CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial

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Summary

Background CT-P6 is a proposed biosimilar to reference trastuzumab. In this study, we aimed to establish equivalence of CT-P6 to reference trastuzumab in neoadjuvant treatment of HER2-positive early-stage breast cancer.

Methods In this randomised, double-blind, active-controlled, phase 3 equivalence trial, we recruited women aged 18 years or older with stage I–IIIa operable HER2-positive breast cancer from 112 centres in 23 countries. Inclusion criteria were an Eastern Cooperative Oncology Group performance status score of 0 or 1; a normal left ventricular ejection fraction of at least 55%; adequate bone marrow, hepatic, and renal function; at least one measureable lesion; and known oestrogen and progesterone receptor status. Exclusion criteria included bilateral breast cancer, previous breast cancer treatment, previous anthracycline treatment, and pregnancy or lactation. We randomly allocated patients 1:1 to receive neoadjuvant CT-P6 or reference trastuzumab intravenously (eight cycles, each lasting 3 weeks, for 24 weeks; 8 mg/kg on day 1 of cycle 1 and 6 mg/kg on day 1 of cycles 2–8) in conjunction with neoadjuvant docetaxel (75 mg/m² on day 1 of cycles 1–4) and FEC (fluorouracil [500 mg/m²], epirubicin [75 mg/m²], and cyclophosphamide [500 mg/m²]; day 1 of cycles 5–8) therapy. We stratified randomisation by clinical stage, receptor status, and country and used permuted blocks. We did surgery within 3–6 weeks of the final neoadjuvant study drug dose, followed by an adjuvant treatment period of up to 1 year. We monitored long-term safety and efficacy for 3 years after the last patient was enrolled. Participants and investigators were masked to treatment until study completion. The primary efficacy endpoint, analysed in the per-protocol population, was pathological complete response, assessed via specimens obtained during surgery, analysed by masked central review of local histopathology reports. The equivalence margin was –0·15 to 0·15. This trial is registered with ClinicalTrials.gov, number NCT02162667, and is ongoing, but no longer recruiting.

Findings Between Aug 7, 2014, and May 6, 2016, we randomly allocated 549 patients (271 [49%] to CT-P6 *vs* 278 [51%] to reference trastuzumab). A similar proportion of patients achieved pathological complete response with CT-P6 (116 [46·8%; 95% CI 40·4–53·2] of 248 patients) and reference trastuzumab (129 [50·4%; 44·1–56·7] of 256 patients). The 95% CI of the estimated treatment outcome difference (–0·04 [95% CI –0·12 to 0·05]) was within the equivalence margin. 19 (7%) of 271 patients in the CT-P6 group reported serious treatment-emergent adverse events versus 22 (8%) of 278 in the reference trastuzumab group; frequent (occurring in more than one patient) serious adverse events were febrile neutropenia (four [1%] *vs* one [<1%]) and neutropenia (one [<1%] *vs* two [1%]). Grade 3 or worse treatment-related adverse events occurred in 17 (6%) of 271 patients in the CT-P6 group versus 23 (8%) of 278 in the reference trastuzumab group; the most frequently reported adverse event was neutropenia in ten (4%) versus 14 (5%).

Interpretation CT-P6 showed equivalent efficacy to reference trastuzumab and adverse events were similar. Availability of trastuzumab biosimilars could increase access to this targeted therapy for HER2-positive early-stage cancer.

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Introduction

Approximately 25% of invasive breast cancers amplify the *HER2* oncogene, resulting in constitutive activation of the type I transmembrane HER2 protein.[1–3] Development of trastuzumab, a humanised monoclonal antibody that binds to the extracellular domain of HER2, was a major advance in treatment of HER2-overexpressing (HER2-positive) cancers. The first clinical trial[4,5] of trastuzumab in the neoadjuvant setting was discontinued prematurely when addition of the antibody to chemotherapy doubled the proportion of patients achieving a pathological complete response (pCR) compared with chemotherapy alone in patients with HER2-positive, early-stage, operable breast cancer. Subsequent studies[6,7] have substantiated the efficacy of trastuzumab with respect to increasing pCR and shown that pCR is associated with favourable long-term survival outcomes.[8] European (European Society for Medical Oncology)[9] and

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Research in context

Evidence before this study

We searched PubMed using the search terms "trastuzumab", "neoadjuvant", and "HER2-positive breast cancer" for articles published between Jan 1, 2000, and Feb 7, 2017, not restricted to the English language. We identified 368 articles, of which 87 (24%) were clinical trials. These trials show the efficacy of trastuzumab for treatment for HER2-positive breast cancer. However, a search for "trastuzumab" and "cost" yielded a further 47 articles, revealing the debate around the financial costs of trastuzumab and the ensuing consequences for global access to the drug.

Added value of this study

We did a randomised, double-blind, active-controlled, phase 3 trial to establish the equivalence of CT-P6 to reference trastuzumab in terms of efficacy in patients with HER2-positive, operable, early-stage breast cancer treated in the neoadjuvant setting. Whereas previous studies of trastuzumab biosimilars have used the proportion of patients with an overall response as a primary endpoint, we used pathological complete response (pCR), which is generally considered to be a better endpoint for equivalence studies than overall response. A similar proportion of patients in the per-protocol population achieved a pCR with CT-P6 and reference trastuzumab, with the 95% CI of the estimated treatment difference falling entirely within the equivalence margin of –0·15 to 0·15. CT-P6 was also similar to reference trastuzumab in terms of overall response, other pCR-related endpoints, pharmacokinetic and pharmacodynamic endpoints, and safety profile. Furthermore, to our knowledge, this study is the first to show equivalent efficacy of a proposed trastuzumab biosimilar and its reference product in early-stage operable breast cancer as opposed to metastatic breast cancer.

Implications of all the available evidence

This study has shown equivalence of biosimilar CT-P6 to reference trastuzumab in terms of efficacy and similarity in terms of pharmacokinetics, pharmacodynamics, safety, and immunogenicity. The availability of biosimilar trastuzumab has the potential to increase global access to this key therapy for patients with HER2-positive, operable, early-stage breast cancer.

US (American Society of Clinical Oncology)[10] guidelines now recommend chemotherapy plus trastuzumab for neoadjuvant treatment of HER2-positive forms of early-stage breast, metastatic breast, and metastatic gastric cancer. However, the high costs associated with trastuzumab place a burden on health-care systems and limit global access to the drug.[11,12]

These cost-related barriers can be addressed, at least in part, by introduction of new biosimilars. A biosimilar drug is a biological product that is highly similar to an already approved drug, known as the reference product or originator, and which shows "no clinically meaningful differences [to the reference product] in terms of the safety, purity and potency".[13] Biosimilars are usually cheaper than their reference products[14] and thus have the potential to broaden access to key drugs. Comprehensive testing is required to show the absence of clinically meaningful differences in safety, efficacy, and purity between a biosimilar and its reference product.[13,15,16]

CT-P6 is a proposed biosimilar to originator trastuzumab (reference trastuzumab). In-vitro studies have shown CT-P6 to be similar to the US-licensed reference trastuzumab in terms of HER2-binding affinity, antibody-dependent cell-mediated toxicity, and antiproliferative activity, and preclinical in-vivo studies have shown that CT-P6 also has a similar toxicological profile to reference trastuzumab (Celltrion Inc, unpublished). A phase 1 trial[17] in healthy volunteers showed pharmacokinetic (PK) equivalence and comparable safety of CT-P6 and the US-licensed reference trastuzumab. Treatment-emergent adverse events were reported in ten (29%) of 35 volunteers in the CT-P6 group and 11 (31%) of 35 in the reference trastuzumab group, and all were mild in intensity. CT-P6 has been approved in South Korea for use in the same indications as the reference product.

The aim of this study was to establish the equivalence of CT-P6 to reference trastuzumab in terms of efficacy in patients with HER2-positive, operable, early-stage breast cancer treated in the neoadjuvant setting. In light of increasing support for use of pCR as an endpoint rather than the proportion of patients with an overall response in neoadjuvant studies of early-stage breast cancer,[7,18–21] including encouragement by the US Food and Drug Administration (FDA) to use pCR as an endpoint for accelerated approval in the neoadjuvant setting,[22] we chose to assess equivalence using pCR. We also compared PKs, pharmacodynamics (PDs), and safety data for both treatments throughout the study, which included additional adjuvant and follow-up periods. We only report data from the neoadjuvant period here.

Methods

Study design and participants

In this randomised, double-blind, active-controlled, phase 3 equivalence trial, we recruited patients from 112 centres in 23 countries (appendix). Eligible patients were women aged at least 18 years with histologically confirmed and newly diagnosed clinical stage I–IIIa (as classified according to the American Joint Committee on Cancer Breast Cancer Staging seventh edition), operable, HER2-positive breast adenocarcinoma. Inclusion criteria were an Eastern Cooperative Oncology Group performance status score of 0 or 1; normal left ventricular ejection fraction (LVEF; ≥55%); adequate bone marrow, hepatic, and renal function; at least one measureable

See Online for appendix

lesion; and known oestrogen and progesterone status. Exclusion criteria included having bilateral breast cancer, previous breast cancer treatment, previous anthracycline treatment, and pregnancy or lactation. Full inclusion and exclusion criteria, and details of amendments, are presented in the appendix. Tumour HER2 overexpression and hormone receptor status were assessed locally, following American Society of Clinical Oncology and College of American Pathologists guidelines,[23] at the screening visit as part of the eligibility assessment but assessed centrally for reporting purposes.

The protocol was reviewed and approved by the relevant independent ethics committees for each centre. All patients provided written informed consent. We did the study in line with the Declaration of Helsinki,[24] Good Clinical Practice guidelines,[25] and all applicable regulatory requirements.

Randomisation and masking

After confirmation of eligibility, we randomly assigned patients in a 1:1 ratio to CT-P6 or reference trastuzumab. We stratified randomisation by clinical stage (stage I or II *vs* IIIa), oestrogen and progesterone receptor status (positive *vs* negative), and country (Europe, the Middle East, and Africa *vs* America *vs* Asia) and used permuted blocks. An interactive web response system was used by the funder to assign patients to study groups as per a predefined randomisation code. Study participants, investigators, and study site personnel remained masked to randomisation codes until all final clinical data had been entered into the database and the database had been locked and released for analysis. pCR was centrally assessed by a masked reviewer. Those assessing other outcomes were also masked.

Procedures

After a 21 day screening period, patients entered a neoadjuvant treatment period (eight cycles of chemotherapy over 24 weeks, followed by surgery within 3–6 weeks of the last dose of study drug), followed by an adjuvant treatment period to bring total treatment up to a maximum of 1 year. The post-treatment follow-up period was 3 years from the date of enrolment of the last patient.

During the neoadjuvant period, we gave CT-P6 (Celltrion Inc, Incheon, South Korea) or reference trastuzumab (herceptin; Genentech, San Francisco, CA, USA) via a 90 min intravenous (IV) infusion at a loading dose of 8 mg/kg on day 1 of cycle 1 and at 6 mg/kg on day 1 of cycles 2–8, with dosing occurring every 3 weeks for 24 weeks (ie, eight cycles in total). Docetaxel (75 mg/m² via a 1 h IV infusion) was administered immediately after CT-P6 or reference trastuzumab on day 1 of cycles 1–4. On day 1 of cycles 5–8, we administered fluorouracil, epirubicin, and cyclophosphamide (FEC; 500 mg/m² fluorouracil via 3–5 min IV bolus or 30 min IV infusion; 75 mg/m² epirubicin via 3–5 min IV bolus or 30 min infusion; 500 mg/m² cyclophosphamide via 3–5 min IV bolus) immediately after CT-P6 or reference trastuzumab. CT-P6 and reference trastuzumab were supplied and administered via the same procedure.

We allowed dose modification up to a maximum of two times (two cycles). We allowed dose delay or modification at the investigator's discretion if a change in grade of toxicity occurred, for grade 3–4 non-haematological toxicity, for asymptomatic cardiac toxicity, for an absolute neutrophil count of fewer than 1500 cells per mm³, for a platelet count of fewer than 100 000/mm³, or if febrile neutropenia occurred. When a cycle had been delayed because of toxicity, we did not reinitiate treatment until neutrophil concentrations were at least 1500 cells per mm³, platelet concentrations were at least 100 000/mm³, and non-haematological toxicity was grade 2 or lower. If we delayed CT-P6 or reference trastuzumab treatment, we also delayed chemotherapy, with both treatments reinitiated on the same date if the dosing delay was 7 days or shorter, using the usual dose of CT-P6 or reference trastuzumab (6 mg/kg). If the dosing delay was longer than 7 days, chemotherapy and CT-P6 or reference trastuzumab administrations could be uncoupled and given on different days as clinically indicated, but were brought back to a common administration schedule as soon as possible. If the delay in CT-P6 or reference trastuzumab treatment was longer than 7 days, we gave a reloading dose (8 mg/kg over 90 min) followed by maintenance doses of 6 mg/kg every 3 weeks from that point. We permitted dose reduction for the chemotherapy agents, but not for CT-P6 or reference trastuzumab.

We collected blood samples for PK analysis before and after each infusion of CT-P6 or reference trastuzumab and analysed them using a Gyrolab system (Gyros, Uppsala, Sweden). We collected blood samples for pharmacodynamic analysis before dosing at cycles 1 and 5 and at the end of treatment for cycle 8. We collected blood samples for immunogenicity studies at screening, at cycle 4, and at the end of treatment for cycle 8. To assess treatment response in the neoadjuvant period, we assessed tumours at baseline, after cycle 4, and at the end of treatment. After eight cycles of neoadjuvant treatment, we did surgery, including axillary lymph node assessment (sentinel lymph node biopsy or axillary lymph node dissection), within 3–6 weeks of the last dose of CT-P6 or reference trastuzumab in the neoadjuvant period. After surgery, patients entered a recovery period of 3–6 weeks. We then readministered CT-P6 or reference trastuzumab in the adjuvant period.

Cardiac function, including LVEF, left ventricular end-systolic diameter, and left ventricular end-diastolic diameter, were assessed locally with echocardiograms or multiple-gated acquisition scans at baseline, after cycle 4, and at the end of treatment. We used the results of local assessment to guide clinical decision making, but we also sent echocardiograms and multiple-gated acquisition

images to independent reviewers for the purpose of safety monitoring. Adverse events could be reported at any time during the study after patient consent and up to 30 days from the last dose of study drug. We assessed adverse events with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

During the adjuvant period, we administered CT-P6 or reference trastuzumab at a dose of 6 mg/kg in 3 week cycles (ten cycles or fewer) to bring total treatment over both the neoadjuvant and adjuvant periods, excluding surgery, up to a maximum of 1 year. During this period, patients could receive hormone therapy or radiotherapy, or both. Treatment after the neoadjuvant period was determined according to the physician's clinical judgement. We assessed disease status during the adjuvant period and 3 year follow-up period (3 years from the date of enrolment of the last patient), until disease progression or recurrence. After disease progression or recurrence, we assessed treatment of recurrence and survival until death or study termination. We also followed up patients with disease progression during neoadjuvant therapy for survival analysis and treatment of recurrent disease.

We assessed overall response with mammograms, sonograms, physical examination, and CT scans. We did chest and abdomen CT and bone scans before patients received the study drug to establish disease stage and rule out metastases and after cycle 4 and at the end of the neoadjuvant period to make a decision regarding surgery and assess the response to neoadjuvant treatment. We did a bone scan at the end of the neoadjuvant period if clinically indicated. We used mammography, sonography, and clinical examination for determination of progressive disease. When results from these three methods were not in agreement, we used the method that implied the most severe disease for establishment of secondary endpoints. When a bone scan was not available at baseline, a CT image could replace the bone scan image. We ordered chest CT scans, bone scans, thyroid function tests, or other radiological tests if required according to clinical symptoms and signs or biochemical alterations. In both groups, trastuzumab maximum serum concentration (C_{max}) and trough serum concentration (C_{trough}) were established via sample analysis in a central laboratory.

Outcomes

The primary efficacy endpoint was pCR (ypT0/is, ypN0)[22] at the time of definitive surgery, defined as the absence of invasive tumour cells in the breast and axillary lymph nodes, regardless of ductal carcinoma in situ. pCR assessment was completed locally and the histopathology reports were assessed centrally by a masked reviewer. Secondary efficacy endpoints evaluable at the end of the neoadjuvant period included the proportion of patients achieving an overall response, defined as partial or complete response as assessed by Response Evaluation Criteria in Solid Tumours version 1.1; breast conservation, measured as the proportion of patients who had lumpectomy; and other pCRs (breast pCR [ypT0/is] and pCR without ductal carcinoma in situ [ypT0, ypN0]). Secondary efficacy endpoints evaluable at the end of the 3 year follow-up period are disease-free, progression-free, and overall survival, which will be reported elsewhere. PK endpoints were the maximum serum trastuzumab C_{max} 15 min after IV infusion for each dose and C_{trough} observed before the next dose for cycles 1–7 and at the end of treatment at cycle 8. The PD endpoint for the neoadjuvant period was central laboratory quantification of serum HER2 extracellular shed antigen. Biomarker data was a further secondary outcome, which will be reported elsewhere.

Safety endpoints were the prevalence and severity of adverse events, laboratory measures, and cardiotoxicity, as assessed by mean change from baseline to endpoint assessment in LVEF, and immunogenicity, as assessed by antidrug antibody incidence. We defined a significant LVEF decrease as a decrease of ten ejection fraction points from the baseline value and a decrease of an absolute value of less than 50%. If this decrease was confirmed by reassessment within 3 weeks, then we considered treatment discontinuation. Other safety endpoints were vital signs, electrocardiogram, chest radiograph, hypersensitivity monitoring, physical examination, and Eastern Cooperative Oncology Group performance status.

Statistical analysis

We calculated sample size using nQuery Advisor. Assuming a dropout rate of 10% and that 50% of patients would achieve a pCR, a sample size of 532 in the neoadjuvant period was required to provide at least 80% power to detect equivalence (at a predefined 15% equivalence margin, with a significance level determined by two one-sided tests of $\alpha=0{\cdot}025$). We defined equivalence as the 95% CIs for the treatment difference being fully contained within the interval of $-0{\cdot}15$ to $0{\cdot}15$. We derived this margin by reviewing historical pCR proportions of taxane, FEC, and trastuzumab combination therapy. Specifically, we did a meta-analysis (unpublished) of six studies[4,26–30] of FEC plus taxane, resulting in an estimated pCR proportion of 15·88%. Pooling of results from four key experimental studies[4,31–33] of trastuzumab, in which patients received a regimen of taxane (paclitaxel or docetaxel) with trastuzumab followed by FEC plus trastuzumab, showed an overall pCR proportion of 53·74%. The difference between patient groups who did and did not receive a trastuzumab-containing regimen was 37·86%. A 15% equivalence margin corresponds to preservation of 60% of the efficacy seen in these studies.

We defined the intention-to-treat (ITT) population as all patients randomly allocated to study drug, regardless of whether or not a dose of study drug was received. The per-protocol (PP) population comprised all patients in the ITT population, except for those who had a major protocol deviation (defined as a deviation that might affect interpretation of study results; appendix). The PP population included patients who withdrew from the study because of confirmed progressive disease after surgery, but excluded those who withdrew before surgery. Final determination of the PP set was carried out at a masked data review meeting, held in accordance with the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guideline E9.[25] The primary outcome was assessed in the PP population. The safety analysis population included all patients who were randomly allocated to study drug and received at least one (full or partial) dose. We considered patients who did not have samples collected for a particular endpoint non-assessable for that endpoint.

We did statistical analysis using SAS software version 9.1.3 or later. For the primary efficacy analysis,

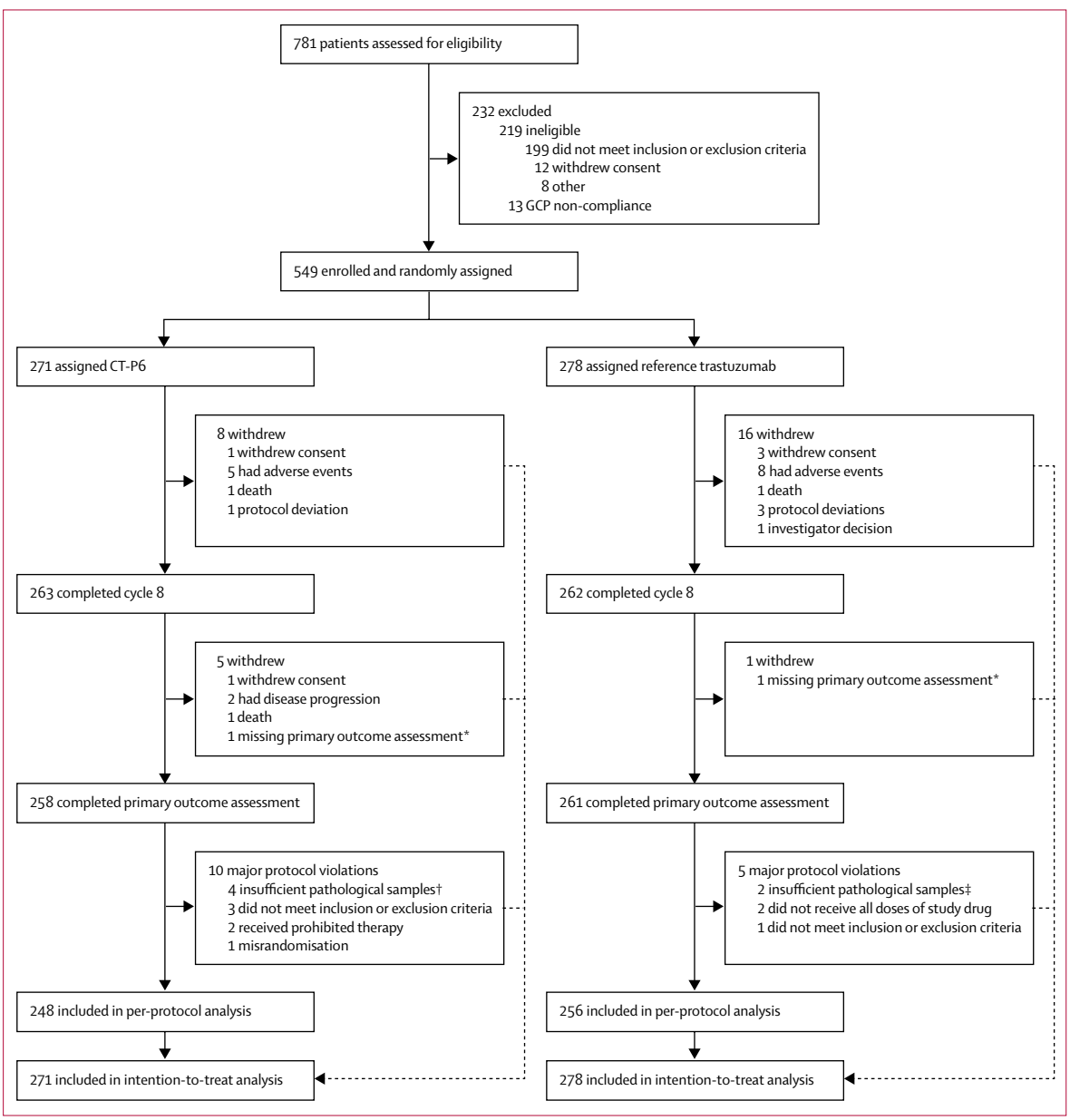

Figure: **Trial profile**
GCP=Good Clinical Practice. *Assessments not available because of lost pathological samples. †Two patients received axillary resection only and two received breast surgery only. ‡Two patients received breast surgery only.

	CT-P6 (n=271)	Reference trastuzumab (n=278)
Age (years)		
Mean	51·8 (11·0)	52·1 (10·5)
Median	53 (24–78)	53 (22–74)
Race		
Asian	51 (19%)	48 (17%)
Black or African American	2 (1%)	5 (2%)
Hispanic or Latino	9 (3%)	8 (3%)
White	207 (76%)	214 (77%)
Other	2 (1%)	3 (1%)*
Weight (kg)		
Mean	69·86 (14·68)	70·80 (14·58)
Median	68·0 (44·0–124·0)	69·0 (43·4–120·0)
Region		
EMEA	209 (77%)	222 (80%)
America	12 (4%)	10 (4%)
Asia	50 (18%)	46 (17%)
ECOG performance status		
0	239 (88%)	250 (90%)
1	32 (12%)	28 (10%)
Location of primary tumour		
Left breast	129 (48%)	139 (50%)
Right breast	142 (52%)	139 (50%)
Clinical stage		
I	23 (8%)	31 (11%)
IIa	75 (28%)	86 (31%)
IIb	105 (39%)	98 (35%)
IIIa	64 (24%)	61 (22%)
IIIb	1 (<1%)	0
IIIc	3 (1%)	1 (<1%)
IV	0	1 (<1%)
Hormone status		
Oestrogen receptor		
Positive	154 (57%)	154 (55%)
Negative	117 (43%)	124 (45%)
Progesterone receptor		
Positive	112 (41%)	108 (39%)
Negative	159 (59%)	170 (61%)
LVEF		
Median	66·0 (55·0–83·0)	66·0 (55·0–79·0)

Data are mean (SD), median (range), or n (%). EMEA=Europe, the Middle East, and Africa. ECOG=Eastern Cooperative Oncology Group. LVEF=left ventricular ejection fraction. *Includes two patients for whom race could not be recorded because of local regulations.

Table 1: **Baseline characteristics in the intention-to-treat population**

we calculated a point estimate and 95% CI for the difference between groups for the proportion of patients achieving pCR using the exact binomial approach. We also did an additional assessment of equivalence in pCR proportion in terms of the risk ratio. For equivalence to be accepted, the 95% CI for the risk ratio estimate had to fall within the margin of 0·74–1·35. We calculated this margin by meta-analysing two previous studies,[4,7] which revealed a pCR proportion with trastuzumab of 50%. In accordance with FDA and ICH guidelines, we used half of the lower bound of the 50% CI for the ratio of pCR between regimens with and without trastuzumab for the equivalence margin calculation. This lower bound was 1·82; back-transformation of half of log(1·82) to the original scale yielded the therapeutic equivalence margin for the risk ratio used in this study.

We also did sensitivity analyses (done separately for the treatment outcome difference and risk ratio) of pCR using a logistic regression model, with treatment group as a fixed effect and disease stage (stage I or II *vs* stage IIIa), oestrogen receptor status (positive *vs* negative), progesterone receptor status (positive *vs* negative), and geographical region (Europe, the Middle East and Africa *vs* America *vs* Asia) as covariates. We used a logistic regression model for treatment outcome difference and a log-binomial sensitivity analysis for risk ratio analysis. For the secondary efficacy analysis, we analysed overall response and breast conservation using descriptive statistics. We analysed other pCR rates (secondary efficacy endpoints) in the same way as for the primary efficacy endpoint.

The study was monitored by an independent data and safety monitoring board, consisting of a PK specialist, statistician, chairing physician, and independent physician. Additionally, an independent tumour review committee reviewed pathology reports and safety assessments and established the tumour response for the purposes of data analysis and reporting. This trial is registered with ClinicalTrials.gov, number NCT02162667.

Role of the funding source

Employees of the funder (SJL and SYL) had a role in study design, data analysis, data interpretation, and writing of the report, and had access to the raw data. Employees of the funder 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

Between Aug 7, 2014, and May 6, 2016, of the 781 patients screened, we randomly assigned 549 (70%) to CT-P6 (271 [49%]) or reference trastuzumab (278 [51%]; ITT population; figure). The PP population comprised 504 patients (248 [49%] in the CT-P6 group *vs* 256 [51%] in the reference trastuzumab group). Major protocol deviations that led to exclusion of patients from the PP set are detailed in the appendix. The safety analysis population comprised all patients in the ITT population (271 [49%] *vs* 278 [51%]). Baseline characteristics were similar between the two groups in the ITT population (table 1). Baseline characteristics in the PP population were similar to those in the ITT population, and were

	CT-P6 (n=248)	Reference trastuzumab (n=256)	Difference (95% CI)	Risk ratio (95% CI)
pCR	116 (46·8%; 40·4 to 53·2)	129 (50·4%; 44·1 to 56·7)	–0·04 (–0·12 to 0·05)	0·93 (0·78 to 1·11)
Breast pCR	128 (51·6%; 45·2 to 58·0)	141 (55·1%; 48·8 to 61·3)	–0·03 (–0·12 to 0·05)	0·94 (0·80 to 1·10)
pCR without DCIS	99 (39·9%; 33·8 to 46·3)	106 (41·4%; 35·3 to 47·7)	–0·01 (–0·10 to 0·07)	0·96 (0·78 to 1·19)
pCR according to clinical stage				
Stage I and II	95/190 (50·0%; 42·7 to 57·3)	111/202 (55·0%; 47·8 to 61·9)	..	..
Stage IIIa	21/58 (36·2%; 24·0 to 49·9)	18/54 (33·3%; 21·1 to 47·5)	..	..
Breast conservation	56 (22·6%; 17·5 to 28·3)	52 (20·3%; 15·6 to 25·8)	..	..
Overall response	216 (87·1%; 82·3 to 91·0)	221 (86·3%; 81·5 to 90·3)	..	..

Data are n (%; 95% CI), unless otherwise indicated. pCR=pathological complete response. DCIS=ductal carcinoma in situ.

Table 2: **Primary and secondary efficacy endpoints in the per-protocol population**

	CT-P6	Reference trastuzumab	Difference (95% CI)	Risk ratio (95% CI)
PP* pCR	116 (46·8%); 40·4 to 53·2	129 (50·4%); 44·1 to 56·7	–0·04 (–0·12 to 0·05)	0·93 (0·78 to 1·11)
PP* sensitivity analysis	..	..	–0·03 (–0·12 to 0·06)	0·93 (0·79 to 1·10)
ITT† pCR	118 (43·5%); 37·6 to 49·7	131 (47·1%); 41·1 to 53·2	–0·04 (–0·12 to 0·05)	0·92 (0·77 to 1·11)

Data are n (%; 95% CI), unless otherwise indicated. PP=per-protocol. pCR=pathological complete response. ITT=intention-to-treat. *n=248 for CT-p6 and n=256 for reference trastuzumab. †n=271 for CT-P6 and 278 for reference trastuzumab.

Table 3: **pCR analyses in the PP and ITT populations**

again similar between groups (appendix). Exposure to study drug and chemotherapy agents was also similar between groups (appendix).

A similar proportion of patients achieved pCR at the time of surgery in the CT-P6 (116 [46·8%; 95% CI 40·4–53·2] of 248 patients) and reference trastuzumab (129 [50·4%; 44·1–56·7] of 256) groups in the PP population according to central review (table 2, 3). The estimated difference in pCR proportion between the two groups was –0·04 (95% CI –0·12 to 0·05), with the 95% CI entirely within the prespecified equivalence margin of ±0·15. The risk ratio estimate for the pCR proportion in the PP population was 0·93 (95% CI 0·78–1·11) and the 95% CI for this estimate fell within the prespecified equivalence margin of 0·74 to 1·35. For both the difference and risk ratio, analyses of local investigator data yielded results identical to those from the central review. The sensitivity analysis of the PP population using treatment group as fixed effect, and clinical stage, oestrogen receptor status, progesterone receptor status, and geographical region as covariates, was similar to the primary analysis, as was the ITT analysis (table 3).

Secondary efficacy endpoints are summarised for the PP set in table 2. pCR proportions in the PP population were similar between groups when analysed according to clinical stage. A similar proportion of patients in each group achieved breast pCR. Results in the ITT population were similar to those in the PP population: 133 (49·1%) of 271 patients in the CT-P6 group achieved breast pCR compared with 145 (52·2%) of 278 in the reference trastuzumab group. The treatment outcome difference was –0·03 (95% CI –0·11 to 0·05), with the 95% CI falling within the prespecified ±0·15 equivalence margin. The risk ratio estimate was 0·94 (95% CI 0·80–1·11), with the 95% CI also falling within the equivalence margin. A similar proportion of patients in the CT-P6 and reference trastuzumab groups achieved pCR without DCIS in the PP population (table 2).

Among patients who were hormone receptor positive in the PP population, 59 (40%) of 149 patients showed a pCR in the CT-P6 group compared with 61 (41%) of 150 in the reference trastuzumab group. Among patients who were hormone receptor negative, 57 (58%) of 99 patients showed a pCR in the CT-P6 group compared with 68 (64%) of 106 in the reference trastuzumab group.

The most common type of surgery in both groups in the PP population was mastectomy (168 [68%] of 248 patients in the CT-P6 group *vs* 173 [68%] of 256 in the reference trastuzumab group). The proportion of patients who had breast-conserving surgery (lumpectomy) was similar between groups in the PP population (table 2). Results in the ITT population were similar to those for the PP population (mastectomy 174 [64%] of 271 in the CT-P6 group *vs* 176 [63%] of 278 in the reference trastuzumab group; lumpectomy 57 [21%] *vs* 53 [19%]). Overall response was similar between groups, based on central review in the PP population (table 2). Overall response for the ITT population was similar to that for the PP population: 230 (84·9% [95% CI 80·0–88·9]) of 271 patients had an overall response in the CT-P6 group compared with 234 (84·2% [79·3–88·3] of 278 in the reference trastuzumab group.

No notable differences occurred in PK endpoints between groups at any cycle in the neoadjuvant period. In cycle 1, mean reference trastuzumab C_{max} was 186·43 µg/mL (coefficient of variation 37·06%) in the

	CT-P6 (n=271)	Reference trastuzumab (n=278)
TEAEs		
Total number of TEAEs	2424	2660
TEAEs	255 (94%)	264 (95%)
Treatment-related	112 (41%)	129 (46%)
Grade 1–2	95 (35%)	106 (38%)
Grade 3	11 (4%)	9 (3%)
Grade 4	6 (2%)	13 (5%)
Grade 5	0	1 (<1%)
Total number of treatment-emergent SAEs	23	32
Treatment-emergent SAEs	19 (7%)	22 (8%)
Treatment-related	5 (2%)*	7 (3%)†
Grade 1–2	0	1 (<1%)
Grade 3	2 (1%)	1 (<1%)
Grade 4	3 (1%)	4 (1%)
Grade 5	0	1 (<1%)
TEAEs leading to discontinuation	7 (3%)	9 (3%)
Treatment-related SAEs leading to discontinuation	0	2 (1%)‡
Deaths	2 (1%)	1 (<1%)
TEAEs of special interest		
Cardiac disorders	23 (8%)	28 (10%)
Treatment-related	17 (6%)	18 (6%)
Infections	55 (20%)	50 (18%)
Treatment-related	12 (4%)	11 (4%)
Infusion-related reactions	23 (8%)	25 (9%)
Treatment-related	14 (5%)	14 (5%)
Treatment-related TEAEs reported in ≥5% of either group		
Alopecia	21 (8%)	25 (9%)
Neutropenia	13 (5%)	25 (9%)
Nausea	15 (6%)	19 (7%)
Infusion-related reaction	14 (5%)	14 (5%)
Anaemia	7 (3%)	18 (6%)
Diarrhoea	14 (5%)	12 (4%)

Data are n or n (%). TEAE=treatment-emergent adverse event. SAE=serious adverse event. *Events occurring in more than one patient in either group occurred in five patients (febrile neutropenia [grade 3, n=1; grade 4, n=3] and neutropenia [grade 4, n=1]) †Events occurring in more than one patient in either group occurred in three patients (febrile neutropenia [grade 4, n=1] and neutropenia [grade 4, n=2]). ‡Acute myocardial infarction (death) and cerebral infarction (grade 4). Full adverse events are available in the appendix.

Table 4: **Summary of adverse events (safety population)**

CT-P6 group versus 178·57 µg/mL (31·01%) in the reference trastuzumab group. C_{max} remained stable and similar between the two groups throughout cycles 2–8. Cycle 1 mean reference trastuzumab C_{trough} values were 18·92 µg/mL (121·58%) versus 18·91 µg/mL (112·65%), remaining stable and similar between the two groups throughout cycles 2–8 (appendix).

The mean concentration of HER2 extracellular shed antigen decreased from baseline in both groups. At baseline, mean concentrations were 12426·8 pg/mL (SD 9176·8) in the CT-P6 group versus 11925·3 pg/mL (8578·6) in the reference trastuzumab group (appendix). After cycle 4, change from baseline was –6284·6 pg/mL (SD 8658·4) versus –6043·2 pg/mL (8594·0). At the end of neoadjuvant treatment (cycle 8), change from baseline was –5569·8 pg/mL (SD 8751·8) versus –5290·2 pg/mL (8708·3). Actual antigen concentrations were also similar between groups at each timepoint measured (appendix).

The proportion of patients reporting at least one treatment-emergent adverse event was similar between the two groups (table 4). The most frequent treatment-emergent adverse events in the CT-P6 group were alopecia, nausea, infusion-related reactions, and diarrhoea, whereas in the reference trastuzumab group, they were alopecia, neutropenia, and nausea. All treatment-emergent adverse events of grade 3 or worse and of grade 1–2 occurring in at least 10% of patients, and all treatment-related cardiac events of any grade that were observed during the study, are given in the appendix. Grade 3 or worse treatment-related adverse events occurred in 17 (6%) of 271 patients in the CT-P6 group versus 23 (8%) of 278 in the reference trastuzumab group; neutropenia was the only frequently reported (>3% of patients) event, occurring in ten (4%) versus 14 (5%). A similar proportion of patients in each group had treatment-emergent adverse events leading to discontinuation (table 4). In the CT-P6 group, one death had no causal relationship to the study drug, but a potential role of metastases could not be fully ruled out, and the other death was due to dyspnoea, with underlying causes of deep vein thrombosis, pulmonary hypertension, and pulmonary embolism, and was considered unrelated to the study drug. The single death in the reference trastuzumab group, due to acute myocardial infarction, was considered possibly related to the study drug. The patient had a history of severe hypertension and ischaemic heart disease.

Treatment-emergent adverse events due to heart failure were reported in five (2%) of 271 patients in the CT-P6 group and three (1%) of 278 in the reference trastuzumab group. Of these patients, only one individual in the reference trastuzumab group was withdrawn from the study (because of a confirmed decrease in LVEF). One patient in the CT-P6 group had grade 1 heart failure, but no substantial decrease in LVEF (6% decrease from baseline; LVEF remained above 55%). The investigator confirmed that this patient had no signs or symptoms of heart failure. LVEF measurements are presented in table 5. Infusion-related reactions were reported in 23 (8%) of 271 patients in the CT-P6 group versus 25 (9%) of 278 in the reference trastuzumab group (table 4), and most were grade 1 or 2 (22 [96%] of 23 in the CT-P6 group *vs* 24 [96%] of 25 in the reference trastuzumab group). No notable differences occurred between the two groups in other safety outcomes (data not shown). All postinfusion antidrug antibody tests were negative.

Discussion

The results of this randomised, double-blind, active-controlled trial substantiate the therapeutic equivalence of CT-P6 and reference trastuzumab using two different predefined equivalence margins. The trial achieved its primary endpoint by showing that an equivalent proportion of patients with HER2-positive, operable, early-stage breast cancer treated in the neoadjuvant setting had a pCR with CT-P6 compared with reference trastuzumab. All secondary endpoints assessable at the end of the neoadjuvant period were similar between groups. CT-P6 was well tolerated, with a similar safety profile to that of reference trastuzumab.

Trastuzumab has greatly improved treatment of HER2-positive breast cancer. In the GeparQuattro study,[6] 32% of patients with operable or locally advanced HER2-positive breast cancer achieved pCR with chemotherapy and trastuzumab compared with 16% of those with HER2-negative tumours receiving chemotherapy alone. In the Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant trial,[8] 39% of patients with HER2-overexpressing breast cancer achieved pCR with trastuzumab and chemotherapy, and pCR was associated with improved proportions of 3 year disease-free and overall survival compared with patients who did not achieve pCR. Similarly, in the Neoadjuvant Herceptin trial,[7] 39% of patients achieved pCR with trastuzumab plus chemotherapy compared with 20% of patients receiving chemotherapy alone. Event-free survival was strongly associated with pCR.[34]

However, despite the importance of trastuzumab for treatment of HER2-positive cancers—including metastatic breast and gastric cancers—the cost of the drug creates barriers to access. A course of trastuzumab can cost up to US$70 000.[35] Almost half of oncologists in one survey[36] reported that they would increase use of trastuzumab if a biosimilar product was available. Total cost savings in individual countries from adoption of CT-P6 will depend on many factors, including market penetration and price; a budget effect model in Croatia has predicted 1 year cost savings of up to €0·69 million from introduction of biosimilar trastuzumab.[37] The Congressional Budget Office previously estimated that biosimilars could reduce total expenditure on biologicals in the USA by approximately $25 billion over a decade.[38] A study in Europe found that the average discount for biosimilars versus reference products was approximately 15% (ranging from 0–32%), but was country and product dependent.[14]

Various potential biosimilars to reference trastuzumab are in development. PF-05280014 (Pfizer, New York, NY, USA) has shown similar PK[39] and non-clinical[40] characteristics to the US-licensed and EU-licensed reference trastuzumab. In metastatic breast cancer, a phase 3 trial[41] has shown non-inferiority of BCD-022 (BIOCAD, St Petersburg, Russia) to reference trastuzumab in terms of overall response. Additionally, Rugo and colleagues[42] showed equivalent efficacy and similar safety profiles of Hertaz (Biocon [Bangalore, India]/Mylan [Canonsburg, PA, USA]) and trastuzumab in the only other full report of a phase 3 study to date. Physicians might consider pCR proportion to be a more credible endpoint than overall response for equivalence studies.[21] This preference is because increasing evidence, including results of a pooled analysis of almost 12 000 patients treated in the neoadjuvant setting,[20] indicates that pCR is associated with overall survival.[7,18,19] The FDA encourages use of pCR[22] as an endpoint to support accelerated approval of agents for neoadjuvant treatment of high-risk, early-stage breast cancer because it can be evaluated after short periods of treatment.

We determined the equivalence margin used in this study by meta-analysis (unpublished) of pCR proportions arising from taxane, FEC, and trastuzumab combination therapy from nine published studies. This analysis, together with consideration of the precision range and European regulatory precedents, led to a proposed margin of 15%, which we considered appropriate and provided adequate assay sensitivity. Furthermore, the margin was in line with those used in trials[42,43] of other trastuzumab biosimilars.

This study showed therapeutic equivalence of biosimilar CT-P6 to reference trastuzumab in patients with early-stage, operable, HER2-positive breast cancer, whereas other studies, including two phase 3 trials of other proposed trastuzumab biosimilars,[20,21] have focused on metastatic disease.[41,42] Patients with early-stage, operable disease might be a more suitable population for equivalence studies than might those with metastatic disease.[44]

	CT-P6 (n=271)	Reference trastuzumab (n=278)
Baseline*	66·0 (55·0–83·0)	66·0 (55·0–79·0)
After cycle 4†	65·0 (38·0–80·0)	65·0(42·0–85·0)
End of neoadjuvant period (cycle 8)‡	64·0 (44·0–82·0)	64·0 (44·0–78·0)
Overall worst value§¶	62·0 (38·0–76·0)	62·8 (37·0–77·0)
No decrease	74 (27%)	89 (32%)
Decrease of <10 points from baseline	160 (59%)	151 (54%)
Decrease of ≥10 points from baseline	33 (12%)	32 (12%)
45 to <50 points	3 (1%)	1 (<1%)
<50 points and decrease of ≥10 points from baseline	5 (2%)	3 (1%)
<45 points and decrease of ≥10 points from baseline	2 (1%)	2 (1%)

Data are median (range) or n (%). LVEF=left ventricular ejection fraction. *n=271 for CT-P6 and n=277 for reference trastuzumab. †n=262 for CT-P6 and n=263 for reference trastuzumab. ‡n=266 for CT-P6 and n=268 for reference trastuzumab. §Lowest postbaseline value. ¶n=267 for CT-P6 and n=272 for reference trastuzumab.

Table 5: **LVEF (safety population)**

This advantage is because those with early-stage, operable disease tend to be a more homogeneous population with similar disease history and have lower disease burden and risk of secondary tumours or serious adverse events than patients with metastatic disease. A further strength of this study is that the dosing regimens in the neoadjuvant and adjuvant settings were the same as those approved for reference trastuzumab in Europe and the USA. Additionally, although the chemotherapy backbone in neoadjuvant trastuzumab-based regimens varies across trials, sequential use of a taxane and an anthracycline-containing regimen, as used in this study, is considered standard of care in this setting.[10] In many countries, trastuzumab and taxane are now used in combination with the HER2 receptor antagonist pertuzumab, as this dual anti-HER2 therapeutic approach has been shown to further improve pCR.[45]

A potential limitation of this study is that, in clinical practice, docetaxel can be administered at doses of up to 100 mg/m² in the neoadjuvant setting.[10] We did, however, select the dosing regimen of docetaxel used in this study (75 mg/m² every 3 weeks) on the basis of literature evidence. Various studies[46,47] have reported neoadjuvant treatment of HER2-positive breast cancer with trastuzumab in combination with this regimen (with or without FEC) to be efficacious. Additionally, some studies suggest that increasing the dose of docetaxel can affect safety and efficacy. A key study by Harvey and colleagues[48] in 2006 examined the effects of increasing docetaxel dose in patients with breast cancer and found a dose-response relationship with respect to efficacy and toxicity. The proportion of assessable patients with a tumour response receiving 60 mg/m² docetaxel every 3 weeks was 22%, receiving 75 mg/m² was 23%, and receiving 100 mg/m² was 36%, with a significant dose-response relationship in the assessable (p=0·007) and ITT (p=0·026) populations. Incidences of most haematological and non-haematological toxicities were also related to increasing dose, with grade 3–4 neutropenia occurring in 76% of patients receiving 60 mg/m², 84% of those receiving 75 mg/m², and 93% of those receiving 100 mg/m², and with febrile neutropenia occurring in 5% of those receiving 60 mg/m², 7% of those receiving 75 mg/m², and 14% of those receiving 100 mg/m². The authors concluded that although all three doses of docetaxel were active and regarded to show manageable toxicity, dose selection should be made on the basis of treatment goals and patient characteristics.[48] In our study, we considered 75 mg/m² docetaxel every 3 weeks, which had moderate efficacy and toxicity in the study by Harvey and colleagues,[48] to be the most appropriate dose. We also considered this regimen to be preferable to a weekly dosing regimen. We also selected the dose of epirubicin used in this study on the basis of literature evidence. Phase 3 randomised controlled trials[5,49] in patients with HER2-positive breast cancer have shown the efficacy of this dose in the neoadjuvant setting, including in combination with trastuzumab. Additionally, the role of fluorouracil in the presence of epirubicin and cyclophosphamide has been the subject of some debate. However, as the chemotherapy regimen used was the same across both treatment groups, we do not believe these factors to have influenced between-group pCR comparisons.

We did the primary analysis in the PP rather than the ITT population as recommended by ICH E9[25] and FDA[50] guidelines for non-inferiority trials. By contrast with a superiority trial for which the ITT population is preferred, analysis of the results of an equivalence trial in the ITT population—which includes patients who withdraw, drop out, or show non-adherence—can bias the results in favour of equivalence and undermine the validity of the trial. We did, however, repeat the analysis in the ITT population and obtained similar results.

After completion of the neoadjuvant period, patients received up to ten further cycles of single-agent CT-P6 or reference trastuzumab in the adjuvant period to bring total treatment up to a maximum of 1 year from the first day of receiving neoadjuvant study drug to the end of the adjuvant period. They then entered a post-treatment follow-up period, which will continue for up to 3 years after the date of enrolment of the last patient. Disease-free, progression-free, and overall survival efficacy endpoints will be evaluated to assess the long-term equivalence of CT-P6 to reference trastuzumab. As pCR is only a surrogate for disease-free and overall survival, long-term follow-up of this study will be important to assess these outcomes, although the trial is not powered for survival. Additional long-term data collection and follow-up analysis is under consideration by the funder.

Contributors

SJL, SYL, and FJE conceived and designed the study, including protocol development. AE, AM, AR, DB, DK, DS, EZ, GD, GM-B, JP, RKL, VB, VM, and YB reviewed the protocol, acquired and managed data, and reviewed study results. SJL and SYL analysed data. SJL, SYL, and FJE interpreted data. JS, SJL, SYL, and FJE developed the manuscript. All authors reviewed the manuscript and approved the final version.

Declaration of interests

SJL and SYL are employees of Celltrion Inc. YB, VB, and AE have received grants from Celltrion Inc during the conduct of this study. YB has also received non-financial support from Roche and Pfizer and personal fees from Roche outside of the submitted work. AE has also received grants from Roche during the conduct of this study and from AstraZeneca and Pfizer outside of the submitted work. FJE has received personal fees from Celltrion Inc during the conduct of this study and personal fees from Celltrion Inc, Genentech, and Pfizer outside of the submitted work. JS is supported by the Biomedical Research Centre, Imperial College London, and the National Institute for Health Research. All other authors declare no competing interests.

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