2 SYNOPSIS

Name of Sponsor Company: Amgen Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: ABP 980	Volume: Page:	
Name of Active Ingredient: ABP 980		

Title of Study: A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel Group Study to Determine the Pharmacokinetic Equivalence of ABP 980 and Trastuzumab (Herceptin®) in Healthy Male Subjects

Investigator: Dr. [redacted], Nucleus Network Limited (The Centre for Clinical Studies)

Study Center: Nucleus Network Limited (The Centre for Clinical Studies), 5th Floor, Burnet Tower, AMREP Precinct, 89 Commercial Road, Melbourne, Victoria, Australia 3004

Publication (reference): Not applicable

Phase of Development: 1

Study Period:
Date of first enrollment: 16 June 2014
Date of last subject end-of-study (EOS)/early termination visit: 15 October 2014

Objectives:
The primary objective of this study was:

- To demonstrate bioequivalence (as assessed principally by area under the serum concentration-time curve [AUC] from time 0 extrapolated to infinity [AUC_{inf}] and the maximum serum concentration [C_{max}]) of ABP 980 following a 6 mg/kg intravenous (IV) infusion relative to that from a 6 mg/kg IV infusion of Food and Drug Administration (FDA)-licensed trastuzumab and European Union (EU)-authorized trastuzumab

The secondary objectives of this study were:

- To demonstrate bioequivalence (as assessed principally by AUC_{inf} and C_{max}) of a 6 mg/kg IV infusion of FDA-licensed trastuzumab relative to a 6 mg/kg IV infusion of EU-authorized trastuzumab
- To determine the safety, tolerability, and immunogenicity of ABP 980 in healthy subjects compared with FDA-licensed trastuzumab and EU-authorized trastuzumab

Methodology: This was a randomized, single-blind, single-dose, 3-arm, parallel-group study in healthy adult male subjects. This study was conducted at a single clinical pharmacology unit (CPU) located in Australia.
Subjects were screened within 28 days prior to dosing.
Subjects were admitted to the CPU on Day -1, at which time eligibility was confirmed. Subjects were randomized on Day -1, according to a computer-generated randomization schedule, to receive an IV infusion over 90 minutes of ABP 980 6 mg/kg (440 mg vial), trastuzumab 6 mg/kg (FDA-licensed; 440 mg vial), or trastuzumab 6 mg/kg (EU-authorized; 150 mg vial) in a ratio of 1:1:1 stratified by ethnicity (Japanese versus non-Japanese).
Dosing occurred on Day 1 after predose baseline procedures were completed. Subjects remained resident in the CPU for at least 24 hours after dosing for safety and pharmacokinetic (PK) assessments. Subjects were discharged on Day 2 after the 24 hour postdose study procedures were completed. Subjects returned to the CPU on Days 3, 5, 9, 15, 22, 29, 36, 43, 50, and Day 64 (EOS visit) for safety evaluations and PK assessments.

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Safety and tolerability were reviewed by the medical monitor on an ongoing basis. No concerns arose during review of the safety data, and no changes were made to the study conduct. Adverse event (AE) monitoring occurred throughout the study, and all AEs and serious AEs (SAEs) were reported.		
Number of Subjects: Approximately 150 subjects were planned for inclusion in this study. One hundred fifty-seven subjects were enrolled, 157 subjects were dosed, and 148 subjects completed the study.		
Diagnosis and Main Criteria for Inclusion: Healthy male subjects aged 18 to 45 years, inclusive. Non-Japanese subjects had a body mass index (BMI) of 18.0 to 30.0 kg/m^2, inclusive. Japanese subjects were first- or second-generation Japanese and had a BMI of 18.0 to 25.0 kg/m^2, inclusive.		
Test Product, Dose and Mode of Administration, Batch Number: ABP 980, 6 mg/kg IV infusion, lot number: [redacted]		
Reference Therapy, Dose and Mode of Administration, Batch Number: FDA-licensed trastuzumab, 6 mg/kg IV infusion, lot number: [redacted] EU-authorized trastuzumab, 6 mg/kg IV infusion, lot numbers: [redacted] and [redacted]		
Duration of Treatment: Each subject received a single dose of either 6 mg/kg ABP 980 (Treatment A), 6 mg/kg FDA-licensed trastuzumab (Treatment B), or 6 mg/kg EU-authorized trastuzumab (Treatment C) via IV infusion over approximately 90 minutes on Day 1.		
Criteria for Evaluation: Pharmacokinetics: Blood samples for serum trastuzumab and ABP 980 concentration determination were collected at predose, at 0.75 (45 minutes), end of infusion (approximately 1.5 hours), 2, 3, 4, 5, 6, 8, and 24 hours after the start of the infusion, at each return visit to the CPU (Days 3, 5, 9, 15, 22, 29, 36, 43, and 50), and at the EOS visit (Day 64). Pharmacokinetic parameters (C_{max}, last measureable serum concentration [C_{last}], the time at which C_{max} was observed [t_{max}], AUC from time 0 to the last quantifiable concentration [AUC_{last}], AUC_{inf}, terminal elimination half-life [$t_{½}$], and terminal elimination rate constant [λ_z]) were calculated from serum trastuzumab and ABP 980 concentration data using noncompartmental methods. Safety: Adverse events were collected and evaluated as they occurred throughout the study. Safety assessments, including physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), echocardiograms, and clinical laboratory tests, were performed at select time points. Blood samples for antidrug antibodies (ADAs) were collected at predose on Day 1 and at the EOS visit (Day 64).		
Endpoints: Primary: • Pharmacokinetic parameters (AUC_{inf} and C_{max}) for ABP 980, FDA-licensed trastuzumab, and EU-authorized trastuzumab after a single IV infusion to healthy male subjects		

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Secondary:

- Pharmacokinetic parameters (AUC_{inf} and C_{max}) for FDA-licensed trastuzumab and EU-authorized trastuzumab after a single IV infusion to healthy male subjects
- $t_{½}$, t_{max}, λ_z, AUC_{last}, and C_{last} for ABP 980, FDA-licensed trastuzumab, and EU-authorized trastuzumab
- Treatment-emergent AEs (TEAEs)
- Clinical laboratory tests and vital signs
- Incidence of ADAs

Statistical Methods:

Pharmacokinetic Analyses: Serum trastuzumab and ABP 980 concentrations were listed and summarized descriptively by treatment and time point using the PK Concentration Population. Mean trastuzumab and ABP 980 serum concentration-time data were presented graphically by treatment as well.

Pharmacokinetic parameters were listed by subject and summarized descriptively by treatment using the PK Parameter Population.

The primary statistical analysis for PK parameters was performed on the PK Parameter Population. Prior to statistical modeling, PK parameters were $\log_e$-transformed. Point estimates and 90% confidence intervals (CIs) for the mean difference in logarithmic PK parameters were estimated using an analysis of variance model adjusted for treatment and ethnicity (Japanese and non-Japanese) for comparisons of ABP 980 and FDA-licensed trastuzumab (Treatment A versus Treatment B), ABP 980 and EU-authorized trastuzumab (Treatment A versus Treatment C), and FDA-licensed trastuzumab and EU-authorized trastuzumab (Treatment B versus Treatment C). The point estimates and 90% CIs for geometric mean test-to-reference ratios were then calculated by transforming back to original scale.

To establish bioequivalence, the 90% CI for the geometric mean test-to-reference ratio for C_{max} and AUC_{inf} was to fall within the bioequivalence criteria of 0.80 to 1.25.

Safety Analyses: Electrocardiogram, echocardiogram, vital signs, and clinical laboratory test data (observed and change from baseline) were summarized by time point and treatment using descriptive statistics.

The number and percentage of subjects reporting any TEAE were tabulated by system organ class and preferred term (PT) for each treatment (coded using Medical Dictionary for Regulatory Activities [MedDRA], Version 17.0). Treatment-emergent AEs were further classified by severity and relationship to treatment.

The number and percentage of subjects who tested positive for binding or neutralizing ADAs were tabulated for each treatment.

All safety analyses were performed using the Safety Population.

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Results:

Subject Disposition: One hundred fifty-seven subjects were randomized, 157 subjects were dosed, and 148 subjects completed the study, including 50 of 50 subjects in the ABP 980 treatment group, 49 of 52 subjects in the FDA-licensed treatment group, and 49 of 55 subjects in the EU-authorized treatment group. All subjects were included in the Safety and PK Concentration Populations, and all but 1 subject in the EU-authorized treatment group was included in the PK Parameter Population. Thirteen subjects (4 subjects in the FDA-licensed treatment group and 9 subjects in the EU-authorized treatment group) were excluded from the Per Protocol PK Parameter Population.

Pharmacokinetic Results:

For the comparison of ABP 980 to FDA-licensed trastuzumab, the 90% CIs of the ratios of the geometric means (GMs) were fully contained within the bioequivalence criteria of 0.80 to 1.25 for both the primary PK parameters (AUC_{inf} and C_{max}) and the secondary PK parameter (AUC_{last}), confirming the PK similarity between ABP 980 and FDA-licensed trastuzumab (Table 1).

For the comparison of ABP 980 to EU-authorized trastuzumab, the 90% CIs of the ratios of the GMs were also fully contained within the bioequivalence criteria of 0.80 to 1.25 for both the primary PK parameters (AUC_{inf} and C_{max}) and the secondary PK parameter (AUC_{last}), confirming the PK similarity between ABP 980 and EU-authorized trastuzumab (Table 1).

For the comparison of FDA-licensed trastuzumab to EU-authorized trastuzumab, the 90% CIs of the ratios of the GMs were also fully contained within the bioequivalence criteria of 0.80 to 1.25 for both the primary PK parameters (AUC_{inf} and C_{max}) and the secondary PK parameter (AUC_{last}), confirming the PK similarity between FDA-licensed trastuzumab and EU-authorized trastuzumab (Table 1).

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Table 1 Summary of Statistical Assessment of Pharmacokinetic Parameters (PK Parameter Population)

Treatment and Comparison	C_{max} (µg/mL) Adjusted LS Geometric Mean [n]	AUC_{inf} (µg·h/mL) Adjusted LS Geometric Mean [n]	AUC_{last} (µg·h/mL) Adjusted LS Geometric Mean [n]
ABP 980	135.90 [50]	34061.43 [50]	33811.67 [50]
FDA-licensed Trastuzumab	131.19 [52]	32271.67 [48]	32113.58 [48]
EU-authorized Trastuzumab	136.85 [54]	33947.00 [46]	33748.19 [46]
	Ratio of Adjusted LS Geometric Means (90% CI)		
ABP 980 vs. FDA-licensed Trastuzumab	1.04 (0.9948, 1.0787)	1.06 (0.9974, 1.1169)	1.05 (0.9967, 1.1122)
ABP 980 vs. EU-authorized Trastuzumab	0.99 (0.9540, 1.0338)	1.00 (0.9476, 1.0624)	1.00 (0.9479, 1.0589)
FDA-licensed Trastuzumab vs. EU-authorized Trastuzumab	0.96 (0.9213, 0.9975)	0.95 (0.8973, 1.0072)	0.95 (0.8998, 1.0063)

Abbreviations: LS = least squares; n = number of nonmissing observations
NOTE: The statistical model includes treatment and ethnicity as fixed effects.

Safety Results:

- There were no deaths or TEAEs leading to study discontinuation.
- Two subjects had SAEs; 1 subject in the EU-authorized trastuzumab treatment group had an SAE of infusion-related reaction (with hypoxia) assessed as Grade 3 and probably related to study drug and 1 subject in the FDA-licensed trastuzumab treatment group had SAEs of tibia fracture, ligament injury, joint dislocation, deep vein thrombosis, and pulmonary embolism assessed as Grade 3 and not related to study drug.
- Treatment-emergent AEs were reported in 42 of 50, 39 of 52, and 43 of 55 subjects (84.0%, 75.0%, and 78.2%), respectively, in the ABP 980, FDA-licensed trastuzumab, and EU-authorized trastuzumab treatment groups.

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Safety Results (continued):

- The most frequently reported TEAEs in > 5% of subjects in any treatment group were headache, upper respiratory tract infection, chills, pyrexia, myalgia, nausea, epistaxis, arthralgia, and lethargy.
- The majority of TEAEs were Grade 1 to Grade 2 in severity; 2 subjects (1 in the FDA-licensed trastuzumab treatment group and 1 in the EU-authorized trastuzumab treatment group) had Grade 3 TEAEs.
- Infusion reaction TEAEs (based on a group of MedDRA PTs used to identify infusion reactions) with onset within 1 day of infusion were reported in 8 of 50, 9 of 52, and 10 of 55 subjects (16.0%, 17.3%, and 18.2%), respectively, in the ABP 980, FDA-licensed trastuzumab, and EU-authorized trastuzumab treatment groups.
- Infusion reaction TEAEs (based on a group of MedDRA PTs used to identify infusion reactions) with onset 2 or more days after infusion were reported in 3 of 50 subjects (6.0%) in the ABP 980 treatment group. Infusion reaction TEAEs with onset 2 or more days after infusion were not reported in the FDA-licensed trastuzumab or EU-authorized trastuzumab treatment groups.
- Hypersensitivity TEAEs (based on a narrow Standardised MedDRA Query for hypersensitivity) were reported in 4 of 50, 1 of 52, and 1 of 55 subjects (8.0%, 1.9%, and 1.8%), respectively, in the ABP 980, FDA-licensed trastuzumab, and EU-authorized trastuzumab treatment groups.
- There were no changes of clinical concern in clinical laboratory tests, vital signs, ECGs, echocardiograms, and physical examinations.
- No subject tested positive for binding ADAs.

Conclusions:

- PK similarity was demonstrated for the comparison of ABP 980 to FDA-licensed trastuzumab as the bioequivalence criteria were met for the primary PK parameters, AUC_{inf} and C_{max}.
- PK similarity was demonstrated for the comparison of ABP 980 to EU-authorized trastuzumab as the bioequivalence criteria were met for the primary PK parameters, AUC_{inf} and C_{max}.
- PK similarity was demonstrated for the comparison of FDA-licensed trastuzumab to EU-authorized trastuzumab as the bioequivalence criteria were met for the primary PK parameters, AUC_{inf} and C_{max}.
- Single doses of ABP 980, FDA-licensed trastuzumab, or EU-authorized trastuzumab administered to healthy subjects were generally safe and well tolerated.
  - The safety profile of ABP 980, FDA-licensed trastuzumab, and EU-authorized trastuzumab were comparable and consistent with what is known for trastuzumab.
- No subject tested positive for binding ADAs.

Date of Report: 03 April 2015