2 SYNOPSIS

Name of Sponsor/Company Amgen Inc.	Name of Finished Product To be determined	Name of Active Ingredient ABP 501

Protocol Number: 20120262

Title of Study: A Randomized, Double-blind, Phase 3 Study of ABP 501 Efficacy and Safety Compared to Adalimumab in Subjects with Moderate to Severe Rheumatoid Arthritis

Investigators and Study Centers: This study was conducted at 92 centers in 12 countries. A listing of participating investigators and their associated study centers is included in Appendix 16.1.4.

Publication (reference): None as of the date of this report

Study Period (years):	1	**Phase of Development:** 3
Date of First Enrollment:	24 October 2013	
Date of Last Completed:	19 November 2014	

Objectives:

Primary Objective: The primary objective for this study was to assess the efficacy of ABP 501 compared with adalimumab.

Secondary Objectives: The secondary objectives were to assess the safety and immunogenicity of ABP 501 compared with adalimumab.

Exploratory Objectives: The exploratory objectives were to assess the injection site pain perception based on subject's rankings for ABP 501 compared with adalimumab and to assess the trough serum concentration of ABP 501 compared with adalimumab.

Methodology: This was a randomized, double-blind, active comparator-controlled study of adalimumab-naïve adult subjects with moderate to severe rheumatoid arthritis (RA) who had an inadequate response to methotrexate (MTX). Subjects were randomized 1:1 to receive either ABP 501 or adalimumab at 40 mg subcutaneous (SC) every 2 weeks until week 22. The assessment of the primary endpoint was at week 24, and there was a subsequent safety follow-up period through week 26 (end of study). The total duration of study was up to 30 weeks (including a screening period of up to 4 weeks). Pharmacogenetic testing was an optional part of this study; samples were collected but not analyzed at the time of this report.

Number of Subjects (planned and analyzed): Approximately 500 subjects (250 subjects per treatment group) were planned for randomization into the study and 526 subjects (264 subjects in ABP 501, 262 subjects in adalimumab) were randomized and analyzed.

Diagnosis and Main Criteria for Inclusion: Eligible subjects met the following key criteria:

- men and women ≥ 18 to ≤ 80 years of age
- diagnosed with RA, as determined by meeting 2010 American College of Rheumatology (ACR) or European League Against Rheumatism classification criteria for RA
- moderate to severe RA duration of at least 3 months
- active RA defined as ≥ 6 swollen joints and ≥ 6 tender joints at screening and baseline and at least 1 of the following at screening: erythrocyte sedimentation rate ≥ 28 mm/hr or serum C-reactive protein (CRP) > 1.0 mg/dL
- positive for rheumatoid factor or anti-cyclic citrullinated peptide at screening
- received MTX for ≥ 12 consecutive weeks, and on a stable dose of 7.5 to 25 mg per week for ≥ 8 weeks before receiving investigational product. Subjects must be willing to remain on stable dose of MTX throughout the study.

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Subjects were ineligible if they had prior use of 2 or more biological therapies for RA, Humira® (adalimumab), or a biosimilar of adalimumab.

The full inclusion and exclusion list is provided in Section 8.4 of the protocol (Appendix 16.1.1 of this report).

Subject Disposition: A total of 526 subjects (264 in ABP 501, 262 in adalimumab) were enrolled and randomized in this study and received at least 1 dose of investigational product, and 494 of these subjects (93.9%) completed the study. A total of 17 subjects (3.2%) withdrew consent, 10 subjects (1.9%) discontinued study because of other reasons (all related to adverse events), 4 subjects (0.8%) were lost to follow-up, and 1 subject (0.2%) discontinued study because of protocol violations.

Key Demographics:

Sex: 426 women (81.0%), 100 men (19.0%)

Age: Mean (SD): 55.9 (11.67) years (range: 21 to 80 years)

Race: White: 500 subjects (95.1%), black or African American: 21 subjects (4.0%), Asian: 3 subjects (0.6%), other: 2 subjects (0.4%)

Ethnicity: Not Hispanic or Latino: 466 subjects (88.6%), Hispanic or Latino: 58 subjects (11.0%), not allowed to collect: 2 subjects (0.4%)

Test Product, Dose and Mode of Administration, Batch Number: ABP 501 was administered SC at a dose of 40 mg every 2 weeks.

The manufacturing batch numbers are provided in Appendix 16.1.6.

Duration of Treatment: 22 weeks

Reference Product, Dose and Mode of Administration, Batch Number: Adalimumab was administered SC at a dose of 40 mg every 2 weeks.

The manufacturing batch numbers are provided in Appendix 16.1.6.

Endpoints for Evaluation:

Primary Efficacy Endpoint: The primary efficacy endpoint was the risk ratio (RR) of the ACR20 (20% improvement in ACR core set measurements) at week 24

Secondary Efficacy Endpoints: The secondary efficacy endpoints of this study were as follows:

- Disease Activity Score 28-CRP (DAS28-CRP) change from baseline at weeks 2, 4, 8, 12, 18, and 24
- RR of ACR20 at weeks 2 and 8
- RR of ACR50 (50% improvement in ACR core set measurements) and ACR70 (70% improvement in ACR core set measurements) responses at week 24

Safety Endpoints: The safety endpoints of this study were as follows:

- treatment-emergent adverse events and serious adverse events
- clinically significant changes in laboratory values
- changes in vital signs
- incidence of antidrug antibodies

Statistical Methods: Descriptive summaries were tabulated by treatment for all endpoints. All categorical variables were summarized using the number and percent of subjects in each category. All continuous variables were summarized using mean, standard deviation, median, minimum, maximum, and number of subjects with observations.

Primary Endpoint: Clinical equivalence for the primary endpoint, the RR of ACR20 at week 24,

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was evaluated by comparing the 2-sided 90% confidence interval (CI) of the RR of ACR20 between ABP 501 and adalimumab with an equivalence margin of (0.738, 1/0.738). The 90% CI was estimated using a generalized linear model (specifically, a log-binomial regression model), with treatment and stratification factors as covariates.

Secondary Endpoints: Inferential analyses were only performed for the primary endpoint, and the analyses on the secondary endpoints were considered descriptive. Treatment differences across assessed time points for the DAS28-CRP change from baseline were evaluated with a repeated-measures analysis. Data from all assessed time points postbaseline through the week 24 visit were included in this analysis. Besides stratification variables, visit (week), treatment group, treatment-by-visit interactions, and baseline DAS28-CRP were included in the model. The 90% and 95% CIs were constructed for mean difference of DAS28-CRP change from baseline between ABP 501 and adalimumab at each time point. The RR of ACR20 at weeks 2 and 8, and the RRs of ACR50 and ACR70 at week 24 were summarized descriptively. Also, the corresponding 90% and 95% CIs for RR and risk difference (RD) are estimated using the generalized linear model adjusted for stratification factors.

Safety Endpoints: Safety endpoints were summarized descriptively. Subgroup analyses (by age, race, sex, and stratification factors as appropriate) are presented.

Summary of Results:

Efficacy: The primary efficacy endpoint results showed that at week 24, 74.6% of subjects (194 of 260) in the ABP 501 group and 72.4% of subjects (189 of 261) in the adalimumab group met the ACR20 response criteria. The RR of ACR20 for ABP 501 versus adalimumab was 1.039 with the 2-sided 90% CI of (0.954, 1.133). The 90% CI fell within the predefined equivalence margin of (0.738, 1/0.738), thus, the clinical equivalence between ABP 501 and adalimumab was demonstrated. The secondary efficacy endpoints show that at week 2, 35.4% of subjects (90 of 254) in the ABP 501 group and 24.5% of subjects (63 of 257) in the adalimumab group met the ACR20 response criteria. The RR of ACR20 for ABP 501 versus adalimumab was 1.421 with the 2-sided 90% CI of (1.134, 1.781). At week 8, 63.5% of subjects (165 of 260) in the ABP 501 group and 62.5% of subjects (163 of 261) in the adalimumab group met the ACR20 response criteria. The RR of ACR20 for ABP 501 versus adalimumab was 1.015 with the 2-sided 90% CI of (0.908, 1.134). At week 24, 49.2% of subjects (120 of 244) in the ABP 501 group and 52.0% of subjects (131 of 252) in the adalimumab group met the ACR50 response criteria. The RR of ACR50 for ABP 501 versus adalimumab was 0.948 with the 2-sided 90% CI of (0.819, 1.097). At week 24, 26.0% of subjects (64 of 246) in the ABP 501 group and 22.9% of subjects (58 of 253) in the adalimumab group met the ACR70 response criteria. The RR of ACR70 for ABP 501 versus adalimumab was 1.130 with the 2-sided 90% CI of (0.872, 1.464). Mean decreases of DAS28-CRP from baseline over time were comparable between the ABP 501 and adalimumab group.

Safety Results: Overall, 52.3% of all subjects had at least 1 adverse event during the study, and this was similar to the proportions in each treatment group. The most frequently reported treatment-emergent adverse events were as follows (ABP 501, adalimumab): nasopharyngitis (6.4%, 7.3%), headache (4.5%, 4.2%), arthralgia (3.0%, 3.4%), cough (2.7%, 3.1%), and upper respiratory tract infection (1.5%, 3.8%). There were no treatment group differences of ≥ 5% between the ABP 501 or adalimumab group for any adverse event by preferred term. Most adverse events were grade 1 or grade 2 in severity. Grade ≥ 3 adverse events were reported for 9 subjects (3.4%) in the ABP 501 group and 17 subjects (6.5%) in the adalimumab group. All grade ≥ 3 adverse events occurred in ≤ 1% of subjects in either group. All but 2 of these grade ≥ 3 adverse events (anemia and right foot deformation [both grade 3]), which occurred in 1 subject each in the adalimumab group, had resolved by the subject's end of study visit.

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Adverse events that led to withdrawal of investigational product were reported in 5 of 264 subjects (1.9%) in the ABP 501 group and 2 of 262 subjects (0.8%) in the adalimumab group. Adverse events that led to study withdrawal were reported in 7 of 264 subjects (2.7%) in the ABP 501 group and 2 of 262 subjects (0.8%) in the adalimumab group.

No deaths occurred during the study. The proportions of subjects who had a serious adverse event were similar between the ABP 501 group (3.8%, 10 of 264 subjects) and adalimumab group (5.0%, 13 of 262 subjects). The only serious adverse event reported for > 1 subject was sepsis, which was reported for 2 subjects in the ABP 501 group; both of these events were reported as resolved by the end of the study.

No clinically significant changes were observed in laboratory values and vital signs.

Immunogenicity Results: Overall, 38.2% of subjects (201 of 526) tested positive for binding antibodies postbaseline, and this was similar to the proportions in each treatment group: 38.3% of subjects (101 of 264) in the ABP 501 group versus 38.2% of subjects (100 of 262) in the adalimumab group. A total of 10.1% of subjects (53 of 526) tested positive for neutralizing antibodies postbaseline, and this was similar to the proportions in each treatment group: 9.1% of subjects (24 of 264) in the ABP 501 group versus 11.1% of subjects (29 of 262) in the adalimumab group.

Conclusions: The study met the stated objectives. The primary efficacy results demonstrated clinical equivalence between ABP 501 and adalimumab in subjects with moderate to severe RA with an inadequate response to methotrexate, and the safety results indicate that ABP 501 and adalimumab have similar safety and immunogenicity profiles.

Date of the Report: 21 May 2015