2 SYNOPSIS

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

Protocol Number: 20120263

Title of Study: A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of ABP 501 Compared with Adalimumab in Subjects with Moderate to Severe Plaque Psoriasis

Investigators and Study Centers: This study was conducted at 49 centers in 6 countries (Australia, Canada, France, Germany, Hungary, and Poland). A list 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):	1.5	**Phase of Development:** 3
Date of First Enrollment:	18 October 2013	
Date of Last Completed:	18 March 2015	

Objectives:

Primary Objective: The primary objective for this study was to evaluate the efficacy of ABP 501 in subjects with moderate to severe plaque psoriasis, as measured by the Psoriasis Area and Severity Index (PASI) percent improvement from baseline, compared with adalimumab.

Secondary Objectives: The secondary objectives of this study were to assess the safety and immunogenicity of ABP 501 compared with adalimumab and to assess efficacy in terms of PASI 75 response (75% or greater improvement from baseline in PASI score), static Physician's Global Assessment (sPGA), and percent body surface area (BSA) affected.

Exploratory Objectives: The exploratory objective was to assess the perception of injection site pain based on subjects' rankings for ABP 501 compared with adalimumab injections.

Methodology: This was a randomized, double-blind, active comparator-controlled study in adult subjects with moderate to severe plaque psoriasis. Randomization was stratified based on prior biologic use for psoriasis and geographic region. After a 4-week screening period, subjects were randomized (1:1) to Treatment Group A (ABP 501) or Treatment Group B (adalimumab). Subjects received ABP 501 or adalimumab at an initial loading dose of 80 mg subcutaneous (SC) on week 1/day 1, followed by 40 mg SC every other week starting 1 week after the loading dose (ie, week 2 and every 2 weeks thereafter). At week 16, subjects with a PASI 50 response (50% or better improvement) continued on study for up to 52 weeks. Subjects without a PASI 50 response at week 16 or who missed the week 16 visit were discontinued from the study.

Subjects who continued treatment beyond week 16 were re-randomized in a blinded fashion such that all subjects initially randomized to Treatment Group A (ABP 501) continued treatment with ABP 501 and subjects initially randomized to Treatment Group B (adalimumab) were re-randomized (1:1) to either continue treatment with adalimumab (Treatment Group B1 [adalimumab/adalimumab]) or were transitioned to ABP 501 (Treatment Group B2 [adalimumab/ABP 501]). All subjects continued with their assigned treatment until week 48, when the last dose of assigned investigational product was administered. The final efficacy assessments were conducted at week 50 and the end of study visit was at week 52. Pharmacogenetic testing was an optional part of this study; samples were collected but not analyzed at the time of this report for subjects who consented to participate.

Number of Subjects (planned and analyzed): Approximately 340 subjects (170 subjects per treatment group) were planned for randomization into the study. A total of 350 subjects were

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randomized and analyzed (175 subjects per treatment group) in the full analysis set.

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

- Subject was ≥ 18 and ≤ 75 years of age at time of screening.
- Subject had stable moderate to severe plaque psoriasis for at least 6 months.
- Subject had involved BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and baseline.
- Subject was a candidate for systemic therapy or phototherapy.
- Subject had previously failed, had an inadequate response, intolerance to, or contraindication to at least 1 conventional anti-psoriatic systemic therapy (eg, methotrexate, cyclosporine, psoralen plus ultraviolet light A).

Subjects were ineligible if they were diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (eg, eczema) that would interfere with evaluations of the effect of investigational product on psoriasis. In addition, subjects were ineligible if they had previously used any of the following: 2 or more biologics for treatment of psoriasis, 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).

Subject Disposition: A total of 350 subjects (175 subjects in each treatment group) were enrolled and randomized in this study, and 347 of these subjects (99.1%) received at least 1 dose of investigational product. A total of 326 of 350 subjects (93.1%) completed the study through week 16 (164 subjects [93.7%] in Treatment Group A [ABP 501], 162 subjects [92.6%] in Treatment Group B [adalimumab]) and 308 subjects (88.0%) were re-randomized at week 16. A total of 42 subjects (12.0%) were not re-randomized at week 16 and the most common reason was protocol-specified criteria (21 subjects [6.0%]).

From baseline to the end of study, 275 of 350 subjects (78.6%) completed the study (135 subjects [77.1%] in Treatment Group A [ABP 501], 140 subjects [80.0%] in Treatment Group B [adalimumab]). Of the 75 subjects (21.4%) who discontinued from study, 42 subjects discontinued before or at week 16, and 33 subjects discontinued post week 16. Overall, the most common reasons for discontinuing study (> 5% in either treatment group) were the following: other (other reasons included adverse events, lack of efficacy, and noncompliance), protocol-specified criteria, and consent withdrawn.

All 308 subjects who were re-randomized received at least 1 dose of investigational product after re-randomization. A total of 275 of 308 subjects (89.3%) completed the study (135 subjects [88.8%] in Treatment Group A [ABP 501/ABP 501], 71 subjects [89.9%] in Treatment Group B1 [adalimumab/adalimumab], 69 subjects [89.6%] in Treatment Group B2 [adalimumab/ABP 501]). The most common reasons for discontinuing study post week 16 were consent withdrawn and other (other reasons included adverse events, lack of efficacy, and noncompliance).

Key Demographics:

Sex: 122 women (34.9%), 228 men (65.1%)

Age: Mean (SD): 44.6 (13.31) years (range: 18 to 74 years)

Race: White: 324 subjects (92.6%), black or African American: 2 subjects (0.6%), Asian: 13 subjects (3.7%), Native Hawaiian or other Pacific Islander: 1 subject (0.3%), mixed race: 1 subject (0.3%), other: 4 subjects (1.1%), and unknown: 5 subjects (1.4%)

Ethnicity: Not Hispanic or Latino: 339 subjects (96.9%), Hispanic or Latino: 6 subjects (1.7%), not allowed to collect: 5 subjects (1.4%)

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Subject demographics were balanced across treatment groups.

Test Product, Dose and Mode of Administration, Batch Number: ABP 501 was administered SC at a dose of 80 mg on week 1/day 1 and 40 mg at week 2 and every 2 weeks thereafter.

The manufacturing batch numbers are provided in Appendix 16.1.6.

Duration of Treatment: 48 weeks

Reference Product, Dose and Mode of Administration, Batch Number: Adalimumab was administered SC at a dose of 80 mg on week 1/day 1 and 40 mg at week 2 and every 2 weeks thereafter.

The manufacturing batch numbers are provided in Appendix 16.1.6.

Endpoints for Evaluation:

Primary Efficacy Endpoint: The primary efficacy endpoint was the PASI percent improvement from baseline at week 16.

Secondary Efficacy Endpoints: The secondary efficacy endpoints were as follows:

- PASI 75 response at weeks 16, 32, and 50
- PASI percent improvement from baseline at weeks 32 and 50
- sPGA responses (0/1) at weeks 16, 32, and 50
- BSA involvement at weeks 16, 32, and 50

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
- change from baseline in vital signs
- incidence of antidrug antibodies

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

Primary Endpoint: The primary efficacy endpoint, PASI percent improvement from baseline at week 16, was analyzed using the full analysis set with missing data imputed using the last observation carried forward (LOCF) method. Clinical equivalence of the primary endpoint was evaluated by comparing the 2-sided 95% confidence interval (CI) of the difference of PASI percent improvement from baseline to week 16 between Treatment A (ABP 501) and Treatment B (adalimumab) with an equivalence margin of (-15, 15). The 2-sided 95% CI of the group difference was estimated using an ANCOVA model adjusted for baseline PASI score and stratification factors (geographic region and prior biologic use for psoriasis) as covariates.

Secondary Endpoints: Inferential analyses were only performed for the primary endpoint. The analyses of the secondary endpoints were considered descriptive. The number and percentage of subjects achieving a PASI 75 response was tabulated by initial treatment through week 16, and by initial/re-randomized treatment post week 16.

PASI percent improvement from baseline at weeks 32 and 50 and difference between treatments were evaluated descriptively together with the 2-sided 95% and 90% CI of the difference in PASI percent improvement from baseline between Treatment Group A (ABP 501/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) and between Treatment Group B2 (adalimumab/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) using the re-randomized analysis set as observed.

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The sPGA categories were summarized by frequency and percentage of subjects in each sPGA category by initial treatment through week 16, and by initial/re-randomized treatment post week 16. The frequency and percentage of subjects achieving sPGA response (defined as a sPGA value of clear [score 0] or almost clear [score 1]) were provided by initial treatment through week 16, and by initial/re-randomized treatment post week 16.

Psoriasis BSA score and change from baseline were summarized descriptively by initial treatment through week 16, and by initial/re-randomized treatment post week 16.

Safety Endpoints: Safety endpoints were summarized descriptively. Subgroup analyses (by age, race, sex and prior biologic use) are presented.

Immunogenicity: The number and percentage of subjects who developed binding and neutralizing anti-drug antibodies were tabulated by initial treatment through week 16, and by initial/re-randomized treatment for the entire study. A 90% and 95% CI for the difference of developing antidrug antibody incidence (binding and neutralizing) between treatments were estimated using a generalized linear model with stratification factors as covariates. For safety in terms of immunogenicity, the non-inferiority was assessed at week 16 in Treatment Group A (ABP 501) versus Treatment Group B (adalimumab); and at week 52 with subjects who received ABP 501 or adalimumab throughout the study in Treatment Group A (ABP 501/ABP 501) versus Treatment Group B1 (adalimumab/adalimumab). The non-inferiority for the incidence of antidrug antibodies was evaluated by estimating the 95% CI of the difference in percentages and comparing the upper CI with the non-inferiority margin of 21.7%.

Summary of Results:

Efficacy:

PASI Percent Improvement from Baseline at Week 16: The primary efficacy endpoint results showed that at week 16 the PASI mean percent improvement from baseline was 80.91 in Treatment Group A (ABP 501) and 83.06 in Treatment Group B (adalimumab). The least-squares mean difference in PASI percent improvement from baseline to week 16 between the 2 treatment groups was -2.18 with the 2-sided 95% CI of (-7.39, 3.02) and the 2-sided 90% CI of (-6.55, 2.18) (p = 0.4096). The 95% CI was within the predefined equivalence margin of (-15, 15), thus demonstrating the clinical equivalence of ABP 501 and adalimumab.

PASI Percent Improvement from Baseline at Weeks 32 and 50: Based on the re-randomized analysis set (observed cases) at week 32, the mean PASI percent improvement from baseline was similar across treatment groups (range: 86.98 to 88.16). The treatment difference in PASI percent improvement from baseline between Treatment Group A (ABP 501/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) was -0.49 with the 2-sided 95% CI of (-5.60, 4.61). The treatment difference in PASI percent improvement from baseline between Treatment Group B2 (adalimumab/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) was -1.05 with the 2-sided 95% CI of (-6.93, 4.84). Similar results were observed at week 50, where the mean PASI percent improvement from baseline was similar across treatment groups (range: 85.82 to 88.11).

PASI 75 Response at Weeks 16, 32, and 50: Based on the full analysis set (LOCF) at week 16, the PASI 75 response was 74.4% and 82.7% for Treatment Group A (ABP 501) and Treatment Group B (adalimumab), respectively. The difference between the treatment groups was -7.729% with the 2-sided 95% CI of (-16.620%, 1.163%) (p = 0.0884).

Based on the re-randomized analysis set (observed cases) at week 32, the PASI 75 response was similar across the treatment groups (range: 82.5% to 84.7%). The treatment difference in PASI 75 response between Treatment Group A (ABP 501/ABP 501) and Treatment Group B1

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(adalimumab/adalimumab) was -2.751% with the 2-sided 95% CI of (-13.935%, 8.433%). The treatment difference in PASI 75 response between Treatment Group B2 (adalimumab/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) was 0.582% with the 2-sided 95% CI of (-12.899%, 14.063%). Similar results were observed at week 50, where the PASI 75 response was similar across treatment groups (range: 81.2% to 87.1%).

sPGA Responses at Weeks 16, 32, and 50: Based on the full analysis set (LOCF) at week 16, the sPGA positive response was 58.7% in Treatment Group A (ABP 501) and 65.3% in Treatment Group B (adalimumab). The difference in sPGA positive response between Treatment Group A and Treatment Group B was -7.365% with the 2-sided 95% CI of (-17.203%, 2.472%) (p = 0.1422).

Based on the re-randomized analysis set (observed cases) at week 32, sPGA positive response across the treatment groups ranged from 66.4% to 72.2%. The difference in sPGA positive response between Treatment Group A (ABP 501/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) was -8.158% with the 2-sided 95% CI of (-20.487%, 4.171%). The difference in sPGA positive response between Treatment Group B2 (adalimumab/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) was -4.195% with the 2-sided 95% CI of (-18.099%, 9.709%). Similar results were observed at week 50, where the sPGA positive response across the treatment groups ranged from 68.7% to 74.3%.

BSA Involvement at Weeks 16, 32, and 50: Based on the full analysis set (LOCF) at week 16, the treatment difference in change from baseline in percent BSA affected by psoriasis between Treatment Group A (ABP 501) and Treatment Group B (adalimumab) was 1.93 with the 2-sided 95% CI of (-0.24, 4.10) (p = 0.0809).

Based on the re-randomized analysis set (observed cases) at week 32, the treatment difference in change from baseline in percent BSA affected by psoriasis between Treatment Group A (ABP 501/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) was 1.51 with the 2-sided 95% CI of (-0.44, 3.46). The treatment difference in change from baseline in percent BSA affected by psoriasis between Treatment Group B2 (adalimumab/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) was 0.83 with the 2-sided 95% CI of (-1.41, 3.07). Similar results were reported at week 50 for treatment difference in change from baseline in percent BSA affected by psoriasis.

Safety Results: From baseline to week 16, 65.4% of subjects had at least 1 adverse event, and the proportions were similar in each treatment group. Treatment-emergent adverse events reported for ≥ 5% of subjects in either treatment group were as follows (Treatment Group A [ABP 501], Treatment Group B [adalimumab]): nasopharyngitis (14.4%, 15.6%), headache (6.9%, 10.4%), and upper respiratory tract infection (5.2%, 5.2%). There were no treatment group differences ≥ 5% between Treatment Group A and Treatment Group B for any treatment-emergent adverse event by preferred term. Grade ≥ 3 adverse events occurred in 8 of 174 subjects (4.6%) in Treatment Group A and 5 of 173 subjects (2.9%) in Treatment Group B. None of the grade ≥ 3 adverse events occurred in more than 1 subject each. Adverse events that led to withdrawal of investigational product were reported in 7 of 174 subjects (4.0%) in Treatment Group A and 5 of 173 subjects (2.9%) in Treatment Group B. Adverse events that led to study withdrawal were reported in 7 of 174 subjects (4.0%) in Treatment Group A and 5 of 173 subjects (2.9%) in Treatment Group B. There was no trend among the types of events leading to investigational product and study withdrawal. The proportions of subjects who had a serious adverse event were similar between Treatment Group A (3.4%, 6 of 174 subjects) and Treatment Group B (2.9%, 5 of 173 subjects). No serious adverse events occurred in more than 1 subject each and all serious adverse events resolved by the subjects' end-of-study visits.

From baseline to week 16, no clinically meaningful changes were observed in laboratory values and vital signs.

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Post week 16 to the end of study, 69.5% of subjects had at least 1 adverse event (71.1% in Treatment Group A [ABP 501/ABP 501], 65.8% in Treatment Group B1 [adalimumab/adalimumab], and 70.1% in Treatment Group B2 [adalimumab/ABP 501]). Treatment-emergent adverse events reported for ≥ 5% of subjects in any treatment group were as follows (Treatment Group A, Treatment Group B1, Treatment Group B2): nasopharyngitis (16.4%, 17.7%, 23.4%), upper respiratory tract infection (5.9%, 7.6%, 9.1%), psoriasis (6.6%, 6.3%, 5.2%), headache (3.3%, 10.1%, 2.6%), diarrhea (2.0%, 5.1%, 10.4%), arthralgia (2.6%, 6.3%, 2.6%), and back pain (3.3%, 6.3%, 1.3%). Grade ≥ 3 adverse events occurred in 7 of 152 subjects (4.6%) in Treatment Group A, 2 of 79 subjects (2.5%) in Treatment Group B1, and 3 of 77 subjects (3.9%) in Treatment Group B2. None of the grade ≥ 3 adverse events occurred in more than 1 subject each. Although the proportion of subjects who had at least 1 adverse event that led to withdrawal of investigational product was higher in Treatment Group A (4.6%, 7 of 152 subjects) compared with Treatment Group B1 (1.3%, 1 of 79 subjects) and Treatment Group B2 (3.9%, 3 of 77 subjects), no emerging safety trend was observed in Treatment Group A. Adverse events that led to study withdrawal were reported in 4 of 152 subjects (2.6%) in Treatment Group A, 1 of 79 subjects (1.3%) in Treatment Group B1, and 2 of 77 subjects (2.6%) in Treatment Group B2. There was no trend among the types of events leading to investigational product and study withdrawal. Four of 152 subjects (2.6%) in Treatment Group A, 4 of 79 subjects (5.1%) in Treatment Group B1, and 4 of 77 subjects (5.2%) in Treatment Group B2 had serious adverse events. No serious adverse events occurred in more than 1 subject each and all serious adverse events resolved by the subjects' end-of-study visits.

Post week 16 to the end of study, no clinically meaningful changes were observed in laboratory values and vital signs.

No deaths occurred during this study. Overall, no clinically meaningful differences were observed in the safety profile of ABP 501 compared with adalimumab from baseline to the end of the study.

Immunogenicity Results: From baseline to week 16, 206 of 347 subjects (59.4%) tested positive for binding antibodies postbaseline; 96 of 174 subjects (55.2%) were in Treatment Group A (ABP 501) and 110 of 173 subjects (63.6%) were in Treatment Group B (adalimumab). The difference in the incidence of developing binding antibodies between Treatment Group A and Treatment Group B was -8.122% with 95% CI of (-18.242%, 1.998%). A total of 41 of 347 subjects (11.8%) tested positive for neutralizing antibodies postbaseline; 17 of 174 subjects (9.8%) were in Treatment Group A (ABP 501) and 24 of 173 subjects (13.9%) were in Treatment Group B (adalimumab). The difference in the incidence of developing neutralizing antibodies between Treatment Group A and Treatment Group B was -3.531% with 95% CI of (-10.392%, 3.331%).

From baseline to the end of study, 251 of 347 subjects (72.3%) tested positive for binding antibodies postbaseline. Among subjects who were not re-randomized and did not continue to receive treatment post week 16, 18 of 22 subjects (81.8%) in Treatment Group A (ABP 501) and 14 of 17 subjects (82.4%) in Treatment Group B (adalimumab) tested positive for binding antibodies postbaseline. For subjects who were re-randomized, 72 subjects (47.4%) in Treatment Group A (ABP 501/ABP 501), 43 subjects (54.4%) in Treatment Group B1 (adalimumab/adalimumab), and 48 subjects (62.3%) in Treatment Group B2 (adalimumab/ABP 501) tested positive for binding antibodies at week 16. From baseline to the end of study, among subjects who were re-randomized, 104 of 152 subjects (68.4%) in Treatment Group A (ABP 501/ABP 501), 59 of 79 subjects (74.7%) in Treatment Group B1 (adalimumab/adalimumab), and 56 of 77 subjects (72.7%) in Treatment Group B2 (adalimumab/ABP 501) tested positive for binding antibodies postbaseline. The difference in the incidence of developing binding antibodies between Treatment Group A (ABP 501/ABP 501) and

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Treatment Group B1 (adalimumab/adalimumab) was -4.064% with 95% CI of (-15.703%, 7.574%). The difference in the incidence of developing binding antibodies between Treatment Group B2 (adalimumab/ABP 501) and Treatment Group B1 (adalimumab/adalimumab) was -0.159% with 95% CI of (-13.293%, 12.974%).

From baseline to the end of study, 76 of 347 subjects (21.9%) tested positive for neutralizing antibodies postbaseline. Among subjects who were not re-randomized and did not continue to receive treatment post week 16, 13 of 22 subjects (59.1%) in Treatment Group A (ABP 501) and 7 of 17 subjects (41.2%) in Treatment Group B (adalimumab) tested positive for neutralizing antibodies postbaseline. For subjects who were re-randomized, 11 subjects (7.2%) in Treatment Group A (ABP 501/ABP 501), 9 subjects (11.4%) in Treatment Group B1 (adalimumab/adalimumab), and 8 subjects (10.4%) in Treatment Group B2 (adalimumab/ABP 501) tested positive for neutralizing antibodies at week 16. From baseline to the end of study, among subjects who were re-randomized, 21 of 152 subjects (13.8%) in Treatment Group A (ABP 501/ABP 501), 16 of 79 subjects (20.3%) in Treatment Group B1 (adalimumab/adalimumab), and 19 of 77 subjects (24.7%) in Treatment Group B2 (adalimumab/ABP 501) tested positive for neutralizing antibodies postbaseline.

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 plaque psoriasis, and the safety results indicate that ABP 501 and adalimumab have similar safety and immunogenicity profiles. A single transition from adalimumab to ABP 501 at week 16 did not impact the efficacy, safety, or immunogenicity results from week 16 to the end of study.

Date of the Report: 22 July 2015