment, age, race, previous adjuvant or neoadjuvant chemotherapy or HER2-targeted treatment [yes or no], number of visceral metastases, number of metastatic sites, central nervous system as first site of metastasis, and stratification factor) as fixed effects.

Protocol Amendment

A protocol amendment changed eligibility criteria after 42 patients were enrolled to exclude patients who had already received first-line therapy based on steering committee recommendations to include a homogeneous patient population. These patients were excluded from the primary ITT analysis population (see protocol amendments in the trial protocol in Supplement 2).

Table 2. Primary Outcome: Ratio and Difference of Overall Response Rate at Week 24 in the Intention-to-Treat Population

Response[a]	Proposed Biosimilar + Taxane (n = 230)	Trastuzumab + Taxane (n = 228)	Difference, %	Rate Ratio
Response type, No. (%)				
Complete	3 (1.3)	0		
Partial	157 (68.3)	146 (64.0)		
Stable disease	48 (20.9)	49 (21.5)		
Progressive disease	9 (3.9)	20 (8.8)		
Not evaluable	13 (5.7)	13 (5.7)		
Overall response rate				
Overall response, No. (%)[b]	160 (69.6)	146 (64.0)	5.53[c]	1.09[d]
90% CI, %	64.57 to 74.56	58.81 to 69.26	−1.70 to 12.69	0.974 to 1.211
95% CI, %	63.62 to 75.51	57.81 to 70.26	−3.08 to 14.04	0.954 to 1.237

[a] Response criteria were based on Response Evaluation Criteria in Solid Tumors version 1.1 criteria. Complete response indicates disappearance of all target lesions; partial response, at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; stable disease, neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started; and progressive disease, at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of 1 or more new lesions.

[b] Overall response includes complete and partial response.

[c] European Medicines Agency–recommended analysis.

[d] US Food and Drug Administration–recommended analysis.

Results

Patient Demographics, Disease History, and Baseline Characteristics

At a total of 95 sites in Bulgaria, Chile, Czech Republic, Georgia, Hungary, India, Latvia, Philippines, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Thailand, and Ukraine, 500 patients with ERBB2-positive metastatic breast cancer were enrolled between December 10, 2012, and August 5, 2015 (last follow-up visit January 25, 2016) (Figure). Forty-two patients (proposed biosimilar, n = 19; trastuzumab, n = 23) were excluded as ineligible after the protocol amendment. The number of patients enrolled per site ranged from 1 to 28 (median, 3 patients; interquartile range, 5 patients [25th percentile, 2 patients; 75th percentile, 7 patients]) (eTable in Supplement 1). Demographic characteristics were similar for patients in the proposed trastuzumab biosimilar and trastuzumab groups. Disease history and baseline characteristics were comparable in both treatment groups and no clinically relevant differences were observed (**Table 1**).

Among the 458 women in the ITT population, the mean (SD) age was 53.6 (11.11) years (median age, 55 years; range, 26-82 years), with a median age of 55 years (range, 26-79 years) for the proposed biosimilar group and 54 years (range, 26-82 years) for the trastuzumab group. The majority of patients were white (69.1% in the proposed biosimilar group vs 67.5% in the trastuzumab group), followed by Asian (30.4% in the proposed biosimilar group vs 31.6% in the trastuzumab group). All patients were female.

Tumors were estrogen receptor negative and progesterone receptor negative in 55.7% of patients in both treatment groups. A higher percentage of patients in the proposed biosimilar group had an ECOG Performance Status of 0 compared with the trastuzumab group (51.4% vs 43.5%, respectively). Among patients with ERBB2 extracellular domain values available, baseline values for ERBB2 extracellular domain were higher in the trastuzumab group compared with the proposed biosimilar group (ERBB2 extracellular domain ≥15 ng/mL in 162 of 222 patients [73.0%] in the proposed biosimilar group vs 172 of 218 patients [78.9%] of the trastuzumab group). Stratification of patients at randomization by type of taxane resulted in similar distribution between treatment groups of docetaxel (83.9% in the proposed biosimilar group and 84.2% in the trastuzumab group) and paclitaxel (15.2% in the proposed biosimilar group and 14.0% in the trastuzumab group).

Patient Disposition

Of the 230 patients in the ITT population randomized to the proposed biosimilar group, 173 (75.2%) completed all 24 weeks of therapy. Patient disposition is summarized in the Figure. Of the 228 patients in the trastuzumab group in the ITT population, 159 (69.7%) completed 24 weeks of therapy. In the proposed biosimilar and trastuzumab groups, respectively, the primary reason for discontinuation was disease progression (17.8% vs 22.4%), followed by withdrawal of consent (0.4% vs 3.1%) and death (2.6% vs 1.3%). In the ITT population, only 1.7% of participants in the proposed biosimilar group and 0.9% in the trastuzumab group discontinued owing to an adverse event.

Primary Efficacy Analysis

The results of the primary efficacy analysis are summarized in **Table 2**. The ORR was 69.6% (160 of 230 patients) (95% CI, 63.62%-75.51%) in the proposed biosimilar group and 64.0% (146 of 228 patients) (95% CI, 57.81%-70.26%) in the trastuzumab group.

The ratio of the ORR (proposed biosimilar to trastuzumab) was 1.09 (90% CI, 0.974-1.211). The 90% CI was within the predefined equivalence boundaries of 0.81 to 1.24, consistent with statistical therapeutic equivalence of proposed biosimilar and trastuzumab. For the same ratio of 1.09, the 95% CI of the ORR ratio between proposed biosimilar and trastuzumab,

Table 3. Secondary Outcomes: Time to Tumor Progression, Progression-Free Survival, and Overall Survival at Week 48 in the Intention-to-Treat Population

Outcome	Proposed Biosimilar + Taxane (n = 230)	Trastuzumab + Taxane (n = 228)	Log-Rank *P* Value	Unstratified		Stratified[a]	
				Hazard Ratio (95% CI)[b]	*P* Value	Hazard Ratio (95% CI)[b]	*P* Value
Time to Tumor Progression[c]							
Events, No. (%)	95 (41.3)	98 (43.0)	.68	0.94 (0.71-1.25)	.69	0.92 (0.69-1.23)	.58
Censored events, No. (%)[d]	135 (58.7)	130 (57.0)					
Kaplan-Meier estimate, median (95% CI), mo	11.1 (8.83-11.20)	11.1 (8.88-11.20)					
Progression-Free Survival[e]							
Events, No. (%)	102 (44.3)	102 (44.7)	.84	0.97 (0.74-1.28)	.85	0.95 (0.71-1.25)	.69
Censored events, No. (%)[d]	128 (55.7)	126 (55.3)					
Kaplan-Meier estimate, median (95% CI), mo	11.1 (8.81-11.20)	11.1 (8.60-11.20)					
Overall Survival[f]							
Events, No. (%)	25 (10.9)	34 (14.9)	.13	0.67 (0.40-1.13)	.13	0.61 (0.36-1.04)	.07
Censored events, No. (%)[d]	205 (89.1)	194 (85.1)					
Kaplan-Meier estimate, median (95% CI), mo	Not estimable	Not estimable					

[a] Stratified by assigned taxane, tumor progression, and tumor endocrine status. The sample size for both the proposed biosimilar and trastuzumab groups was 220.

[b] The hazard ratio estimates were obtained from the Cox proportional hazards model. A hazard ratio less than 1.0 indicates a lower average event rate and a longer progression-free survival for the proposed biosimilar relative to trastuzumab.

[c] Defined as the time from randomization to the date of first documentation of objective progression, divided by (365.25/12).

[d] Events not occurring before the data cutoff were censored at the date of cutoff or the date of the last tumor assessment.

[e] Defined as the time from randomization to first documentation of objective progression or to death due to any cause, divided by (365.25/12).

[f] Defined as the time from randomization to the date of death due to any cause, divided by (365.25/12).

calculated for exploratory purposes, was 0.954 to 1.237, also within the equivalence boundaries.

The difference in ORR (proposed biosimilar minus trastuzumab) was 5.53 (95% CI, −3.08 to 14.04). This 95% CI was also within the predefined equivalence boundaries of −15% and 15%, consistent with statistical therapeutic equivalence of proposed biosimilar and trastuzumab per EMA recommendation.

The primary efficacy analysis for ORR was also replicated in the per protocol population (n = 438). The ratio between both treatment groups (proposed biosimilar to trastuzumab) was 1.06 (90% CI, 0.954 to 1.178).

Secondary Efficacy Analyses

The 48-week exploratory findings of the secondary efficacy analysis are summarized in **Table 3**.

Time to Tumor Progression

In the proposed biosimilar group, 95 patients (41.3%) had tumor progression at week 48 compared with 98 patients (43.0%) in the trastuzumab group. According to the log-rank test, this difference was not statistically significant (−1.7%; 95% CI, −11.1% to 6.9%; *P* = .68). Hazard ratios for TTP for the proposed biosimilar group compared with the trastuzumab group by Cox proportional hazards model were 0.94 (95% CI, 0.712 to 1.254) (unstratified) and 0.92 (95% CI, 0.692 to 1.231) (stratified). There was no statistically significant difference in TTP between the proposed biosimilar and trastuzumab groups.

Progression-Free Survival

In PFS, the rate of events at week 48 for the proposed biosimilar group was 44.3% compared with 44.7% for trastuzumab, a difference of −0.4% (95% CI, −9.4% to 8.7%; *P* = .84) by log-rank test. Hazard ratios for PFS for the proposed biosimilar group compared with the trastuzumab group obtained from the Cox proportional hazards model were 0.97 (95% CI, 0.740 to 1.282) (unstratified) and 0.95 (95% CI, 0.714 to 1.251) (stratified). There was no statistically significant difference in PFS between the proposed biosimilar and trastuzumab groups.

Overall Survival

Regarding overall survival, in the proposed biosimilar group, 205 patients (89.1%) survived at week 48 compared with 194 patients (85.1%) in the trastuzumab group; this difference of 4.0% (95% CI, −2.1% to 10.3%; *P* = .13) was not statistically significant by log-rank test. Hazard ratios for the proposed biosimilar group compared with the trastuzumab group obtained from the Cox proportional hazards model were 0.67 (95% CI, 0.402 to 1.129) (unstratified) and 0.61 (95% CI, 0.360 to 1.039) (stratified). At 48 weeks, more than 50% of patients had not shown progression; therefore, the median in the time event efficacy parameters may be longer at longer data cutoff.

The median Kaplan-Meier estimates for TTP and PFS at 48 weeks were 11.1 months for both groups. At 48 weeks, fewer than 50% patients had disease progression; therefore, the median in the time event efficacy parameters may be longer in later analyses. The median for overall survival was not reached.

Additional Analysis

The results of an unplanned mixed-effect analysis to evaluate site effects indicated that the covariance parameter estimate of random effect site was 0 and that there was not enough

Table 4. Treatment-Emergent Adverse Events and Serious Adverse Events by Week 24 in the Overall Safety Population

Event	Participants, No. (%)		
	Proposed Biosimilar + Taxane (n = 247)	Trastuzumab + Taxane (n = 246)	Overall (n = 493)
Treatment-Emergent Adverse Events[a]			
≥1 Treatment-emergent adverse event	239 (96.8)	233 (94.7)	472 (95.7)
CTCAE preferred term			
Alopecia	142 (57.5)	135 (54.9)	277 (56.2)
Neutropenia	142 (57.5)	131 (53.3)	273 (55.4)
Peripheral neuropathy	57 (23.1)	61 (24.8)	56 (23.9)
Diarrhea	51 (20.6)	51 (20.7)	102 (20.7)
Asthenia	54 (21.9)	40 (16.3)	94 (19.1)
Leukopenia	42 (17.0)	51 (20.7)	93 (18.9)
Nausea	49 (19.8)	34 (13.8)	83 (16.8)
Anemia	40 (16.2)	40 (16.3)	80 (16.2)
Peripheral edema	35 (14.2)	28 (11.4)	63 (12.8)
Fatigue	28 (11.3)	33 (13.4)	61 (12.4)
Pyrexia	21 (8.5)	30 (12.2)	51 (10.3)
Myalgia	23 (9.3)	23 (9.3)	46 (9.3)
Vomiting	26 (10.5)	19 (7.7)	45 (9.1)
Decreased appetite	21 (8.5)	24 (9.8)	45 (9.1)
Rash	21 (8.5)	23 (9.3)	44 (8.9)
Arthralgia	30 (12.1)	11 (4.5)	41 (8.3)
Alanine aminotransferase increased	18 (7.3)	21 (8.5)	39 (7.9)
Urinary tract infection	21 (8.5)	16 (6.5)	37 (7.5)
Nail disorder	17 (6.9)	20 (8.1)	37 (7.5)
Aspartate aminotransferase increased	13 (5.3)	22 (8.9)	35 (7.1)
Hyperglycemia	13 (5.3)	17 (6.9)	30 (6.1)
Bone pain	17 (6.9)	13 (5.3)	30 (6.1)
Headache	15 (6.1)	15 (6.1)	30 (6.1)
Cough	14 (5.7)	16 (6.5)	30 (6.1)
Dyspnea	13 (5.3)	16 (6.5)	29 (5.9)
Infusion-related reaction	17 (6.9)	11 (4.5)	28 (5.7)
Serious Adverse Events[b]			
≥1 Serious adverse event	94 (38.1)	89 (36.2)	183 (37.1)
CTCAE preferred term			
Neutropenia	68 (27.5)	62 (25.2)	130 (26.4)
Neutropenia with fever	11 (4.5)	10 (4.1)	21 (4.3)
Leukopenia	4 (1.6)	12 (4.9)	16 (3.2)
Pneumonia	4 (1.6)	5 (2.0)	9 (1.8)

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

[a] Treatment-emergent adverse events by week 24 in more than 5% of patients in either treatment group, in descending order of frequency in the overall safety population.

[b] Serious adverse events, defined by the investigator as grade 4 or requiring hospitalization, by week 24 in at least 2% of patients in either treatment group, in descending order of frequency in the overall safety population.

variation of response to attribute variation to random effect, controlling for everything else in the model. In addition, type III test results showed that all fixed effects in the model were not significant, with $P > .11$.

Population Pharmacokinetic Analysis

In the pharmacokinetic population, the mean concentrations of trastuzumab from the 2 treatments were similar (eFigure in Supplement 1). Trough (minimum) drug concentrations were comparable between the treatment groups at cycle 6 (week 15). In the proposed biosimilar and trastuzumab groups, geometric least squares means were 34.011 and 32.740 µg/mL, respectively, with a ratio of 103.88% (90% CI, 93.7%-115.11%). Dose-normalized mean maximum drug concentrations were 0.4321 and 0.4196 µg/mL/mg, respectively, while dose-normalized mean areas under the curve were 98.350 and 94.391 µg · d/mL/mg, respectively, with a coefficient of variation ranging from 21.87% to 31.06%; both of these parameters were comparable.

Safety Evaluation

Extent of Exposure

The extent of exposure was similar between the 2 treatment groups in terms of dose and duration of exposure. The mean (SD) loading dose was 8.0 (0) mg/kg in both treatment groups with similar subsequent dose intensity (2.011 mg/kg/wk for

Table 5. Descriptive Statistics for Cardiac Function (LVEF Values) by Visit in the Safety Population

	LVEF, %			
	Proposed Biosimilar + Taxane (n = 247)		Trastuzumab + Taxane (n = 246)	
Visit and Statistic	Observed	Change From Baseline	Observed	Change From Baseline
Baseline[a,b]	(n = 246)		(n = 244)	
Mean (95% CI)	64.0 (63.3 to 64.7)		64.1 (63.4 to 64.8)	
Median (range)	64.0 (51 to 82)		63.0 (51 to 84)	
Week 12[b]	(n = 212)	(n = 212)	(n = 209)	(n = 207)
Mean (95% CI)	63.3 (62.4 to 64.1)	−1.0 (−1.7 to −0.2)	63.4 (62.6 to 64.2)	−0.8 (−1.5 to −0.2)
Median (range)	63.0 (28 to 79)	−1.0 (−29 to 14)	63.0 (52 to 82)	0.0 (−16 to 14)
Week 24[b]	(n = 148)	(n = 148)	(n = 140)	(n = 138)
Mean (95% CI)	63.6 (62.8 to 64.4)	−0.6 (−1.5 to 0.2)	63.2 (62.2 to 64.2)	−0.9 (−1.8 to −0.1)
Median (range)	63.5 (50 to 81)	−1.0 (−13 to 21)	63.0 (41 to 82)	−1.0 (−19 to 13)

Abbreviation: LVEF, left ventricular ejection fraction.

[a] Screening visit, prior to the first dose of study drug.

[b] Sample sizes are the numbers of patients with available data within the treatment group.

the proposed biosimilar and 2.028 mg/kg/wk for trastuzumab). For part 1, the mean (SD) total exposure was 21.038 (6.4383) weeks for the proposed biosimilar and 20.327 (6.8221) weeks for trastuzumab. The mean (SD) number of cycles received was 7.8 (2.13) for the proposed biosimilar group and 7.5 (2.27) for the trastuzumab group.

Treatment-Emergent Adverse Events

The overall incidence of patients with at least 1 treatment-emergent adverse event was 96.8% (n = 239) in the proposed biosimilar group and 94.7% (n = 233) in the trastuzumab group. The majority of events were mild or moderate in severity in both treatment groups. In the safety population, a total of 14 participants (7 patients [2.8%] in each group) reported an adverse event leading to discontinuation of treatment.

The incidence rates of treatment-emergent adverse events of neutropenia, leukopenia, and anemia were 57.5% (n = 142), 17.0% (n = 42), and 16.2% (n = 40), respectively, in the proposed biosimilar group and 53.3% (n = 131), 20.7% (n = 51), and 16.3% (n = 40), respectively, in the trastuzumab group. Adverse events with Common Terminology Criteria for Adverse Events grade 3 or higher were reported for 312 (63.3%) of all participants, with neutropenia (221 patients [44.8%]) and leukopenia (69 patients [14.0%]) the most frequently reported. The most frequent nonhematologic treatment-emergent adverse events in patients in the proposed biosimilar and trastuzumab groups, respectively, included peripheral neuropathy (57 [23.1%] and 61 [24.8%]), diarrhea (51 [20.6%] and 51 [20.7%]), asthenia (54 [21.9%] and 40 [16.3%]), and nausea (49 [19.8%] and 34 [13.8%]). Common Terminology Criteria for Adverse Events grade 3 events were reported for less than 2% of all participants with these nonhematologic events. Treatment-emergent adverse events are summarized in **Table 4**.

Serious Adverse Events

The overall incidence of patients with at least 1 serious adverse event (SAE) was 38.1% (n = 94) in the proposed biosimilar group and 36.2% (n = 89) in the trastuzumab group (Table 4).

Only 4 SAE preferred terms were reported in at least 2% in either treatment group (Table 4). Overall, the most frequently reported SAE terms were neutropenia (130 patients [26.4%]), febrile neutropenia (21 patients [4.3%]), and leukopenia (16 [3.2%]). No other SAEs were reported in at least 2% of participants.

Eight participants (4 in each group) had SAEs that resulted in death. One death due to respiratory failure in each group was considered "possibly related" to study drug. Other adverse events with fatal outcome were considered related to taxane therapy, related to underlying or progressive disease, or of unknown etiology.

Left Ventricular Ejection Fraction

The LVEF values at baseline in the proposed biosimilar group (median, 64.0%; range, 51%-82%) and in the trastuzumab group (median, 63.0%; range, 51%-84%) did not change appreciably at week 24 (proposed biosimilar group: median, −1.0%; range, −13% to 21%; trastuzumab group: median, −1.0%; range, −19% to 13%) (**Table 5**).

Immunogenicity

Fourteen participants (5.9%) in the proposed biosimilar group and 21 participants (8.9%) in the trastuzumab group were positive for antidrug antibody prior to exposure to study treatment. The number of patients with detectable antibody declined over time.

Using a conservative approach that considers all patients who tested positive for antidrug antibody at least once at any time point after baseline regardless of the antidrug antibody result at baseline, the overall antidrug antibody rate was 2.4% (6 of 245 patients) in the proposed biosimilar group and 2.8% (7 of 246 patients) in the trastuzumab group. The mean and median titers for patients with positive results were low (proposed biosimilar group: mean, 3.2; median, 2.5; trastuzumab group: mean, 2.0; median, 2.3). The highest titers reported at baseline or any time after baseline (7.1 and 8.1, respectively, in the proposed biosimilar group and 5.2 and 5.5, respectively, in the trastuzumab group) confirmed low immunogenicity.

Discussion

Among women with ERBB2-positive metastatic breast cancer, the use of a proposed trastuzumab biosimilar compared

with trastuzumab, each combined with a taxane, resulted in an equivalent ORR after 24 weeks of treatment; specifically, the ORR was 69.6% (160 of 230 patients) (95% CI, 63.62%-75.51%) for the proposed biosimilar and 64.0% (146 of 228 patients) (95% CI, 57.81%-70.26%) for trastuzumab.

Treatment with the anti-ERBB2 humanized monoclonal antibody trastuzumab in combination with chemotherapy, compared with chemotherapy alone, significantly improved PFS and overall survival among patients with ERBB2-positive metastatic breast cancer.[14,15] However, trastuzumab is not widely available around the world.[4] A biosimilar treatment option may increase global access to biological cancer therapies, provided, among other issues, that the price of the biosimilar is sufficiently inexpensive to enable women in non-high-income countries to access this therapy.[6,17,18]

A biosimilar drug is a biological product that is highly similar to a licensed biological product, with no clinically meaningful differences in terms of safety, purity, or potency.[19-21] Confirmation of biosimilarity is based on a stepwise process starting with analytical and nonclinical comparison of structural and in vitro functional characteristics as well as in vivo animal studies, including assessments of toxicity. The nature and extent of data required for regulatory approval are determined on a product-specific basis and depend on the level of evidence obtained in the preceding steps.

This confirmatory efficacy and safety study was the last step in the multistep process to demonstrate similarity of a trastuzumab biosimilar and was adequately powered to demonstrate equivalence with trastuzumab. Pertuzumab (a HER2 dimerization inhibitor) was not added to the treatment groups in this study owing to the lack of worldwide availability of this antibody; the equivalence comparison predated pertuzumab approval.[16] The results of this study are consistent with the physicochemical and functional similarity shown in vitro and in vivo and with the similar pharmacokinetics shown in healthy participants between the candidate biosimilar and trastuzumab.[11]

At week 24, the ORR was 69.6% in the proposed trastuzumab biosimilar group and 64.0% in the trastuzumab group. Therapeutic equivalence of the proposed trastuzumab biosimilar and trastuzumab was statistically supported by the primary efficacy as well as the results of sensitivity analysis in the per protocol population. Additionally, the ORR data were consistent with the published data for trastuzumab.[16,22,23] All secondary efficacy analyses (TTP, PFS, and overall survival) at week 24 and PFS and overall survival in patients followed up for at least 48 weeks supported the conclusion of therapeutic equivalence.

There were no notable differences between the treatment groups with regard to the type, incidence, or severity of treatment-emergent adverse events or between the incidence and type of SAEs reported. The population pharmacokinetic analysis was consistent with the findings from studies in healthy volunteers[11] that demonstrated similar pharmacokinetics between the proposed biosimilar and trastuzumab.

The immunogenicity profile was low, similar between the 2 products and consistent with published data with trastuzumab showing a low immunogenic potential. Baseline positivity for antidrug antibody in a small number of patients is expected. A similar positive rate was observed in previous reports and may be due to potential cross-reactivity with preexisting antibodies and the test's high sensitivity level (previous trastuzumab treatments, high level of extracellular domain).[24,25] Potential interference of trastuzumab with the antitrastuzumab antibody detection assay needs to be considered when assessing the results from posttreatment samples, although the assay was designed to minimize these effects.

This study was designed to assess efficacy and safety in a biosimilar development program in which there is an underlying presumption that a molecule shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting.[6] The limitations of this study are consistent with the planned development of biosimilars, which uses short-term efficacy end points as the final step in assessing biosimilarity. The choice of the 24-week evaluation period for part 1 of this study was related to the ability to analyze the ORR as a short-term measure of clinical activity and safety directly related to the combination of taxanes with trastuzumab and the proposed biosimilar as first-line treatment. This report includes the 48-week TTP, PFS, and overall survival, which add to the efficacy end point assessment. Ongoing follow-up will assess longer-term efficacy and safety information to evaluate the use of the proposed trastuzumab biosimilar alone during the maintenance phase.

Conclusions

Among women with ERBB2-positive metastatic breast cancer receiving taxanes, the use of a proposed trastuzumab biosimilar compared with trastuzumab resulted in an equivalent overall response rate at 24 weeks. Further study is needed to assess safety and long-term clinical outcome.

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