Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): a randomised, double-blind, phase 3 trial

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Summary
Background ABP 980 (Amgen Inc, Thousand Oaks, CA, USA) is a biosimilar of trastuzumab, with analytical, functional, and pharmacokinetic similarities. We compared the clinical safety and efficacy of ABP 980 with that of trastuzumab in women with HER2-positive early breast cancer.

Methods We did a randomised, multicentre, double-blind, active-controlled equivalence trial at 97 study centres in 20 countries, mainly in Europe and South America. Eligible women were aged 18 years or older, had histologically confirmed HER2-positive invasive early breast cancer, an Eastern Cooperative Oncology Group performance status score of 0 or 1, and were planning to have surgical resection of the breast tumour with sentinel or axillary lymph node dissection and neoadjuvant chemotherapy. After four cycles of run-in anthracycline-based chemotherapy, patients were assigned 1:1 to receive ABP 980 or trastuzumab with a permuted block design (blocks of four) computer-generated randomisation schedule. Patients received neoadjuvant therapy with a loading dose (8 mg/kg) of ABP 980 or trastuzumab plus paclitaxel 175 mg/m² in a 90 min intravenous infusion, followed by three cycles of 6 mg/kg intravenous ABP 980 or trastuzumab plus paclitaxel 175 mg/m² every 3 weeks in 30 min intravenous infusions (or 80 mg/m² paclitaxel once per week for 12 cycles if that was the local standard of care). Randomisation was stratified by T stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographical region. Surgery was completed 3–7 weeks after the last dose of neoadjuvant treatment, after which adjuvant treatment with ABP 980 or trastuzumab was given every 3 weeks for up to 1 year after the first dose in the study. Patients had been randomly assigned at baseline to continue ABP 980, continue trastuzumab, or switch from trastuzumab to ABP 980 as their adjuvant treatment. The co-primary efficacy endpoints were risk difference and risk ratio (RR) of pathological complete response in breast tissue and axillary lymph nodes assessed at a local laboratory in all patients who were randomly assigned and received any amount of neoadjuvant investigational product and underwent surgery. We assessed safety in all patients who were randomly assigned and received an adequate amount of investigational product. This trial is registered with ClinicalTrials.gov, number NCT01901146 and Eudra, number CT 2012-004319-29.

Findings Of 827 patients enrolled, 725 were randomly assigned to receive ABP 980 (n=364) or trastuzumab (n=361). The primary endpoint was assessable in 696 patients (358 who received ABP 980 and 338 who received trastuzumab). Pathological complete response was recorded in 172 (48%, 95% CI 43–53) of 358 patients in the ABP 980 group and 137 (41%, 35–46) of 338 in the trastuzumab group (risk difference 7.3%, 90% CI 1.2–13.4; RR 1.188, 90% CI 1.033–1.366), with the upper bounds of the CIs exceeding the predefined equivalence margins of 13% and 1.318, respectively. Pathological complete response in the central laboratory assessment was seen in 162 (48%) of 339 patients assigned to ABP 980 at baseline and 138 (42%) of 330 assigned to trastuzumab at baseline (risk difference 5.8%, 90% CI –0.5 to 12.0, and RR 1.142, 90% CI 0.993 to 1.312). Grade 3 or worse adverse events during the neoadjuvant phase occurred in 54 (15%) of 364 patients in the ABP 980 group and 51 (14%) of 361 patients in the trastuzumab group, of which the most frequent grade 3 or worse event of interest was neutropenia, occurring in 21 (6%) patients in both groups. In the adjuvant phase, grade 3 or worse adverse events occurred in 30 (9%) of 349 patients continuing ABP 980, 11 (6%) of 171 continuing trastuzumab, and 13 (8%) of 171 who switched from trastuzumab to ABP 980, the most frequent grade 3 or worse events of interest were infections and infestations (four [1%], two [1%], and two [1%], neutropenia [three [1%], two [1%], and one [1%]], and infusion reactions [two [1%], two [1%], and three [2%]]. Two patients died from adverse events judged to be unrelated to the investigational products: one died from pneumonia while receiving neoadjuvant ABP 980 and one died from septic shock while receiving adjuvant ABP 980 after trastuzumab.

Interpretation Although the lower bounds of the 90% CIs for RR and risk difference showed non-inferiority, the upper bounds exceeded the predefined equivalence margins when based on local laboratory review of tumour samples, meaning that non-superiority was non-conclusive. In our sensitivity analyses based on central laboratory evaluation of tumour samples, estimates for the two drugs were contained within the predefined equivalence margins, indicating similar efficacy. ABP 980 and trastuzumab had similar safety outcomes in both the neoadjuvant and adjuvant phases of the study.
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Introduction

Trastuzumab is approved in many countries for the treatment of metastatic breast cancer, early breast cancer, and metastatic gastric cancer, and it is the standard of care for patients with HER2-overexpressing breast cancers. Trastuzumab is a monoclonal antibody that binds to the extracellular domain of HER2, blocking receptor activation and the subsequent proliferation of cells expressing HER2. It also induces the downstream effects of antibody-dependent cellular cytotoxicity in and cellular phagocytosis of HER2-expressing cells.

Several trastuzumab biosimilars are in development. Guidelines for the development of biosimilars recommend a totality of evidence approach with stepwise development to ensure comprehensive analytical characterisation. Studies should include structural and functional assessments followed by phase 1 pharmacokinetic and, if feasible, pharmacodynamic studies to show similarity to the reference product. At least one comparative clinical study in a representative population with sensitive endpoints (ie, are clinically relevant, readily assessable, and show a size of treatment effect that is large enough to detect differences between similar treatments if any exist) is also needed to confirm similarities in safety, efficacy, and immunogenicity.

Results from phase 3 studies have shown clinical similarity to trastuzumab reference product for CT-P6 (Celltrion, Incheon, South Korea), MYL-1401O (Biocon, Bangalore, India, and Mylan, Canonsburg, PA, USA), and SB3 (Samsung Bioepis, Incheon, South Korea and Merck, Kenilworth, NJ, USA). Two studies were done in the neoadjuvant setting and one in the metastatic setting. No studies, however, have been designed to assess the effect of switching from the trastuzumab reference product to the biosimilar. The trastuzumab biosimilar ABP 980 (Amgen Inc, Thousand Oaks, CA, USA) is analytically similar to trastuzumab with respect to structure, function, and pharmacokinetic profile, which suggests that there should be no clinically meaningful differences between these drugs in efficacy, safety, or immunogenicity.

We assessed the clinical similarity of ABP 980 and trastuzumab in women with HER2-positive early breast cancer in the neoadjuvant and adjuvant settings, based on the proportion of patients achieving a pathological complete response. We compared safety, tolerability, and immunogenicity, including after switching treatment from trastuzumab to ABP 980 to generate data about clinical use.

Research in context

Evidence before this study

We searched PubMed on June 11, 2012, for papers on trastuzumab in the neoadjuvant treatment of early breast cancer with the search terms (“trastuzumab” AND “neoadjuvant”) AND (“treatment” OR “study”). We identified 220 papers that included clinical studies and reviews of trastuzumab and papers on other topics that discussed trastuzumab. We selected studies in which data were collected for HER2-positive patients; neoadjuvant treatment included at least epirubicin or doxorubicin and cyclophosphamide in combination with a taxane (docetaxel or paclitaxel) for at least 18 weeks; pertuzumab or lapatinib were not allowed; the definition of pathological complete response was consistent with that proposed for this study; and patients received neoadjuvant trastuzumab treatment for at least 18 weeks. We also included data from an abstract presented at the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, USA, June 3-7, 2011, and two studies that were unpublished at the time of the literature search but have since been published. Together, the studies showed that trastuzumab was safe and effective for the neoadjuvant treatment of early breast cancer.

Added value of this study

In this randomised, double-blind, phase 3 comparative trial, we assessed ABP 980 (Amgen Inc, Thousand Oaks, CA, USA) as a potential biosimilar to trastuzumab for the treatment of HER2-positive early breast cancer. We assessed safety based on pathological complete response in breast tissue and axillary lymph nodes. During the adjuvant phase some patients in the trastuzumab group switched to ABP 980, which allowed assessment of the clinical safety and immunogenicity. We were also able to assess the feasibility of central independent pathological review of response in a large multicentre study. To our knowledge, these are novel study design features. Our results add to the totality of evidence generated in analytical, functional, and pharmacokinetic studies and support clinical similarity of ABP 980 to the trastuzumab reference product.

Implications of all the available evidence

All the data indicate that there are no clinically meaningful differences between ABP 980 and trastuzumab. Our findings add to the growing body of evidence supporting the potential clinical usefulness of ABP 980. Additionally, switching from trastuzumab to a biosimilar seems to be safe. The use of trastuzumab biosimilars could expand treatment options for clinicians, mitigate cost barriers for payers, and increase patients’ access to important therapy.
Methods

Study design and participants

We designed a randomised, multicentre, double-blind, active-controlled, phase 3 equivalence trial to compare ABP 980 with trastuzumab in adult women with HER2-positive early breast cancer. Patients were recruited from 97 study centres in 20 countries, mainly in Europe and South America (appendix pp 14–16).

Eligible patients were women aged 18 years or older with histologically confirmed invasive breast cancer and an Eastern Cooperative Oncology Group performance status score of 0 or 1, who were planning to have surgical resection of their breast tumour with sentinel or axillary lymph node dissection and neoadjuvant chemotherapy. Inclusion criteria were HER2-positive disease confirmed by a central laboratory before randomisation (defined as 3+ overexpression on immunohistochemistry or HER2 amplification on fluorescence in situ hybridisation), known oestrogen-receptor and progesterone-receptor status at study entry, measurable disease in the breast after diagnostic biopsy (defined as longest tumour diameter ≥2.0 cm), and left ventricular ejection fraction (LVEF) of at least 55% on a two-dimensional echocardiogram. Exclusion criteria were presence of bilateral breast cancer or known distant metastases; previous treatment for primary breast cancer, including chemotherapy, a biological agent, radiotherapy, or surgery; concomitant active malignancy; and malignant disease in the previous 5 years, except treated basal-cell carcinoma of the skin or carcinoma in situ of the cervix.

The protocol was reviewed and approved by the relevant independent ethics committees for each centre. All patients provided written informed consent. This study was done in accordance with the terms of the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements.

Randomisation and masking

All patients had to complete screening and a 12-week run-in period of chemotherapy to be eligible for randomisation. After run-in, patients were randomly assigned 1:1 to receive ABP 980 or trastuzumab. Randomisation was stratified by T stage (T1 vs T4), node status (yes vs no), hormone receptor status (positive for oestrogen receptor, progesterone receptor, or both vs negative for oestrogen receptor and progesterone receptor), planned paclitaxel dosing schedule (once weekly for 12 weeks vs every 3 weeks for four cycles), and geographical region (eastern Europe vs western Europe vs other). Sentinel lymph node assessment was not a stratification factor.

We used a computer-generated randomisation schedule with a permuted block design (blocks of four) in each stratum, which was prepared by PRA International (Paris, France) before the start of the study, to assign patients to treatment groups. At the start of screening, each patient received a unique identification number before undergoing any study procedures. This number was used for individual patient identification throughout the study, although it was not necessarily the same as the randomisation number. Upon completion of run-in chemotherapy, researchers at the study sites used an interactive voice and web response system (IXRS, Almac, Souderton, PA, USA) to receive a centrally assigned unique randomisation number that was used for central randomisation of each patient to treatment group and treatment allocation. Patients were randomly assigned to receive ABP 980 throughout the study, trastuzumab throughout the study, or neoadjuvant trastuzumab followed by adjuvant ABP 980.

The pharmacists who prepared investigational products were aware of treatment allocation. Patients, physicians, the sponsor, investigators, and study site staff were masked to treatment allocation until the final database was locked. The pathologists who assessed complete response at the local and central laboratories were also masked to treatment allocation.

Procedures

During the 28-day screening period, we took patients’ medical histories, did physical examinations, electrocardiograms, two-dimensional echocardiograms, and laboratory testing in blood samples, assessed vital signs, serious adverse events, and disease progression or recurrence, and established Eastern Cooperative Oncology Group performance status score (assessed locally) and HER2 and hormone receptor statuses (assessed centrally).

After screening, patients entered the 24-week neo-adjuvant treatment phase. This phase began with a 12-week run-in chemotherapy period (during which clinical response was not assessed) when patients received intravenous epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for four cycles. After run-in chemotherapy and surgery, patients with adequate cardiac function, assessed by left ventricular ejection fraction on two-dimensional echocardiograms, were randomly assigned to one of three treatment groups: ABP 980, trastuzumab, or neoadjuvant trastuzumab followed by adjuvant ABP 980. Neoadjuvant treatment began with one cycle of 8 mg/kg investigational product (ie, either ABP 890 or trastuzumab) given in an intravenous infusion over 90 min as a loading dose; administration as a push or bolus dose was not allowed. Trastuzumab and ABP 980 were received in 150 g vials of lyophilised sterile powders that were qualitatively and quantitatively the same. The containers, however, differed in appearance, and to achieve masking the products were reconstituted with 7.2 mL sterilised water for injection, yielding 7.4 mL solutions containing approximately 21 mg/mL of either drug, and transferred to intravenous bags labelled with patients’ randomisation numbers.

If the loading dose was tolerated, patients received three cycles of trastuzumab or ABP 980 6 mg/kg given as 30 min intravenous infusions once every 3 weeks. All
patients also received intravenous paclitaxel 175 mg/m² with all doses of investigational product (or 80 mg/m² every week for 12 cycles if that was the local standard of care). Patients were observed to check for infusion-related symptoms for at least 6 h after the start of the first infusion and for 2 h after the start of subsequent infusions. Interruption or slowing of the rate of the infusion was allowed if infusion-related symptoms occurred, and could be resumed at the 30 min infusion rate once symptoms abated.

Patients underwent surgery (lumpectomy or mastectomy with sentinel or axillary lymph node dissection) within 3–7 weeks of receiving the last dose of neoadjuvant investigational product, then entered the adjuvant phase. During the adjuvant phase, patients either continued with ABP 980 or trastuzumab (dose 6 mg/kg) or switched from trastuzumab to ABP 980 6 mg/kg intravenous infusions given over 30 min every 3 weeks for up to 1 year after the first dose of neoadjuvant treatment.

Laboratory assessments were done during screening (visit 1), during treatment (neoadjuvant phase visits 2–9 and adjuvant phase visits 10–22), and at the end of the study, 30 days after the end of treatment (visit 23). These assessments were serum chemistry (visits 1, 2–9, 14, 18, 22, and 23), haematology (visits 1, 2–9, 10–22, and 23), measurements of antibodies against the investigational product (immunogenicity; visits 1, 5, 9, 10, 14, 18, 22, and 23); and pharmacokinetics (visits 5–9, 10, 14, 18, 22, and 23).

Patients could withdraw from the study at any time and for any reason. Safety concerns (eg, due to an adverse event, failure to use contraception, or protocol requirements) and disease progression or recurrence were clinically assessed at each visit as potential causes for withdrawing patients from the investigational product or procedural assessments per protocol.

We did not allow investigational product dose adjustments, but if LVEF decreased from the value seen on echocardiograms after chemotherapy run-in and before randomisation by 10 percentage points or more and to less than 50%, treatment was suspended and a repeat LVEF assessment was done within approximately 3 weeks. If LVEF had not improved or had declined further, the investigational product was discontinued. If symptomatic cardiac failure developed, it was treated according to local standard of care. Administration of an investigational product could be delayed or discontinued for decreases in LVEF, symptomatic cardiac failure, or other adverse events. Based on the known safety profile of trastuzumab, we prespecified cardiac failure, neutropenia, infusion reactions, pulmonary toxicity, hypersensitivity, and infections and infestations as events of interest. We used Standardized MedDRA Queries to retrieve relevant system organ classes and preferred terms in the Medical Dictionary for Regulatory Activities version 19.0, if available. If no standardised query was available for a given event of interest, we used a customised search strategy to identify relevant terms. Investigators graded adverse events according to Common Terminology Criteria for Adverse Events version 4.0. Previous and concomitant medications were coded with the WHO Drug Dictionary version 2015 DEC01.

Adverse events and disease progression or recurrence were assessed at all visits during the neoadjuvant and the adjuvant phases. Two-dimensional echocardiography was done at screening, and at visits 5 and 9 of the neoadjuvant phase, and results were assessed before administration of the investigational product. During the adjuvant phase, we assessed patients for adverse events, concomitant medications, and disease progression or recurrence at all visits and did two-dimensional echocardiograms at visits 14 and 18.

The efficacy analysis was done after the last patient had had surgery and been assessed for pathological complete response or had withdrawn from the study. Here we present the pathological complete response efficacy analysis and the safety and immunogenicity data from the final database lock. All tumour samples were assessed by local pathologists. Representative tumour samples were sent to the central laboratory for assessment by two independent central pathologists who were unaware of each other’s findings. The pathologists determined the samples as adequate or inadequate for evaluation based on the presence or absence of tumour bed and integrity or loss of nuclear detail. The central pathology findings were documented on worksheets specifically developed for the study and included the following items: adequate or inadequate specimen quality; presence or absence of tumour bed; presence or absence of invasive breast cancer; results differing from the local assessment for the number of blocks with invasive breast cancer present; results differing from the local assessment for the estimated percentage of viable residual tumour; presence or absence of ductal carcinoma in situ; presence or absence of lymph nodes; and presence or absence of lymph-node-invasive cancer. If the central results were discordant, those from first central pathologist were entered into the database and were deemed to be representative. If results were discordant, the worksheets were reviewed by an adjudicating pathologist who made a final independent interpretation, which was entered into the database.

Assays validated according to FDA guidance were used to detect antibodies against the investigational products. All samples were first tested in an electrochemiluminescence-based bridging immunoassay that used ABP 980 as antigen to detect binding antibodies. Samples were then tested to confirm specificity of response. Those that showed signal inhibition greater than the drug depletion cutoff point in the presence of excess soluble drug were reported as positive for binding antibodies against investigational products. Positive samples were tested in a non-cell-based, time-resolved, fluorescence-based competitive target-binding assay to determine neutralising activity. A confirmatory assay was done on
all samples to determine whether the inhibition of drug activity was due to neutralising antibodies to ABP 980. A post-treatment sample was defined as positive for neutralising antibodies if it was simultaneously positive for binding antibodies and neutralising activity.

We recorded the numbers and percentages of patients in each treatment group who had pre-existing or developed binding and neutralising binding antibodies against investigational products. Pre-existing antibody incidence was defined as the number of patients with positive antibody results at the time of or before the first dose of investigational product divided by the number of patients with an immunoassay result on or before the first dose. We defined patients who developed antibodies as the number of patients with a negative antibody result or no result available at or before baseline and a positive antibody result at any time after the first dose of investigational product divided by the number of patients with at least one immunoassay result after baseline. A transient antibody result was defined as a positive result after baseline with a negative result at the patient’s last time tested within the study period.

Outcomes
The co-primary efficacy endpoints were risk difference and risk ratio (RR) of pathological complete response, defined as the absence of invasive tumour cells in the breast tissue and in axillary lymph nodes regardless of ductal carcinoma in situ (as defined by the FDA). The primary analysis was based on local laboratory findings in patients with assessable tumour samples. We did sensitivity analyses based on central pathology findings to reduce variability between pathologists at the local level. Efficacy results are reported for the neoadjuvant phase (ABP 980 and trastuzumab groups).

Secondary efficacy endpoints were risk differences and RRs for pathological complete response in breast tissue (absence of invasive tumour cells, regardless of residual ductal carcinoma in situ); risk differences and RRs for pathological complete response in breast tissue and axillary lymph nodes in the absence of ductal carcinoma in situ (defined as the absence of invasive tumour cells in breast tissue and axillary lymph nodes and absence of ductal carcinoma). These results will be reported separately.

Safety assessments reported in this Article are the incidence of treatment-emergent adverse events, changes in LVEF, exposure to investigational product and paclitaxel, and formation of antibodies against an investigational product (immunogenicity). Safety results are presented for the neoadjuvant phase (ABP 980 and trastuzumab groups) and adjuvant phase (ABP 980, trastuzumab, and switching groups). Other safety outcomes that will be reported elsewhere were on-study event-free survival, overall survival, pharmacokinetics, concomitant medications, laboratory tests (including serum chemistry and haematology), vital signs, and physical examination.

Subgroup analyses done in prespecified groups for the neoadjuvant phase, adjuvant phase, and entire study. These included age group, race, T stage, axillary lymph node involvement, hormone receptor status, paclitaxel dosing schedule, and geographical region, and will be reported separately.

Statistical analysis
The primary efficacy hypothesis was that ABP 980 would be equivalent to trastuzumab when each was given in combination with standard-of-care neoadjuvant cancer treatment (paclitaxel). The planned sample size was 808 to ensure that 768 patients (384 in each group) were randomly assigned treatment. We calculated that this number would achieve 90% power to show equivalence when assessed by RR for pathological complete response with 5% dropout during run-in chemotherapy phase. This sample size was also calculated to provide at least 90% power to show equivalence when assessed by risk difference between groups for pathological complete response with margins of –13% and 13% and a two-sided 0·05 significance level. We assumed that the proportion of patients who would achieve a pathological complete response would be approximately 42·5% in the ABP 980 and trastuzumab groups.

We initially used a sequential testing method to test similarity between ABP 980 and trastuzumab by comparing the two-sided 90% CI for risk difference between the ABP 980 and trastuzumab groups with statistical margins of –13% and 13%. If the test on the risk difference was successful, similarity was then tested by RR of pathological complete response at a two-sided significance level of 0·05 by comparing the two-sided 90% CI between the ABP 980 and trastuzumab groups with statistical margins of 0·759 and 1·318.

The population assessable for pathological complete response was defined as all randomised patients who received any amount of investigational product, underwent surgery, and had an available pathological complete response assessment from the local laboratory. The safety analysis population consisted of all patients who were randomised and received any amount of investigational product. We did sensitivity analyses in the intention-to-treat and per-protocol populations (data not shown). The intention-to-treat population included all patients randomly assigned to a study group, regardless of whether they received any investigational product. The per-protocol population included all patients who were randomised, had local laboratory pathological complete response results, and had no protocol deviations that prevented assessment of the primary objective.

All statistical analyses were done with SAS version 9.1.3 or later. This study is registered with ClinicalTrials.gov, number NCT01901146, and Eudra, number CT 2012-004319-29.
Figure 1: Trial profile
HBsAg=hepatitis B surface antigen. HCV=hepatitis C virus. *Nine patients were assigned to the trastuzumab group because of a delay in manufacturing of ABP 980 at the start of the study. These patients were excluded from the primary efficacy analysis but included in the final safety analysis.
Role of the funding source
The funder had a role in study design, data analysis, data interpretation, and writing of the report, and had access to the raw data, but had no role in data collection. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
We enrolled patients between April 29, 2013, and Sept 29, 2015. The data cutoff for the primary analysis was May 5, 2016, and the database lock for the final analysis was March 29, 2017. Of 906 patients screened, 79 were excluded (figure 1). 827 patients were enrolled and 725 were randomised (figure 1). The treatment groups were well balanced in terms of baseline characteristics (table 1). The baseline distribution of sentinel lymph node biopsies was balanced the two groups (39 [11%] patients in the ABP 980 group and 29 [9%] in the trastuzumab group). Lymph node surgery was not done in 13 patients after neoadjuvant treatment because they had negative or only up to two positive sentinel nodes; these patients were equally distributed between the two treatment groups during both the neoadjuvant and adjuvant phases (tables 3, 4, appendix pp 3–7). Patients’ exposure to investigational products is shown in table 2. Exposure to paclitaxel during the neoadjuvant phase was similar in the ABP 980 and trastuzumab groups. Paclitaxel was administered only in the neoadjuvant phase. All patients who underwent surgery were assessable for the primary endpoint of pathological complete response (696 patients in total; 358 of whom received ABP 980 and 338 who received trastuzumab). 172 (48%, 95% CI 43–53) of 358 patients who received neoadjuvant ABP 980 and 137 (41%, 35–46) of 338 patients who received neoadjuvant trastuzumab achieved a pathological complete response in breast tissue and axillary nodes based on local laboratory assessments. The risk difference between groups and RR of pathological complete response was 7·3% (90% CI 1·2–13·4). The RR (ABP 980 vs trastuzumab) of pathological complete response was 1·188 (90% CI 1·033–1·366). The primary endpoint, however, was not met, because the upper boundaries of the 90% CIs for risk difference and RR exceeded the predefined equivalence margins (figure 2).

In the sensitivity analyses based on central pathology review of tumour samples, 162 (48%, 95% CI 42–53) of 339 patients in the ABP 980 group and 138 (42%, 36–47) of 330 in the trastuzumab group showed pathological complete response in breast tissue and axillary nodes. The risk difference between groups and RR of pathological complete response were within the predefined equivalence margins (figure 2).

The overall incidence of adverse events in the two treatment groups during both the neoadjuvant and adjuvant phases was similar (tables 3, 4, appendix pp 3–7). In the neoadjuvant phase, 19 (5%) of 364 patients in the ABP 980 group and 23 (6%) of 361 in the trastuzumab group had adverse events that led to dose delays of investigational products, three (1%) and two (1%), respectively, had events that led to discontinuation of treatment, and four (1%) and two (1%), respectively, had events that led to withdrawal from the study. In the adjuvant phase, 16 (5%) of 349 patients in the ABP 980 group and 23 (6%) of 361 in the trastuzumab group had adverse events that led to dose delays of investigational products, three (1%) and two (1%), respectively, had events that led to discontinuation of treatment, and four (1%) and two (1%), respectively, had events that led to withdrawal from the study.
ABP 980 group, six (4%) of 171 in the trastuzumab group, and eight (5%) of 171 in the switching group had adverse events that led to dose delay of investigational products, seven (2%), three (2%), and four (2%), respectively, had events that led to treatment discontinuation, and seven (2%), two (1%), and two (1%), respectively, had events that led to withdrawal from the study.

Grade 3 or worse adverse events during the neo-adjuvant phase occurred in 54 (15%) of 364 patients in the ABP 980 group and 51 (14%) of 361 patients in the trastuzumab group, of which the most frequent grade 3 or worse event of interest was neutropenia, occurring in 21 (6%) patients in both groups. In the adjuvant phase, grade 3 or worse adverse events occurred in 30 (9%) of 349 continuing ABP 980, 11 (6%) of 171 continuing trastuzumab, and 13 (8%) of 171 who switched from trastuzumab to ABP 980; the most frequent grade 3 or worse events of interest were infections and infestations (four [1%], two [1%], and two [1%]), neutropenia (three [1%], two [1%], and one [1%]), and infusion reactions (two [1%], two [1%], and three [2%]).

We recorded no differences in the incidence of events of interest between treatment groups in the neo-adjuvant or adjuvant phases (tables 5, 6). Overall, the incidence of adverse events of interest was lower in the adjuvant phase than in the neo-adjuvant phase (tables 5, 6). In patients who initially received neo-adjuvant trastuzumab, the incidence of adverse events of interest did not differ between patients who continued receiving trastuzumab in the adjuvant phase and those who switched to ABP 980 in the adjuvant phase (table 6).

A complete list of treatment-emergent serious adverse events is provided in the appendix (pp 8–10). In the neo-adjuvant phase, serious adverse events occurred in 18 (5%) of 364 patients in the ABP 980 group and five (1%) of 361 in the trastuzumab group. The most common were infections and infestations. Three (<1%) of 364 patients in the ABP 980 group and two (<1%) of 361 patients in the trastuzumab group had serious adverse events that were judged to be related to the investigational products. In the adjuvant phase, 18 (5%) of 349 patients in the ABP 980 group, six (4%) of 171 in the trastuzumab group, and six (4%) of 171 in the switching group had serious adverse events. One (<1%) of 171 patients in the switching group had a serious adverse event (ventricular extrasystoles) that was judged to be related to the investigational product. Six patients in the ABP 980 treatment group and one in the trastuzumab group had serious adverse events from accidents or surgery that were deemed to be unrelated to the investigational products. The most common serious treatment-emergent adverse events during the adjuvant therapy phase were gastrointestinal disorders, injury, poisoning, and procedural complications, and infections and infestations (appendix pp 8–10).

Six patients died during the study, among whom four died before or more than 30 days after treatment with an investigational product. Two patients died from adverse events not judged to be related to the investigational products. One patient in the ABP 980 group died from pneumonia during the neo-adjuvant phase and the other, in the switching group, died from septic shock in the adjuvant phase.

Overall, the incidence of adverse events was lower in the adjuvant phase, when there was no run-in chemotherapy, than in the neo-adjuvant phase, which was preceded by chemotherapy (tables 3, 4). Switching patients from trastuzumab to ABP 980 did not affect safety; the incidence of adverse events in the switching
group was consistent with that reported in patients who continued receiving trastuzumab in the adjuvant phase (appendix pp 3–10).

The incidence of LVEF decline from the value after chemotherapy run-in and before randomisation by at least 10 percentage points and to less than 50% ranged from 1·8% to 3·5% across the treatment groups (appendix p 11), and the median LVEF values did not change in any treatment group over the full course of the study (data not shown). The trastuzumab and switching groups had similar LVEF results (appendix p 11).

Of the seven patients who had cardiac failure adverse events during the neoadjuvant phase (six [2%] of 364 patients in the ABP 980 group and one [<1%] of 361 in the trastuzumab group), none experienced cardiac failure coincident with LVEF decline of at least 10 percentage points and to less than 50%. All cardiac failure events were grade 1 or 2, and patients completed all planned doses of investigational product with no worsening of the cardiac failure event. During the adjuvant phase, two (1%) of 349 patients in the ABP 980 group, one (1%) of 171 in the trastuzumab group, and one (1%) of 171 in the switching group had cardiac failure events. One patient in the switching group had a grade 3 cardiac failure event and all others were grade 1 or 2. One patient in the trastuzumab group had a cardiac failure event that was coincident with LVEF decline of at least 10 percentage points and to less than 50%. No patients discontinued investigational products due to cardiac failure in the adjuvant phase.

Two patients in the ABP 980 group and two in the trastuzumab group developed binding antibodies during the neoadjuvant phase. Neither of these patients tested positive for neutralising antibodies.

During the course of the entire study, eight patients (two [1%] in the ABP 980 group, two [1%] in the trastuzumab group, and four [2%] in the switching group) tested positive for binding antibodies at any time during the study (appendix p 12). No patients tested positive for neutralising antibodies. Two (1%) patients in the ABP 980 group, one (1%) in the trastuzumab group, and two (1%) in the switching group who were negative for binding antibodies at baseline later had positive results, all of which were transient (ie, results were negative at the last time the patient was tested). None of these patients tested positive for neutralising antibodies after baseline.

**Discussion**

We designed this equivalence study to compare the effects of the biosimilar ABP 980 with those of reference product trastuzumab on pathological complete response in women with HER2-positive early breast cancer in the...
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neoadjuvant setting. Although the primary efficacy endpoint of our study was not met because, based on local laboratory review of tumour samples, the upper bounds of the 90% CIs for RR and risk difference exceeded the predefined equivalence margins, our sensitivity analyses based on central laboratory evaluation of tumour samples indicated similar efficacy of the two drugs, with both risk estimates contained within the predefined equivalence margins. ABP 980 and trastuzumab had similar safety outcomes in both the neoadjuvant and adjuvant phases of the study. The incidence of serious adverse events was slightly higher in the ABP 980 group than in the trastuzumab group during the neoadjuvant phase, including a higher number of infectious adverse events, but many adverse events were probably confounded by concomitant paclitaxel or were surgical complications or trauma unrelated to the investigational products. The numbers of patients with serious adverse events in the neoadjuvant phase were similar in the two groups. Similarly, most of the serious adverse events in the adjuvant phase were unrelated to investigational products, and only one patient in the switching group had a serious event that was associated with treatment. Overall, therefore, the safety profiles of ABP 980 and trastuzumab for adverse events, serious

Table 4: Adverse events during adjuvant treatment in the safety analysis population

Table 5: Adverse events during neoadjuvant treatment in the safety analysis population

Table 6: Adverse events during adjuvant treatment in the safety analysis population
adverse events, and events of interest were similar. The frequencies, types, and severities of adverse events were consistent with the historical safety profile of trastuzumab.1,2

We chose women with early-stage breast cancer as the study population for this trial because this population is more homogeneous than patients who have metastatic disease, and, therefore, is more suitable for an equivalence study.3,4 We selected pathological complete response as the primary efficacy endpoint to be consistent with previous studies of trastuzumab and because it is a clinically meaningful and validated endpoint that is directly associated with increased event-free survival.5 The proportions of patients in the ABP 980 and the trastuzumab groups were consistent with those previously reported for trastuzumab,1,5–22 but, despite clinically similar efficacy, in the local review of tumours the risk difference and RR for pathological complete response between the two groups slightly exceeded the upper statistical margins for equivalence. In the central review of tumour samples, however, the point estimates for risk difference and RR were lower and fell within the similarity margins.

A potential limitation of the study is that we did not assess clinical response of breast cancer to the neoadjuvant treatment; clinical tumour response is highly variable and there is no validated standard method to differentiate between two very similar products. Histopathological assessment of pathological complete response remains the standard method to investigate whether breast cancer patients have residual disease after receiving neoadjuvant treatment. The choice of locally reviewed pathological complete response as the primary endpoint is another potential limitation of this study. Central assessment is generally more conservative and reduces variability, which provides greater confidence in the results. We chose to base the primary endpoint on local review of tumour samples partly because of concerns about potential logistical difficulties associated with transfer of tissue across the four different regions in which the study was done (eg, ensuring integrity of the samples is maintained during international transport). Use of local laboratories increased the likelihood that we would have sufficient tissue from patients to make meaningful comparisons of treatment effects, despite the risk of higher variability. We found, however, that transport of samples for central review was feasible and did prespecify sensitivity analyses of the central findings to address the issue of pathologist variability at the local level. In most cases, the amount and integrity of the samples that were transported to the central laboratory were adequate to assess pathological complete response. To our knowledge, this study is the first to show that including central pathology review of pathological complete response is feasible in a large, international, multicentre clinical trial.

Treatment with trastuzumab has been associated with an increased risk of cardiac toxicity, possibly due to previous exposure to anthracyclines.23 Therefore, we carefully assessed LVEF and cardiac adverse events. We found no change in median LVEF values over the course of the study, and decreases in LVEF were seen in few patients, with the frequencies being similar across treatment groups. The frequency of cardiac disorders was low throughout the study and none resulted in discontinuation of investigational product. Only seven patients had cardiac failure in the neoadjuvant phase, and all events were grade 1 or 2. Moreover, all seven patients received the planned doses of investigational products, which suggests resolution or no worsening of cardiac failure. Furthermore, LVEF decline and a cardiac failure adverse event coincided in only one patient in the adjuvant phase, which suggests very low cardiac toxicity in this study.

To our knowledge, this is the first study of a trastuzumab biosimilar encompassing a single-switch design from the reference product to a biosimilar, which allowed us to assess the clinical safety and immunogenicity of this approach to treatment. Safety and immunogenicity were similar in patients who were switched and in those who continued to receive trastuzumab as adjuvant therapy.

Safety, efficacy, and clinical outcomes did not differ for the biosimilar ABP 980 and trastuzumab reference product in women with HER2-positive early breast cancer. The frequencies, types, and severities of adverse events, including cardiac events, did not differ between treatment groups and were consistent with the known safety profile of trastuzumab. Immunogenicity was low for both drugs. Similarities persisted in the neoadjuvant and adjuvant phases, and switching from trastuzumab to ABP 980 did not lead to any new or unexpected safety signals. Overall, our results add to the evidence from analytical, functional, and pharmacokinetic studies supporting the clinical similarity of ABP 980 and trastuzumab.

Contributors
GvM, NZ, and VH conceived and designed the study and analysed the data. MC, H-CK, SM, PS, and ZT acquired patients’ data. All authors reviewed the study results and interpreted the data, contributed substantially to development of the manuscript, and reviewed and approved the final version for submission.

Declaration of interests
GvM is a consultant for Amgen. MC is a consultant for AstraZeneca, Celldex, Novartis, OBI Pharma, Pfizer, Pierre Fabre, and Puma Biotechnology. H-CK is a consultant for Amgen, Carl Zeiss Meditec, Genomic Health, GSK, Janssen, LIV Pharma, Novartis, Pfizer, Roche, SurgVision, TEVA, and Theracron. NZ and VH are employees and stockholders of Amgen. The other authors declare no competing interests.

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