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 501	Volume: Page:	
Name of Active Ingredient: ABP 501		

Title of Study: A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel-Group Study to Determine the Pharmacokinetic Equivalence of ABP 501 and Adalimumab (Humira®) in Healthy Adult Subjects

Investigators:

[redacted], MD, PhD, [redacted]
[redacted], MD, [redacted]

Study centers:

[redacted]

Publication (reference): Not applicable

Phase of development: 1

Study Period:

Date of first enrollment: 03 July 2012

Date of last subject end-of-study/early termination visit: 26 October 2012

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 observed serum concentration [C_{max}]) of ABP 501 following a 40-mg subcutaneous (SC) injection relative to that from a 40-mg SC injection of adalimumab (US) and adalimumab (EU)

The secondary objective of this study was:

- To determine the safety, tolerability, and immunogenicity of ABP 501 in healthy adult subjects compared with adalimumab (US) and adalimumab (EU)

Methodology:

This was a randomized, single-blind, single-dose, 3-arm, parallel group study in healthy adult male and female subjects. The study was conducted at 1 clinical pharmacology unit (CPU) located in the US and 1 CPU located in the EU.

Screening occurred within 28 days of dosing.

Eligible subjects were admitted to the CPU on day -1 and randomized within each region prior to dosing on day 1 to receive either ABP 501 40 mg or adalimumab 40 mg in a ratio of 1:2.

Subjects received a single 40-mg SC dose of ABP 501, adalimumab (US), or adalimumab (EU) on day 1. Subjects were discharged from the CPU on day 2 after 24-hour postdose study procedures were completed, and they returned to the CPU on days 3, 4, 5, 6, 7, 8, 9, 11, 14, 16, 22, 29, 36, 43, 50, 57, and 63 (end-of-study [EOS] visit) for safety evaluations, pharmacokinetic

(PK) sample collections, and antidrug antibody (ADA) tests.

Safety and tolerability were reviewed by a study data review team (DRT) after 30 subjects (irrespective of region and treatment group) had been dosed. Dosing of additional subjects continued during this time. Voting members of the DRT included the investigators, the sponsor's medical officer, and [redacted] medical monitor. The DRT performed a review of the aggregate safety data for all subjects collected through at least study day 8. Adverse event (AE) monitoring occurred throughout the study. No concerns arose during DRT review of the safety data, and no changes were made to the study conduct.

Number of subjects: Approximately 198 subjects were planned for enrollment in this study (99 subjects in the US and 99 subjects in the EU). Two hundred and three subjects were enrolled, 203 subjects were dosed, and 196 subjects completed the study.

Diagnosis and main criteria for inclusion:

Healthy men and women, 18 to 45 years of age (inclusive) with body mass indices between 18 and 30 kg/m^2 (inclusive) were included in this study.

Test product, dose and mode of administration, batch/lot number:

ABP 501, 40-mg SC injection, [redacted] (US) and [redacted] (EU)

Reference therapy, dose and mode of administration, batch/lot number:

Adalimumab (US), 40-mg SC injection, [redacted]

Adalimumab (EU), 40-mg SC injection, [redacted]

Duration of treatment:

Each subject received a single dose of ABP 501 40 mg, adalimumab (US) 40 mg, or adalimumab (EU) 40 mg in the morning on day 1.

Criteria for evaluation:

Pharmacokinetic:

Blood samples for serum adalimumab or ABP 501 concentration determination were collected predose and 1, 4, 8, 12, and 24 hours (day 2) after dosing, at each return visit to the CPU (days 3, 4, 5, 6, 7, 8, 9, 11, 14, 16, 22, 29, 36, 43, 50, and 57), and at the EOS visit (day 63).

Pharmacokinetic parameters (C_{max}, last measurable serum concentration [C_{last}], 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 the terminal elimination rate constant [λ_z]) were calculated from serum adalimumab and ABP 501 concentration data using noncompartmental methods.

Safety:

Subjects were monitored for AEs throughout the study. Safety assessments, including clinical laboratory tests, physical examinations, vital signs measurements, 12-lead electrocardiograms (ECGs), and ADA tests were performed at prespecified time points.

Endpoints:

Primary Endpoint:

- Pharmacokinetic parameters (AUC_{inf} and C_{max}) of ABP 501, adalimumab (US), and adalimumab (EU)

Secondary Endpoints:

- Subject incidence of treatment-emergent AEs (TEAEs), vital signs, laboratory safety tests, ECGs, and subject incidence of ADAs
- Pharmacokinetic parameter, AUC_{last} of ABP 501, adalimumab (US), and adalimumab (EU)

Statistical Methods:

Pharmacokinetic Analyses:

[redacted]

[redacted]

Safety Analyses:

Safety data were listed by subject and analyzed using the Safety Population.

The number and percentage of subjects reporting any TEAE were tabulated by system organ class and preferred term (Medical Dictionary for Regulatory Activities, Version 15.0) for each treatment. Treatment-emergent AEs were further classified by severity and relationship to treatment.

The number and percentage of subjects developing ADAs were tabulated for each treatment and overall.

Clinical laboratory tests, vital signs, and ECG data (observed and change from baseline) were summarized by time point and treatment using appropriate descriptive statistics.

Results:

Disposition:
Two hundred and three subjects were randomized to the study, and all subjects were dosed. Sixty-six out of 67 subjects in the ABP 501 treatment group, 66 out of 69 subjects in the adalimumab (US) treatment group, and 64 out of 67 subjects in the adalimumab (EU) treatment group completed the study.
All subjects who were dosed (N = 203) were included in the Safety Population, the PK Concentration Population, the PK Parameter Population, and the Per-protocol PK Parameter Population.

Pharmacokinetic Results:

Summary of Statistical Assessment of ABP 501, Adalimumab (US), and Adalimumab (EU) Pharmacokinetic Parameters

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 501	3.22 [67]	2140 [58]	2000 [67]
Adalimumab (US)	3.11 [69]	1920 [61]	1880 [69]
Adalimumab (EU)	3.37 [67]	2050 [57]	2020 [66]
	Ratio of Adjusted LS Geometric Means (90% CI)		
ABP 501 vs. Adalimumab (US)	1.04 (0.964, 1.12)	1.11 (1.00, 1.24)	1.07 (0.964, 1.18)
ABP 501 vs. Adalimumab (EU)	0.96 (0.889, 1.03)	1.04 (0.935, 1.17)	0.99 (0.892, 1.10)
Adalimumab (US) vs. Adalimumab (EU)	0.92 (0.857, 0.994)	0.94 (0.840, 1.04)	0.93 (0.836, 1.03)

Abbreviations: CI = confidence interval; LS = least squares; n = number of nonmissing observations

On average, C_{max}, AUC_{inf}, and AUC_{last} were 4%, 11%, and 7% higher following a single SC injection of ABP 501 compared to adalimumab (US). For all 3 parameters, the 90% CIs of the ratios of the GMs were fully contained within 0.80 to 1.25, confirming the bioequivalence between ABP 501 and adalimumab (US). The C_{max} and AUC_{last} were, on average, 4% and 1% lower, and AUC_{inf} was, on average, 4% higher, following a single SC injection of ABP 501 compared to adalimumab (EU). The corresponding 90% CIs of the ratios of the GMs for all 3 parameters were fully contained within 0.80 to 1.25, confirming the bioequivalence of ABP 501 and adalimumab (EU).
Following a single SC injection of adalimumab (US), C_{max}, AUC_{inf}, and AUC_{last} were, on average, 8%, 6%, and 7% lower compared to adalimumab (EU). The 90% CIs of the ratios of GMs for all 3 parameters were fully contained within 0.80 to 1.25, confirming the bioequivalence between adalimumab (US) and adalimumab (EU).

Safety Results:

- There were no deaths, serious AEs (SAE) considered related to the study drug, or TEAEs leading to discontinuation from the study that were related to the study drug.
- One subject in the adalimumab (EU) treatment group reported an SAE of dermoid cyst (onset: day 18, resolution: day 19) considered unrelated to the study drug and assessed as severe in intensity. The subject was withdrawn from the study due to this SAE.
- Treatment-emergent AEs were reported for 58.2%, 47.8%, and 68.7% of subjects in the ABP 501, adalimumab (US), and adalimumab (EU) groups, respectively.
- Treatment-related AEs were reported for 35.8%, 24.6%, and 41.8% of subjects in the ABP 501, adalimumab (US), and adalimumab (EU) groups, respectively. All treatment-related AEs were considered mild (Grade 1) or moderate (Grade 2) in intensity.
- The most frequently reported treatment-related AEs by preferred term included headache, nausea, nasopharyngitis, and oropharyngeal pain.
- There were no clinically relevant changes in clinical laboratory tests, ECGs, vital signs, and physical examinations.
- Thirty-six (53.7%), 38 (55.1%), and 45 (67.2%) of subjects in the ABP 501, adalimumab (US), and adalimumab (EU) treatment groups, respectively, developed ADAs at some point during the study.

Conclusions:

Pharmacokinetic:

- Pharmacokinetic bioequivalence of ABP 501 following a single 40-mg SC injection relative to that from a 40-mg SC injection of adalimumab (US) and adalimumab (EU) has been demonstrated.
- Pharmacokinetic bioequivalence between adalimumab (US) and adalimumab (EU) has been demonstrated following a single 40-mg SC injection.

Safety:

- Single doses of ABP 501, adalimumab (US), and adalimumab (EU) administered to healthy subjects were safe and well tolerated. No new safety signals with regard to treatment with ABP 501 were identified.
- Similar ADA rates were observed with single dose administration of ABP 501, adalimumab (US), and adalimumab (EU) to healthy subjects.

Date of Report: 18 April 2013