

Development of a Subcutaneous Fixed-Dose Combination of Pertuzumab and Trastuzumab: Results From the Phase Ib Dose-Finding Study

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Abstract

Adding pertuzumab to trastuzumab (both monoclonal antibodies targeting human epidermal growth factor receptor 2 [HER2]) has proven survival benefits when combined with chemotherapy for patients with HER2-positive breast cancer. The combination of pertuzumab and trastuzumab together in 1 vial for subcutaneous (SC) administration is being developed as a ready-to-use formulation to reduce the treatment burden on patients while improving healthcare efficiency. An open-label, 2-part, phase Ib dose-finding study (NCT02738970) was undertaken in healthy male volunteers (part 1) and female patients with HER2-positive early breast cancer who had completed standard (neo)adjuvant treatment (part 2). This study aimed to identify an SC pertuzumab dose given with recombinant human hyaluronidase that results in comparable exposure to that of the intravenous (IV) pertuzumab dose, based on pertuzumab serum trough concentration and area under the serum concentration–time curve. Pharmacokinetics (PK), safety, and tolerability of a single dose of SC pertuzumab given alone or in a fixed-dose combination (comixed or coformulated) with trastuzumab were also assessed. A maintenance dose of 600 mg for SC pertuzumab resulted in an equivalent exposure to that of IV pertuzumab, and no new safety signals were identified for SC pertuzumab or trastuzumab. A loading dose of 1200 mg for SC pertuzumab was selected based on approximate dose proportionality. The PK and safety results support further development of a fixed-dose coformulation combination of pertuzumab and trastuzumab for SC administration, which will be investigated in an upcoming phase III trial in patients with HER2-positive early breast cancer.

Keywords

pertuzumab, trastuzumab, subcutaneous, population pharmacokinetics, HER2-positive, breast cancer, dose-finding

Overexpression or gene amplification of human epidermal growth factor receptor 2 (HER2) occurs in approximately 15% to 20% of breast cancers¹ and is associated with a poor prognosis.² Adding pertuzumab (PERJETA; F. Hoffmann-La Roche Ltd, Basel, Switzerland) to trastuzumab (Herceptin; F. Hoffmann-La Roche Ltd)—both monoclonal antibodies targeting HER2—has proven survival benefits when combined with chemotherapy for patients with HER2-positive breast cancer across the neoadjuvant,^{3,4} adjuvant,⁵ and metastatic treatment settings.^{6,7}

Pertuzumab and trastuzumab bind to distinct epitopes on HER2 and do not compete for binding sites. As such, they have complementary mechanisms of action in the disruption of HER2 signaling, which results in augmented antiproliferative activity in vitro and in vivo when the 2 antibodies are administered as a combination.⁸

The subcutaneous (SC) route of administration is preferred by patients over intravenous (IV) administration for drugs such as trastuzumab

(Herceptin SC; F. Hoffmann-La Roche Ltd)^{9,10} and rituximab (MabThera; F. Hoffmann-La Roche Ltd),^{11,12} and is associated with reduction in patients' infusion chair time, healthcare professionals' time, and other hospital resources.^{13,14} SC trastuzumab is given

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over 2–5 minutes,¹⁵ compared with IV trastuzumab, which is given over 30–90 minutes, similar to IV pertuzumab, which is given over 30–60 minutes.^{16,17} Similar benefits have also been reported for SC trastuzumab given with IV pertuzumab.^{18,19} However, repeated, invasive IV access can be associated with increased risk of infection, thrombosis, discomfort, and higher costs.^{20,21} In order to further reduce the treatment burden on patients while also further improving efficiency of treatment facility utilization, a fixed-dose combination (FDC, ie, coformulation) of pertuzumab and trastuzumab together in 1 vial for SC administration has been developed as a ready-to-use formulation to provide another convenient treatment option for patients and healthcare professionals.

Bridging from IV to SC dosing relies on the development strategy of using the same antibody in the IV and SC formulations and conducting dedicated preclinical and toxicology studies for the SC formulation. Additionally, the aims of a clinical development program include demonstrating pharmacokinetic (PK) noninferiority between the IV and SC formulations (lower bound of the 90%CI of the serum trough concentration [C_{trough}] geometric mean ratio [GMR] SC/IV ≥ 0.8), showing a consistent safety profile between the SC and IV formulations and providing supportive efficacy data. To date, trastuzumab and rituximab have successfully bridged from IV to SC by following this clinical development plan.^{15,22–25}

Fixed-dose SC trastuzumab has a similar safety profile to that of IV trastuzumab and is noninferior in terms of pathologic complete response and C_{trough} in patients with early breast cancer,²² supported by long-term safety and efficacy results (6-year event-free survival and overall survival)²⁶ in the HannaH (enHANced treatment with NeoAdjuvant Herceptin) study (NCT00950300). Similarly, the SABRINA (Subcutaneous Administration BRIdgiNg for PhAse 3) study (NCT01200758) showed that the SC formulation of rituximab had comparable efficacy and safety to the IV formulation and was demonstrated to be noninferior in terms of PK.^{23,27}

The FDC of pertuzumab and trastuzumab contains the permeation-enhancer recombinant human hyaluronidase PH20 (rHuPH20; ENHANZE Drug Delivery Technology, Halozyne, Inc., San Diego, California), an enzyme that allows absorption and dispersion of large fluid volumes by temporarily degrading hyaluronan at the local injection site.²⁸

The current study aimed to identify an SC pertuzumab dose that results in comparable exposure to the IV pertuzumab dose, based on SC pertuzumab C_{trough} and area under the serum concentration–time curve (AUC) when administered with or without SC trastuzumab.

Additionally, the safety and tolerability of a single dose of SC pertuzumab given alone or in combination with trastuzumab (both therapies in a single injection [comixed] or coformulated in a ready-to-use single injection) were assessed in healthy male volunteers and in female patients with early breast cancer who had completed standard breast cancer therapy (chemotherapy and biologic therapy).

The PK and safety data generated in this phase Ib study were used to identify a pertuzumab dose for the SC FDC (coformulation) of pertuzumab and trastuzumab for investigation in a phase III trial in patients with HER2-positive early breast cancer. The FDC is expected to achieve noninferior trastuzumab and pertuzumab steady-state C_{trough} ($C_{\text{trough,ss}}$) and AUC (AUC_{ss}) compared with those achieved with 3-weekly IV trastuzumab or pertuzumab administrations.

Methods

Approval for the protocol and for any modifications was obtained from an independent ethics committee (Health and Disability Ethics Committees, Ministry of Health, Wellington, New Zealand). All subjects provided written, informed consent before the start of the study, and the study was conducted in full concordance with the International Council for Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The study was conducted at Christchurch Clinical Studies Trust and Auckland Clinical Studies in New Zealand.

Study Objectives

This open-label, 2-part, phase Ib dose-finding study (BO30185; NCT02738970) was conducted at 2 centers in New Zealand. The study consisted of 2 parts: dose finding (part 1; cohorts 1–8) and dose confirmation (part 2; cohort A or cohorts B and C) (Figure 1).

The primary objectives for part 1 of the study were to select an SC loading and maintenance dose of pertuzumab that resulted in comparable exposure to IV pertuzumab with or without coadministered/comixed SC trastuzumab and to assess whether additional rHuPH20 is required when pertuzumab and trastuzumab are administered as a comixed SC formulation in healthy male volunteers.

For part 2, the primary objective was to confirm the dose of SC pertuzumab comixed or coformulated with SC trastuzumab. Fixed-dose pertuzumab and trastuzumab were administered as a single injection, either comixed at the study site (cohort B) or as a ready-to-use FDC (cohort C) administration in patients with early breast cancer.

The secondary objective was to assess the safety and tolerability of SC pertuzumab given alone or in combination with trastuzumab (comixed or coformulated) in

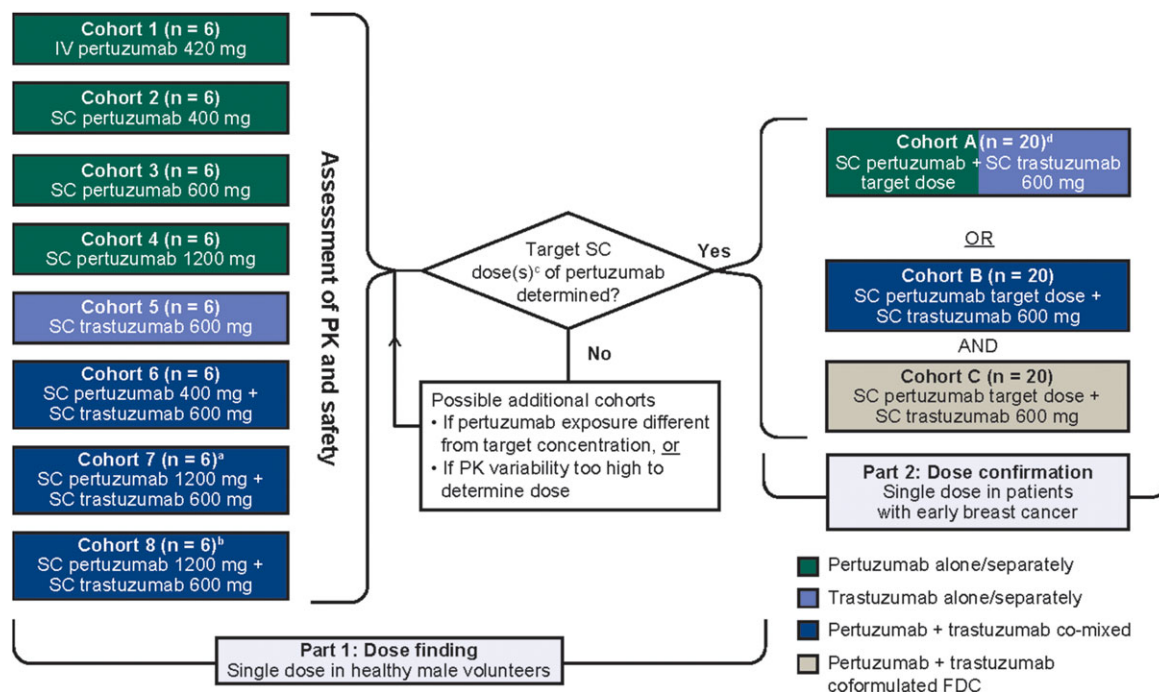


Figure 1. Study design. ^arHuPH20 concentration = 2000 U/mL. ^brHuPH20 concentration = 667 U/mL. ^cCalculated to deliver a similar exposure to a 420 mg IV dose. ^dOnly if coformulated FDC is not feasible. FDC indicates fixed-dose combination; IV, intravenous; PK, pharmacokinetics; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

healthy male volunteers and female patients with early breast cancer.

Study Design

The selection of the SC pertuzumab doses for investigation in part 1 (cohorts 2, 3, 4, 6, and 7) was based on an IV pertuzumab population PK (popPK) model²⁹ with the addition of SC absorption-related parameters based on human SC trastuzumab PK.³⁰ Using part 1 PK data, an SC pertuzumab dose was selected to achieve a similar pertuzumab exposure to that of IV pertuzumab at 420 mg (maintenance dose) and at 840 mg (loading dose). The selected maintenance dose from part 1 was subsequently confirmed in part 2 of the study in patients with early breast cancer. All participants received a single dose of study treatment(s).

The selection of 600 mg SC trastuzumab for all monotherapy (part 1, cohort 5), comixed (part 1, cohorts 6, 7, and 8; part 2, cohort B) and coformulation administrations (part 2, cohort C) was based on the established, clinically approved dose.^{15,22,31}

The impact of a lower concentration of rHuPH20 on PK was assessed in part 1, cohorts 7 and 8 (both comixed). In cohort 7 both SC trastuzumab (600 mg in 5-mL injection) and SC pertuzumab (1200 mg in 10-mL injection) contained 2000 U/mL rHuPH20 (total injection 15 mL with 2000 U/mL rHuPH20), whereas in cohort 8, SC trastuzumab (600 mg in 5-mL injection) contained 2000 U/mL rHuPH20,

and SC pertuzumab (1200 mg in 10-mL injection) contained 0 U/mL rHuPH20 (total injection 15 mL with 667 U/mL rHuPH20).

If during part 1 of the study there was a PK interaction between pertuzumab and trastuzumab when these drugs were administered in a comixed SC injection, or if the development of the FDC was not technically feasible, only cohort A (coadministration) was to be enrolled in part 2. Otherwise, cohorts B and C (and not cohort A) were to be enrolled in part 2. This allowed for the selection of an SC pertuzumab dose and formulation option for further evaluation in a phase III study while enrolling the smallest number of subjects. Additionally, the comixed formulation (part 1, cohorts 6, 7, and 8; part 2, cohort B), which was nearly identical to the coformulation, was used as a surrogate placeholder while manufacture of the coformulated FDC was under way.

Subjects

For part 1, eligible healthy male volunteers were 18–45 years of age, had a left ventricular ejection fraction (LVEF) $\geq 55\%$ with no history of cardiac conditions, had a body mass index of 18–32 kg/m², and had normal intact thigh skin. For part 2, eligible female patients with early breast cancer who had completed standard (neo)adjuvant treatment >7 months prior to study drug administration, per local practice and guidelines, were ≥ 18 years of age, had an Eastern

Cooperative Oncology Group Performance Status of 0, nonmetastatic adenocarcinoma of the breast, and baseline LVEF $\geq 55\%$. Adjuvant endocrine therapy was also permitted.

The sample sizes for both parts 1 and 2 were determined by using simulations, given the sampling time schedule and assumptions on the PK parameters. The uncertainty on the estimates of the fixed parameters was expected to be lower than 30% for a number of 6 subjects per cohort in part 1 and lower than 20% with 20 additional patients receiving SC in part 2.

Procedures

Each healthy male volunteer or female patient with early breast cancer received a single dose of assigned study treatment, and all SC administrations were made into the anterior thigh region. A single dose of SC pertuzumab was given alone (part 1, cohorts 2–4) or comixed (part 1, cohorts 6–8), where SC pertuzumab was given mixed with SC trastuzumab 600 mg as a single injection. Patients in part 1, cohort 1 received a single dose of IV pertuzumab 420 mg, and patients in part 1, cohort 5 received a single dose of SC trastuzumab 600 mg. Patients in part 2, cohort B received a single comixed injection of SC pertuzumab and trastuzumab 600 mg as prepared by the pharmacist at the study site. The cohort B dose was based on the pertuzumab PK data from part 1 of the study and the previously established trastuzumab dose. Patients in part 2, cohort C received a single FDC of pertuzumab and trastuzumab 600 mg, prepared as a ready-to-use formulation for SC injection. The cohort C dose was based on the pertuzumab PK data from part 1, cohorts 2–4 and 6–8, and part 2, cohort B and the previously established trastuzumab dose. The single SC pertuzumab doses evaluated in cohorts B and C were maintenance doses and were intended to be equivalent to IV pertuzumab 420 mg maintenance doses. The SC pertuzumab coadministration with SC trastuzumab (2 separate SC injections) arm of the study was not enrolled (part 2, cohort A) following the results of part 1 of the study and the positive technical feasibility assessment of manufacturing the ready-to-use FDC.

Different pertuzumab SC doses were administered by adjusting the dosing volume. The concentrations of pertuzumab and trastuzumab were 120 mg/mL, and rHuPH20 was 2000 U/mL (cohorts 2–7) in the SC dosing solutions. Cohorts 6 and 7 received comixed SC pertuzumab and SC trastuzumab containing 2000 U/mL rHuPH20, the same concentration used in marketed SC trastuzumab and SC rituximab. Cohort 8 received a lower concentration of rHuPH20 (667 U/mL), as 10 mL SC pertuzumab with no rHuPH20 was comixed with 5 mL SC trastuzumab with 2000 U/mL rHuPH20.

Pertuzumab and trastuzumab PK samples for SC administration were collected at predose; 6, 8, and 12 hours postdose; on days 2, 3, 5, 8, 10, 15, 22, 43, and 85; and at follow-up (approximately 7 months after study drug administration). Pertuzumab PK samples for IV administration were collected at predose; 1.5 and 3 hours postdose; on days 2, 3, 5, 8, 15, 22, 35, 43, and 85; and at follow-up. The end of study was defined as the date when the last subject's last visit occurred, and for each subject (healthy male volunteers and female patients with early breast cancer), the screening period was up to 4 weeks, and follow-up was performed approximately 7 months after study drug administration.

Bioanalytical Methods and Data Handling

A validated high-performance immunoaffinity liquid chromatography tandem mass spectrometry assay was used to measure the concentration of pertuzumab and trastuzumab in serum samples, where the minimum quantifiable concentration for both analytes was 100 ng/mL.²¹ For trastuzumab, the assay showed acceptable interassay precision (percent coefficient of variation) and accuracy (percent difference) with ranges of 3.07% to 8.44% and -8.08% to -1.47% , respectively. For pertuzumab, the assay showed acceptable interassay precision (percent coefficient of variation) and accuracy (percent difference) with ranges of 3.18% to 5.90% and -6.74% to -2.35% , respectively. The PK results presented here for trastuzumab and pertuzumab were based on the PK data collected throughout part 1 (until the end of day 85 or discontinuation) and part 2 (until the end of day 43 or discontinuation).

The PK results for rHuPH20 are based on PK data collected on days 1 and 2 in parts 1 and 2 of the study. rHuPH20 serum concentrations were measured by a validated sandwich immunoassay using electrochemiluminescence with a minimum quantifiable concentration of 0.6144 ng/mL. Standards and quality controls were prepared by spiking human tripotassium ethylenediaminetetraacetic acid plasma with rHuPH20, and then standards, controls, and samples were added to a plate coated with a mouse anti-rHuPH20 monoclonal antibody mixture. Biotin-labeled rabbit anti-rHuPH20 monoclonal antibody, SULFO-TAG Streptavidin (Meso Scale Diagnostics LLC, Rockville, Maryland), and MSD Read Buffer T (Meso Scale Diagnostics LLC) were also added. Raw electrochemiluminescent signals/counts at 620 nm were directly proportional to the amount of rHuPH20 in calibrators as described by a 5-parameter logistic Marquardt equation with a weighting factor of $1/Y^2$. The interpolation of electrochemiluminescent counts was performed using Watson LIMS data reduction software (v7.3; Thermo Fisher Scientific, Inc., Rockville, Maryland).

The PK analysis population included all enrolled patients who received a dose of the study drug and had at least 1 PK sample collected.

PK Analyses and Clinical Trial Simulations to Select the SC Pertuzumab Dose

Noncompartmental and statistical methods were used to describe pertuzumab and trastuzumab PK data following SC administration with rHuPH20, to confirm a lack of drug-drug interaction between SC pertuzumab and SC trastuzumab when comixed and to assess the impact of rHuPH20 concentration on pertuzumab PK.

Noninferior loading and maintenance doses for SC pertuzumab were evaluated by analyzing SC and IV pertuzumab PK data in a nonlinear mixed-effects model with NONMEM software (Version 7.2, ICON plc, Dublin, Ireland), using the first-order conditional estimation method with interaction. A 2-compartment model was built to estimate pertuzumab PK parameters using the SC and IV results from part 1. Absorption of the SC formulation was modeled as first-order, and uncertainty in model parameters was derived from 1000 bootstrap runs. Interindividual variability of clearance, central volume, and first-order absorption rate constant were modeled as diagonal. The proportional residual error was estimated for SC and IV pertuzumab independently in order to estimate σ most accurately.

The popPK model was used to simulate 400 phase III clinical trials of 250 patients per arm receiving chemotherapy beginning in cycle 1 and 3 doses of pertuzumab (1 loading and 2 maintenance) and trastuzumab beginning in cycle 5 (all cycles are 21 days). Per simulated trials, the GMR SC/IV and 90%CI of cycle 7 $C_{\text{trough,ss}}$ (ie, cycle 8 predose) and AUC_{ss} were calculated. The aim of the simulations at the end of part 1 was to determine the dose that would give a mean SC $C_{\text{trough,ss}}$ noninferior to IV $C_{\text{trough,ss}}$. The probabilities of the lower bound of the 90%CI of the GMR being ≥ 0.8 (noninferiority criteria for bioequivalence) were determined following different SC pertuzumab doses (400, 500, 550, 600, and 700 mg). The probabilities resulting from the simulations were used to select the minimum SC pertuzumab dose with sufficiently high probability (ie, $\geq .099$) of resulting in noninferior exposure to IV pertuzumab (420 mg) in a phase III study.

Following the pertuzumab SC dose decision in part 1, the popPK model was refreshed with additional PK data collected from part 1 (day 85) and part 2, cohort B, the phase III trial simulations repeated, and the resulting probabilities of the lower bound 90%CI of the SC/IV GMR ≥ 0.8 redetermined. The popPK model and clinical trial simulations were similarly refreshed

once part 2, cohort C data became available. The final phase III trial simulations were based on the results from part 1 and part 2, cohorts B and C.

The phase III trial simulations accounted for the model uncertainty and inter- and intraindividual variability. Individual PK exposures were simulated by sampling the interindividual variability of the PK models. Intraindividual variability was also included by sampling the residual of the models. Different treatment scenarios were simulated in separate phase III trials, and geometric mean ratios of the compared scenarios were calculated from the individual exposure of each trial. To include uncertainty of the PK model, the simulations were repeated 400 times using the PK parameters sampled from the bootstrap runs of the final PK models.

Safety Assessments

Safety was assessed in all subjects who received a dose of study drug, from enrollment to clinical cut-off (part 1, April 6, 2017; part 2, December 28, 2017). Safety was evaluated based on the incidence and severity of adverse events (AEs) (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v4.03), LVEF, symptomatic left ventricular systolic dysfunction (per New York Heart Association classification), and changes in clinical laboratory results. In an individual subject, the administration of study treatment had to be stopped if, during SC administration, the subject experienced a severe drug-related AE or an NCI-CTCAE grade ≥ 3 hypersensitivity reaction. Overall, dosing should not have been further administered in any other healthy male volunteer or patient with early breast cancer if any of the following events occurred (unless it was obvious that the occurrence was not related to the administration of the treatment): severe drug-related AE, hypersensitivity reactions according to the NCI-CTCAE (grade ≥ 3), LVEF drop of >10 percentage points or to $<50\%$ (for healthy male volunteers), an LVEF drop of >10 percentage points and to $<50\%$ (for patients with early breast cancer). Results are descriptive.

Results

Study Population and Demographics

Forty-eight healthy male volunteers were enrolled in part 1 of the study and randomized into cohorts 1–8 ($n = 6$ per cohort). Healthy male volunteers' ages ranged from 18 to 38 years, and body weight ranged from 54 to 105 kg across cohorts (Supplemental Table S1). Each healthy male volunteer received a single injection of study drug(s) according to his assigned cohort.

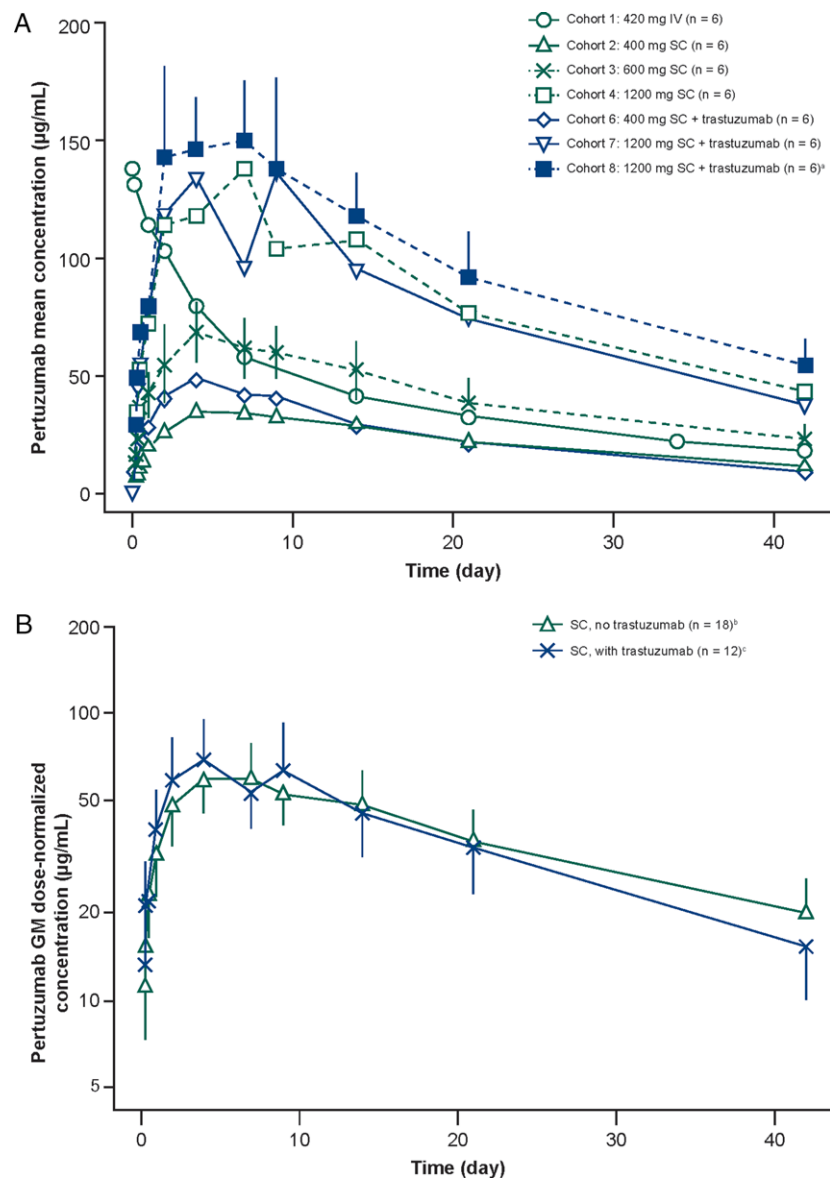


Figure 2. Mean serum pertuzumab concentration–time profiles (A), and geometric mean dose-normalized serum pertuzumab concentration–time profiles (B) for pertuzumab with and without concomitant trastuzumab by cohort in healthy male volunteers (part 1). ^arHuPH20 concentration = 667 U/mL only. ^bCohorts 1, 3, and 4 (n = 18). ^cCohorts 6 and 7 (n = 12). Error bars represent the 95% CIs of the mean. GM indicates geometric mean; IV, intravenous; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

Forty female patients with early breast cancer who had completed standard (neo)adjuvant breast cancer therapy were enrolled into part 2 of the study (n = 20 per cohort). The ages of patients in part 2 ranged from 37 to 77 years, and body weight ranged from 52.5 to 119.5 kg across cohorts (Supplemental Table S1). Each patient received SC pertuzumab and trastuzumab either comixed (cohort B) or coformulated (cohort C) and completed the day 43 study assessments.

PK—Part 1: Healthy Male Volunteers

As expected, the pertuzumab concentrations after an IV 420 mg dose followed a biphasic pattern with distinct

distribution and elimination phases (Figure 2A). SC pertuzumab administration resulted in a time to maximum serum concentration of 5–7 days. The observed absolute bioavailability of SC pertuzumab in healthy male volunteers was approximately 70%. Dose-proportional increases in pertuzumab exposures were observed across SC pertuzumab doses (Table 1). Pertuzumab and trastuzumab PK parameters following a noncompartmental analysis are also provided in Table 1.

There was no apparent impact of the addition of SC trastuzumab on the PK of SC pertuzumab when the 2 antibodies were comixed (Figure 2B). There was

Table 1. Serum Pertuzumab and Trastuzumab PK Parameters

Parameter	Part 1: Healthy Male Volunteers (n = 48)				Part 2: Early Breast Cancer (n = 40)					
	Cohort 1: IV Pertuzumab 420 mg (n = 6)	Cohort 2: SC Pertuzumab 400 mg (n = 6)	Cohort 3: SC Pertuzumab 600 mg (n = 6)	Cohort 4: SC Pertuzumab 1200 mg (n = 6)	Cohort 5: SC Trastuzumab 600 mg (n = 6)	Cohort 6: Comixed Pertuzumab 400 mg and Trastuzumab 600 mg (n = 6)	Cohort 7: Comixed Pertuzumab 1200 mg and Trastuzumab 600 mg (n = 6)	Cohort 8: Comixed Pertuzumab 1200 mg and Trastuzumab 600 mg (n = 6)	Cohort B: Comixed FDC Pertuzumab Target Dose (600 mg) and Trastuzumab 600 mg (n = 20)	Cohort C: Coformulated FDC Pertuzumab Target Dose (600 mg) and Trastuzumab 600 mg (n = 20)
Serum pertuzumab, mean (CV%)										
C _{max} (μg/mL)	142.0 (6.7)	36.1 (18.0)	68.8 (19.4)	147.0 (13.9)	N/A	49.0 (15.6)	151.0 (14.9)	160.0 (19.2)	62.9 (35.9)	62.3 (18.8)
C _{rough} (μg/mL)	32.7 (11.5)	21.9 (17.6)	38.3 (26.7)	77.1 (20.3)	N/A	21.8 (10.1)	74.7 (27.5)	92.1 (20.7)	33.0 (41.0)	35.4 (21.7)
HL (d)	11.3 (17.7)	9.7 (18.3)	14.6 (40.1)	22.2 (17.7)	N/A	8.5 (9.8)	20.7 (10.9)	24.5 (14.5)	15.9 (46.4)	15.0 (35.0)
AUC _{inf} (μg·d/mL)	2180 (10.9)	1190 (19.9)	2390 (31.3)	4930 (16.2)	N/A	1230 (12.1)	4630 (25.5)	6160 (22.7)	2050 (40.6)	2010 (25.5)
Serum trastuzumab, mean (CV%)										
C _{max} (μg/mL)	N/A	N/A	N/A	N/A	65.6 (15.7)	71.3 (15.6)	68.5 (17.6)	73.6 (20.1)	56.1 (35.3)	57.7 (19.6)
C _{rough} (μg/mL)	N/A	N/A	N/A	N/A	32.0 (20.2)	28.4 (11.6)	27.8 (27.2)	34.0 (23.2)	25.4 (47.2)	28.9 (18.5)
HL (d)	N/A	N/A	N/A	N/A	8.9 (21.6)	7.6 (9.3)	7.2 (8.4)	7.9 (15.3)	8.7 (19.3)	8.1 (28.1)
AUC _{inf} (μg·d/mL)	N/A	N/A	N/A	N/A	1690 (24.8)	1580 (13.1)	1440 (26.5)	1860 (26.6)	1380 (44.2)	1440 (20.8)

AUC_{inf} indicates area under the serum concentration–time curve from 0 to infinity; C_{max}, maximum serum concentration; C_{rough}, minimum serum concentration (measured at 504 hours [day 21]); CV%, coefficient of variation; FDC, fixed-dose combination; HL, half-life; IV, intravenous; N/A, not applicable; PK, pharmacokinetics; SC, subcutaneous.

Table 2. Pertuzumab PopPK Model Parameter Estimates

Parameter	Model 1a: Part 1		Model 1b: Part 1 and Part 2, Cohort B		Model 2: Part 1 and Part 2, Cohorts B and C	
	(n = 48)		(n = 20)		(n = 20)	
	Estimate (%RSE)	Interindividual Variability, %	Estimate (%RSE)	Interindividual Variability, %	Estimate (%RSE)	Interindividual Variability, %
Clearance (L/d)	0.176 (6.3)	25	0.181 (8.9)	37	0.176 (5.5)	35
Volume of distribution of central compartment (L)	3.73 (11.2)	21	3.67 (15.7)	19	3.30 (10.5)	7.9
Distributional clearance (L/d)	0.372 (7.2)	...	0.315 (8.8)	...	0.280 (13.1)	...
Volume of distribution of peripheral compartment (L)	2.25 (8.9)	...	2.42 (6.7)	...	2.43 (8.3)	...
Bioavailability	0.701 (7.9)	...	0.691 (10.1)	...	0.654 (6.8)	...
Apparent first-order absorption rate constant (L/d)	0.528 (12.6)	51	0.367 (15.2)	70	0.289 (11.9)	68
Residual error for SC (%)	19	...	25	...	29	...
Residual error for IV (%)	7.2	...	7.0	...	7.3	...

IV indicates intravenous; popPK, population pharmacokinetics; RSE, relative standard error; SC, subcutaneous.

Table 3. Simulated GMR of Exposure and Probabilities of the Lower Bound of the 90%CI SC/IV GMR ≥ 0.8 at Different SC Pertuzumab Doses

Parameter	SC Pertuzumab Doses (mg)				
	400	500	550	600	700
Part 1					
GMR (5th–95th percentiles)					
$C_{trough,ss}$	0.71 (0.63–0.78)	0.89 (0.78–0.97)	0.98 (0.86–1.08)	1.06 (0.93–1.18)	1.24 (1.10–1.37)
AUC_{ss}	0.68 (0.61–0.75)	0.85 (0.75–0.94)	0.94 (0.83–1.03)	1.01 (0.90–1.12)	1.19 (1.06–1.31)
Probability SC/IV GMR ≥ 0.8					
$C_{trough,ss}$	<0.01	0.78	0.99	>0.99	>0.99
AUC_{ss}	<0.01	0.70	0.97	>0.99	>0.99
Part 2					
GMR (5th–95th percentiles)					
$C_{trough,ss}$	0.72 (0.64–0.82)	0.91 (0.80–1.03)	0.99 (0.88–1.15)	1.07 (0.93–1.24)	1.27 (1.12–1.45)
AUC_{ss}	0.67 (0.60–0.75)	0.84 (0.74–0.94)	0.92 (0.82–1.05)	1.00 (0.89–1.13)	1.18 (1.04–1.32)
Probability SC/IV GMR ≥ 0.8					
$C_{trough,ss}$	<0.01	0.78	0.98	>0.99	>0.99
AUC_{ss}	<0.01	0.59	0.91	>0.99	>0.99

AUC_{ss} indicates area under the serum concentration–time curve at steady state; $C_{trough,ss}$, trough serum concentration at steady state; GMR, geometric mean ratio; IV, intravenous; SC, subcutaneous.

no apparent impact of lowering the rHuPH20 concentration from 2000 U/mL to 667 U/mL on the PK of pertuzumab (Supplemental Figure S1) or trastuzumab (data not shown). Plasma rHuPH20 concentrations were below the limit of quantification at all time points, indicating no quantifiable systemic exposure of rHuPH20 at all doses used in this study (667–2000 U/mL).

Pertuzumab popPK model parameter estimates and interindividual variability based on the first popPK model are shown in Table 2 (model 1a). SC pertuzumab PK was described by a clearance rate of 0.176 L/d (interindividual variability 25%), volume of distribution of the central compartment of 3.73 L (interindividual variability 21%), apparent first-order rate constant of 0.528 L/d (interindividual variability

51%) and bioavailability of 0.701. Higher residual error, in line with previous experience,³⁰ was seen after SC administration compared with IV, reflecting variability in the absorption process.

Clinical trial simulations indicated that an SC pertuzumab dose of 550 mg resulted in noninferior $C_{trough,ss}$ and AUC_{ss} >99% of the time when compared with IV pertuzumab 420 mg (Table 3). Given the potential higher variability of a phase III study in patients with early breast cancer versus the observed variability of the phase I study in healthy male volunteers as well as the overall safety results for pertuzumab, 600 mg of SC pertuzumab was selected to ensure that all patients in the future phase III study achieve noninferior exposures. Clinical trial simulations for the SC pertuzumab dose of 600 mg are shown in Figure 3.

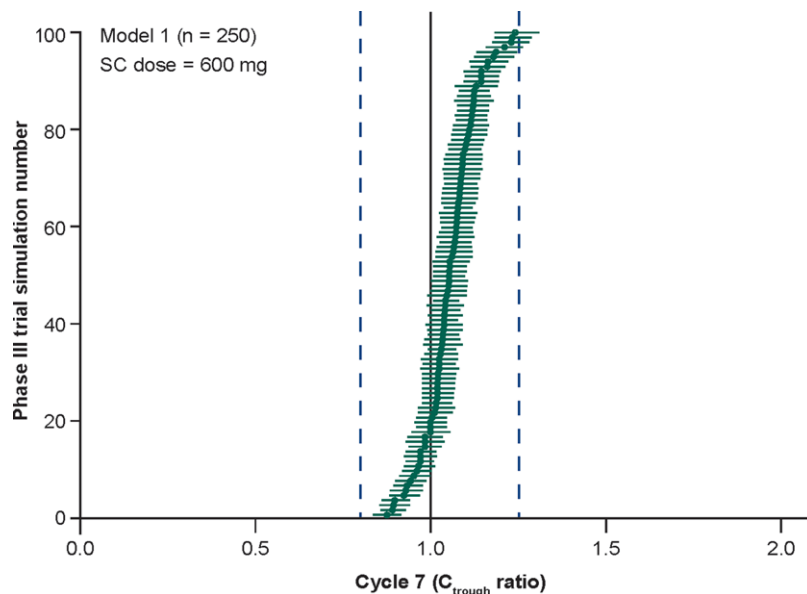


Figure 3. Phase III clinical trial simulations of SC/IV GMR and 90%CI estimates using part I data. Circles represent the GMR (SC/IV) C_{trough} point estimates; horizontal solid lines represent the 90%CIs. Each circle/horizontal line represents a unique clinical trial simulation. Only 100 of the 400 clinical trial simulations are shown for clarity. Vertical dashed lines represent GMR 0.8–1.25. C_{trough} indicates trough serum concentration; GMR, geometric mean ratio; IV, intravenous; SC, subcutaneous.

Although PK data from part 1 indicated that an rHuPH20 concentration as low as 667 U/mL might sufficiently deliver SC pertuzumab and SC trastuzumab, due to manufacturing and assay variability 1000 U/mL rHuPH20 was selected to further explore its effects in part 2 of the study. Therefore, SC pertuzumab 600 mg was selected as the dose to confirm in patients with early breast cancer in part 2, cohort B in a co-mixed formulation with SC trastuzumab 600 mg and rHuPH20 1000 U/mL.

PK—Part 2: Patients With Early Breast Cancer

No drug-drug interactions were shown in part 1, and the FDC for cohort C was technically feasible; therefore, cohort A of part 2 of the study was not enrolled.

PK parameters for part 2, cohort B (pertuzumab SC 600 mg with 1000 U/mL rHuPH20) following a noncompartmental analysis are provided in Table 1. Pertuzumab exposures (observed single-dose PK/noncompartmental single-dose C_{trough} and AUC) were similar between 600 mg SC (patients with early breast cancer [part 2, cohort B]) and 420 mg IV (healthy male volunteers [part 1, cohort 1]) (Figure 4A). The popPK model described above was refreshed with the additional PK data collected in part 2 (cohort B). Additionally, pertuzumab concentrations through day 85 in part 1 (healthy male volunteers) were available at the time of the model refresh and were incorporated into the dataset. PopPK model parameter estimates and interindividual variability based on the

refreshed popPK model are shown in Table 2 (model 1b). PopPK model-based simulations and resulting probabilities following the 600 mg SC pertuzumab dose with 1000 U/mL rHuPH20 in part 2, cohort B were nearly identical to the data obtained in part 1 healthy male volunteers (data not shown).

Based on part 2 cohort B data, the FDC maintenance coformulated product was finalized as SC pertuzumab 600 mg, SC trastuzumab 600 mg, and rHuPH20 2000 U/mL. The pertuzumab PK profile following an FDC single coformulated dose was comparable with the co-mixed formulation used in cohort B (Figure 4B). The popPK model was refreshed with cohort C data, and model parameter estimates and interindividual variability are shown in Table 2 (model 2). Exposure and half-life values for cohort C following a noncompartmental analysis are provided in Table 1. When clinical trial simulations were repeated using the refreshed popPK model with all PK data collected in part 1 and part 2, cohorts B and C, the probability of meeting the phase III end point (lower bound of the 90%CI of the pertuzumab SC/IV GMR ≥ 0.8) following 3 FDC doses was determined to be >0.99 for $C_{trough,ss}$ and AUC_{ss} .

The PK of SC pertuzumab was approximately dose proportional (Table 1). Therefore, the FDC loading coformulated product was finalized as SC pertuzumab 1200 mg, SC trastuzumab 600 mg, and rHuPH20 2000 U/mL. Additionally, C_{trough} and AUC following a pertuzumab 840 mg IV loading dose (historical pertuzumab popPK model)²⁹ and pertuzumab 1200 mg SC

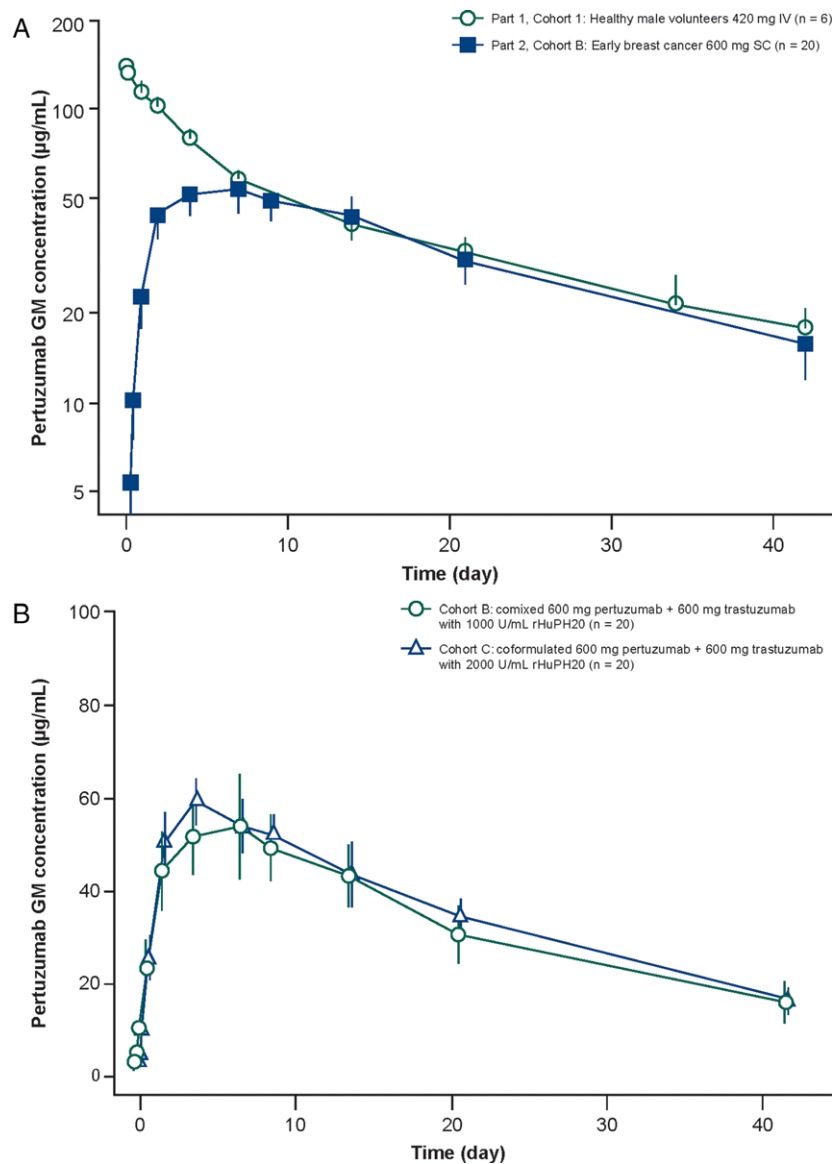


Figure 4. Mean serum pertuzumab concentration–time profiles following 420 mg IV (part 1, cohort 1) and 600 mg SC doses in female patients with early breast cancer (part 2, cohort B) (A), and geometric mean dose-normalized serum pertuzumab concentration–time profiles for pertuzumab comixed (part 2, cohort B) or coformulated (part 2, cohort C) as an SC fixed-dose combination with trastuzumab in female patients with early breast cancer (B). Error bars represent the 95% CIs of the mean. GM indicates geometric mean; IV, intravenous; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

dose (part 1 cohort 4) were found to be comparable (data not shown).

Safety

Most subjects in part 1 (44/48; 91.7%) and all in part 2 (20/20; 100%) of the study experienced at least 1 AE (Table 4), with the majority of AEs reported as grade 1 or 2. One grade 3 AE (diarrhea), not treatment-related, and 2 cardiac disorder AEs (ejection fraction decrease and electrocardiogram T-wave inversion) were reported in part 2 of the study. No serious AEs, AEs of special interest, fatal AEs, or AEs leading to discontinuation of study drug were reported in part 1 or 2. No

new safety signals were identified for pertuzumab and trastuzumab. The most common AE reported across all cohorts in part 1 was upper respiratory tract infection (13/48; 27.1%). The most common AEs reported in part 2 were headache (cohort B 13/20 [65.0%]; cohort C 12/20 [60.0%]) and diarrhea (cohort B 6/20 [30.0%]; cohort C 17/20 [85.0%]).

One injection-site reaction was reported in part 1 (cohort 7, grade 2), and 13 in part 2 (Table 4). All injection-site (any local morphological or physiological change at or near the injection site), or injection-related (systemic reaction in response to an injection), reactions in parts 1 and 2 were grade 1 or 2. A summary of

Table 4. Overall Incidence and Most Common AEs

Parameter	Part 1: Healthy Male Volunteers (n = 48)						Part 2: Early Breast Cancer (n = 40)			
	Cohort 1: IV Pertuzumab 420 mg (n = 6)		Cohort 2: SC Pertuzumab 400 mg (n = 6)		Cohort 3: SC Pertuzumab 600 mg (n = 6)		Cohort 4: SC Pertuzumab 1200 mg (n = 6)		Cohort 5: SC Trastuzumab 600 mg (n = 6)	
	Cohort 6: Comixed Pertuzumab 400 mg and Trastuzumab 600 mg (n = 6)		Cohort 7: Comixed Pertuzumab 1200 mg and Trastuzumab 600 mg (n = 6)		Cohort 8: Comixed Pertuzumab 1200 mg and Trastuzumab 600 mg (n = 6)		Cohort B: Comixed FDC Pertuzumab Target Dose and Trastuzumab 600 mg (n = 20)		Cohort C: Coformulated FDC Pertuzumab Target Dose and Trastuzumab 600 mg (n = 20)	
Total patients with ≥ 1 AE, n (%)	5 (83.3)	5 (83.3)	5 (83.3)	5 (83.3)	5 (83.3)	6 (100)	6 (100)	6 (100)	20 (100)	20 (100)
Total number of AEs n	15	10	10	26	10	34	18	14	115	111
AE, MedDRA preferred term, n (%)										
Headache	1 (16.7)	0	1 (16.7)	2 (33.3)	1 (16.7)	0	4 (66.7)	0	13 (65.0)	12 (60.0)
Upper respiratory tract infection	2 (33.3)	0	2 (33.3)	2 (33.3)	0	3 (50.0)	2 (33.3)	2 (33.3)	5 (25.0)	2 (10.0)
Diarrhea	3 (50.0)	1 (16.7)	2 (33.3)	1 (16.7)	0	1 (16.7)	1 (16.7)	0	6 (30.0)	17 (85.0)
Drug eruption	1 (16.7)	0	0	1 (16.7)	0	2 (33.3)	3 (50.0)	2 (33.3)	1 (5.0)	0
Angular cheilitis	2 (33.3)	0	1 (16.7)	0	0	3 (50.0)	0	1 (16.7)	0	0
Rash	0	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	0	0	0	1 (5.0)	3 (15.0)
Epistaxis	1 (16.7)	0	0	1 (16.7)	0	3 (50.0)	0	0	3 (15.0)	3 (15.0)
Injection-site reaction ^a	0	0	0	0	0	0	1 (16.7)	0	6 (30.0)	7 (35.0)
Myalgia	0	0	0	0	0	0	0	0	7 (35.0)	2 (10.0)
Dry skin	0	0	1 (16.7)	1 (16.7)	0	2 (33.3)	0	0	2 (10.0)	2 (10.0)
Nausea	0	0	0	1 (16.7)	0	1 (16.7)	0	0	4 (20.0)	8 (40.0)
Injection-related reaction ^b	0	0	0	0	1 (16.7)	2 (33.3)	0	1 (16.7)	1 (5.0)	0

AE indicates adverse event; FDC, fixed-dose combination; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; SC, subcutaneous.

As of the clinical cutoff date, April 6, 2017, there were no cardiac disorders, serious AEs, deaths, or withdrawals due to AEs. Only treatment-emergent AEs with ≥ 5 cases are reported. Multiple occurrences of the same AE in an individual are counted separately.

^aInjection-site reaction: any local morphological or physiological change at or near the injection site.

^bInjection-related reaction: systemic reaction in response to the injection.

injection-site reactions in comixed and FDC cohorts (part 1, cohorts 6–8, and part 2, cohorts B and C) is given in Supplemental Table S2.

Discussion

This was a phase Ib dose-finding study of SC pertuzumab and SC trastuzumab in healthy male volunteers and female patients with early breast cancer who have completed their (neo)adjuvant treatment. The study was designed to identify an SC pertuzumab dose that is noninferior to IV pertuzumab (for C_{trough} and AUC) when administered with or without SC trastuzumab.

Healthy male volunteers were used to study preselected doses of pertuzumab in part 1 based on experience in the development of SC trastuzumab.³¹ Female patients had undergone surgical removal of tumor tissue, which might have affected PK, but there was no anticipated difference in the PK profile between female patients and healthy male volunteers. Healthy female volunteers were not used in order to avoid the potential formation of antidrug antibodies in individuals who are more likely to require trastuzumab and pertuzumab treatment for a future breast cancer diagnosis than male equivalents.

A single SC pertuzumab dose, given at 600 mg to early breast cancer patients, provided similar C_{trough} and AUC to those of a single dose of IV pertuzumab given at 420 mg to healthy male volunteers. Model-based clinical trial simulations reflect steady-state pertuzumab concentrations following 3 doses (1 loading and 2 maintenance) of pertuzumab, which is cycle 7 in the planned phase III trial (chemotherapy begins in cycle 1, and pertuzumab and trastuzumab IV or SC begin in cycle 5; all cycles are 21 days). Per simulated trials of SC pertuzumab 600 mg, the GMR of cycle 7 $C_{\text{trough,ss}}$ (ie, cycle 8 predose) and AUC_{ss} for SC/IV were calculated. Although these clinical trial simulations indicated that the lower dose of 550 mg SC pertuzumab would be noninferior, given the potential higher variability of a phase III study in patients with early breast cancer versus the observed variability of the phase Ib study in healthy male volunteers, as well as supportive safety data from the study, 600 mg of SC pertuzumab was selected. The IV pertuzumab PK parameters estimated in part 1 of this study were consistent with those reported previously.²⁹

SC pertuzumab 600 mg in part 2 in patients with early breast cancer provided similar C_{trough} and AUC values to the 420 mg IV and 600 mg SC cohorts in healthy male volunteers in part 1, and the dose proportionality through PK linearity confirms an SC pertuzumab 1200 mg loading dose. Based on the PK and safety findings of the current study, as well as clinical experience with rHuPH20, 1200 mg pertuzumab

with 600 mg trastuzumab and 2000 U/mL rHuPH20, and 600 mg pertuzumab with 600 mg trastuzumab and 2000 U/mL rHuPH20, were recommended for the loading and maintenance FDC SC coformulations, respectively, to be studied in a phase III trial.

The findings of the popPK model from this phase Ib study were further supported by an additional model (data not shown). In the additional model, the historical, robust IV pertuzumab popPK data set in patients was added to the IV pertuzumab data collected in 6 healthy male volunteers in the phase Ib study. The new IV data set, coupled with the SC data from the current study in healthy male volunteers and female patients with early breast cancer produced similar pertuzumab PK parameter estimates, as shown (Table 2). Using healthy male volunteers (part 1, cohort 1) or historical IV data gave slightly different GMR and CI estimates in phase III trial simulations. An SC pertuzumab dose that would likely maximize clinical benefit for patients based on either scenario was selected. An exposure-response analysis to compare efficacy and safety among GMR/exposure quantiles in the phase III study is planned.

Following single comixed and coformulated doses, similar pertuzumab and trastuzumab PK and safety profiles were observed when 2000, 1000, or 667 U/mL rHuPH20 was used. Because different concentrations of rHuPH20 were assessed in healthy male volunteers and female patients with early breast cancer—2 distinctly different groups with a small number of subjects each—a potential impact of 1000 or 667 U/mL rHuPH20 on pertuzumab PK could not be excluded, particularly on C_{trough} . However, plasma rHuPH20 concentrations were below the limit of quantification for all sampling time points, indicating no quantifiable systemic exposure at the rHuPH20 doses used in this study. Although no pertuzumab or trastuzumab PK differences were observed with 1000 U/mL rHuPH20, based on the PK and safety findings of the current study, as well as clinical experience with trastuzumab or rituximab formulated with rHuPH20, 1200 mg pertuzumab with 600 mg trastuzumab and 2000 U/mL rHuPH20 or 600 mg pertuzumab with 600 mg trastuzumab and 2000 U/mL rHuPH20 was recommended for the loading and maintenance FDC SC coformulations, respectively, to be studied in a phase III trial.

Safety results were generally consistent with the known safety profile of combination treatment with IV pertuzumab and IV or SC trastuzumab,^{3,32–34} with no new safety signals identified. Most AEs were of low intensity, and there were no serious AEs, deaths, or AEs leading to study withdrawal. Although there were high rates of upper respiratory tract infection seen in healthy male volunteers, this may have been due to seasonal

illness in the study country and/or the close proximity of patients within the study unit.

Female patients with early breast cancer experienced higher incidences of injection-site reactions compared with healthy male volunteers following a co-mixed SC injection of pertuzumab and trastuzumab. Given the different subject populations and the small number of subjects in each cohort, this result should be interpreted with caution. The phase I/Ib dose-finding study of SC trastuzumab similarly showed a higher incidence of administration-site reactions in female patients, although all but 2 of the events reported overall in the study were of mild intensity.³¹ There were also documented differences in the hypodermis depending on body mass index, age, and sex. The thickness of hypodermis increases with body mass, and decreases with age.³⁵ Women also tend to have a thicker hypodermis compared with men of the same body mass index and age.³⁵

Patients in part 2, cohort C experienced higher levels of diarrhea than those in part 2, cohort B. Diarrhea is a known AE with pertuzumab,¹⁷ although clinical experience has shown that diarrhea is more frequent at the start of treatment, decreases over time, and can be easily managed.³⁶ All diarrhea events in cohort C were of low intensity (grades 1 or 2), manageable, and reversible; antidiarrheal treatment was required for 3 patients only. Although the current study has a small sample size, the data are consistent with those of previous studies of pertuzumab and trastuzumab, where the majority of diarrhea events were also low intensity.^{5,36-38}

Like trastuzumab, pertuzumab specifically binds to the HER2 receptor. The specific and saturable interaction of antibodies with their target influences the PK disposition, and once target sites are saturated, linear PK is observed.³⁹ The popPK model for pertuzumab has shown that pertuzumab PK is linear in the range of clinical serum concentrations in this study, indicating that all target sites were saturated. Therefore, it is expected that the maximal clinical benefit will be achieved at these serum concentrations (with SC pertuzumab 600 mg). Because the approved IV pertuzumab regimen is assumed to saturate HER2 receptor binding, predicting maximum clinical efficacy with an SC pertuzumab dose with a noninferior $C_{\text{trough,ss}}$ should be appropriate; a noninferior C_{trough} would ensure at least the same degree of target saturation as with IV administration and therefore ensure similar efficacy, as was seen with the development of both SC trastuzumab^{22,26,40} and SC rituximab.^{23,27}

Conclusions

A loading dose of 1200 mg and maintenance dose of 600 mg for SC pertuzumab are predicted to result

in an equivalent exposure to IV pertuzumab 840 mg and 420 mg, respectively. No new safety signals for SC pertuzumab administered alone, or co-mixed or coformulated with trastuzumab, were identified in this phase Ib study. The dose-finding processes used here for SC pertuzumab were similar to those used successfully in phase I studies for both SC trastuzumab³¹ and SC rituximab.^{24,41} Development of pertuzumab and trastuzumab as a ready-to-use coformulated FDC is expected to further reduce the treatment burden on patients and at the same time to improve efficiency of treatment facility utilization. The PK and safety results of this phase Ib study support further development of an FDC of pertuzumab and trastuzumab for SC administration. With the doses identified here, the FDC will be investigated in a planned phase III trial (WO40324) in patients with HER2-positive early breast cancer.

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Data-Sharing Statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform: www.clinicalstudydatarequest.com. Further details on Roche's criteria for eligible studies are available here: <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

References

- Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997–4013.
- Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. 2009;14(4):320–368.
- Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25–32.
- Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791–800.
- von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122–131.
- Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109–119.
- Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724–734.
- Hubalek M, Brantner C, Marth C. Role of pertuzumab in the treatment of HER2-positive breast cancer. *Breast Cancer (Dove Med Press)*. 2012;4:65–73.
- Pivot X, Gligorov J, Müller V, et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. *Lancet Oncol*. 2013;14(10):962–970.
- Pivot X, Gligorov J, Müller V, et al. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. *Ann Oncol*. 2014;25(10):1979–1987.
- Rummel M, Kim TM, Plenteda C, et al. PrefMab: Final analysis of patient satisfaction with subcutaneous versus intravenous rituximab in previously untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma. *Value Health*. 2015;18(7):A469.
- Rummel M, Kim TM, Aversa F, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). *Ann Oncol*. 2017;28(4):836–842.
- De Cock E, Pivot X, Hauser N, et al. A time and motion study of subcutaneous versus intravenous trastuzumab in patients with HER2-positive early breast cancer. *Cancer Med*. 2016;5(3):389–397.
- De Cock E, Kritikou P, Sandoval M, et al. Time savings with rituximab subcutaneous injection versus rituximab intravenous infusion: a time and motion study in eight countries. *PLoS One*. 2016;11(6):e0157957.
- Roche Registration Ltd. Herceptin® (trastuzumab). Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000278/WC500074922.pdf. Accessed September 4, 2018.
- Genentech Inc. Herceptin® (trastuzumab). Prescribing Information (USA). http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf. Accessed September 4, 2018.
- Genentech Inc. Perjeta™ (pertuzumab). Prescribing Information (USA). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125409s113s118lbl.pdf. Accessed September 4, 2018.
- Woodward N, de Boer RH, Redfern A, et al. Interim results from the first open-label, multicenter, phase IIb study investigating the combination of pertuzumab with subcutaneous trastuzumab and a taxane in patients with HER2-positive metastatic breast cancer (SAPPHIRE). *Cancer Res*. 2016;76(4 suppl):Abstract P4-14-12.
- Kümmel S, Crepelle-Fléchais A, Schlegel M, et al. MetaPHER: A phase IIb multicenter, open-label, single-arm safety study of subcutaneous trastuzumab, in combination with pertuzumab and docetaxel in patients with HER2-positive advanced breast cancer. *Cancer Res*. 2016;76(4 suppl):Abstract OT3-01-13.
- Shivakumar SP, Anderson DR, Couban S. Catheter-associated thrombosis in patients with malignancy. *J Clin Oncol*. 2009;27(29):4858–4864.
- Poorter RL, Lauw FN, Bemelman WA, Bakker PJM, Taat CW, Veenhof CHN. Complications of an implantable venous access device (Port-a-Cath) during intermittent continuous infusion of chemotherapy. *Eur J Cancer*. 1996;32A(13):2262–2266.
- Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre randomised trial. *Lancet Oncol*. 2012;13(9):869–878.
- Davies A, Merli F, Mihaljević B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2017;4(6):e272–e282.
- Assouline S, Buccheri V, Delmer A, et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. *Lancet Haematol*. 2016;3(3):e128–e138.
- US Food and Drug Administration (FDA). RITUXAN HYCELA™ (rituximab and hyaluronidase human). Prescribing Information (USA). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf. Accessed September 4, 2018.
- Jackisch C, Stroyakovskiy D, Pivot X, et al. Efficacy and safety of subcutaneous or intravenous trastuzumab in patients with HER2-positive early breast cancer after 5 years' treatment-free follow-up: final analysis from the phase III, open-label, randomized HannaH study. *Cancer Res*. 2017;78(4 suppl):Abstract PD3-11 (and associated poster presentation).
- Davies A, Merli F, Mihaljević B, et al. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study. *Lancet Oncol*. 2014;15(3):343–352.
- Bookbinder LH, Hofer A, Haller MF, et al. A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J Control Release*. 2006;114(2):230–241.
- Garg A, Quartino A, Li J, et al. Population pharmacokinetic and covariate analysis of pertuzumab, a HER2-targeted monoclonal antibody, and evaluation of a fixed, non-weight-based dose in patients with a variety of solid tumors. *Cancer Chemother Pharmacol*. 2014;74(4):819–829.
- Quartino AL, Hillenbach C, Li J, et al. Population pharmacokinetic and exposure-response analysis for trastuzumab administered using a subcutaneous “manual syringe” injection or

- intravenously in women with HER2-positive early breast cancer. *Cancer Chemother Pharmacol*. 2016;77(1):77–88.
31. Wynne C, Harvey V, Schwabe C, Waaka D, McIntyre C, Bittner B. Comparison of subcutaneous and intravenous administration of trastuzumab: a phase I/Ib trial in healthy male volunteers and patients with HER2-positive breast cancer. *J Clin Pharmacol*. 2013;53(2):192–201.
 32. Jackisch C, Kim SB, Semiglazov V, et al. Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study. *Ann Oncol*. 2015;26(2):320–325.
 33. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24(9):2278–2284.
 34. Gligorov J, Ataseven B, Verrill M, et al. Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients. *Eur J Cancer*. 2017;82:237–246.
 35. Richter WF, Bhansali SG, Morris ME. Mechanistic determinants of biotherapeutics absorption following SC administration. *AAPS J*. 2012;14(3):559–570.
 36. Swain SM, Schneeweiss A, Gianni L, et al. Incidence and management of diarrhea in patients with HER2-positive breast cancer treated with pertuzumab. *Ann Oncol*. 2017;28(4):761–768.
 37. Swain SM, Ewer MS, Viale G, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol*. 2018;29(3):646–653.
 38. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2018;19(1):115–126.
 39. Kamath AV. Translational pharmacokinetics and pharmacodynamics of monoclonal antibodies. *Drug Discov Today Technol*. 2016;21-22:75–83.
 40. Jackisch C, Hegg R, Stroyakovskiy D, et al. HannaH phase III randomised study: association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. *Eur J Cancer*. 2016;62:62–75.
 41. Assouline S, Buccheri V, Delmer A, et al. Pharmacokinetics and safety of subcutaneous rituximab plus fludarabine and cyclophosphamide for patients with chronic lymphocytic leukaemia. *Br J Clin Pharmacol*. 2015;80(5):1001–1009.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.