U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	761024 / 0
Drug Name:	ABP 501
Indication(s):	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)
Applicant:	Amgen
Dates:	Submitted: 11/25/2015 BSUFA: 9/23/2016
Review Priority:	Standard review
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Keywords: biosimilar

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1 Executive Summary

ABP 501 is a proposed biosimilar to US-licensed Humira (adalimumab). As part of the development program, the applicant conducted a comparative clinical study of ABP 501 versus European Union (EU)-approved Humira in subjects with moderate to severe psoriasis (Study 263). Study 263 was a randomized, double-blind comparative clinical study of ABP 501 and EU-approved Humira in subjects age 18 to 75 years old with moderate to severe plaque psoriasis. The study enrolled 350 subjects, 175 randomized to the ABP 501 arm and 175 randomized to the EU-approved Humira arm, of which 347 received at least one dose of study product. Subjects were enrolled in Europe, Canada, and Australia. The primary endpoint was the percent improvement in PASI (Psoriasis Area Severity Index) from Week 1 to Week 16. The pre-specified similarity margin for the confidence interval for the difference in means was ±15. At Week 16, subjects who achieved at least PASI 50 response (at least 50% improvement from baseline) continued into the second treatment period. All subjects originally randomized to ABP 501 continued treatment with ABP 501 through Week 48. Subjects originally randomized to EU-approved Humira were re-randomized 1:1 to either continue treatment with EU-approved Humira or transition to ABP 501 through Week 48. Subjects were evaluated in the second treatment period for efficacy, safety, and immunogenicity outcomes.

The mean percent improvement in PASI at Week 16 was similar on the ABP 501 and EU-approved Humira arms and the confidence interval for the difference was within the pre-specified margin of ±15. In the applicant's full analysis set (FAS), defined as all subjects randomized and dispensed medication who had at least one post-baseline efficacy assessment, the mean percent improvement in PASI values on the ABP 501 and EU-approved Humira arms were 80.9 vs 83.1. Results on the per protocol population and an analysis population that includes all subjects randomized and dispensed medication whether or not they had post-baseline efficacy assessments were similar and also fell within the pre-specified margin. See Table 1. The results of the secondary endpoints of PASI 75, clear or almost clear on the static Physician's Global Assessment, and reduction from baseline in body surface area were consistent with the primary endpoint.

Table 1 – Percent Improvement in PASI at Week 16

	ABP 501	EU-approved Humira	Difference[d]	90% Conf. Int.
Full Analysis Set[a] (LOCF)	N=172 80.9	N=173 83.1	-2.2	(-6.6, 2.2)
Sensitivity Analysis[b] (LOCF)	N=174 80.0	N=173 83.1	-3.1	(-7.5, 1.4)
Per protocol[c] (Observed)	N=155 82.6	N=152 85.3	-2.6	(-6.2, 0.9)

[a] Randomized, dispensed medication, and at least one post-baseline efficacy assessment
[b] Randomized, dispensed medication
[c] Completed the treatment period without protocol violations that affected the evaluation of the primary objective
[d] Model estimate adjusted for prior biologic use, region, and baseline PASI

Because Study 263 was conducted completely outside the US, the applicant did not discuss the proposed similarity margin with the FDA prior to conducting the study. The applicant did not provide a rationale for their choice of similarity margin in the protocol or study report. Therefore, this reviewer evaluated the applicant's proposed margin using information from the published literature on the percent improvement in PASI from published placebo-controlled studies of Humira and other TNF-α inhibitors. Based on this evaluation, the assumptions of consistency and assay sensitivity appear reasonable for Study 263, and the confidence interval for the primary endpoint of percent improvement in PASI is sufficiently narrow to conclude that the study met the criteria for demonstrating similarity.

Adverse event rates were similar on both the ABP 501 and EU-approved Humira arms. During the initial treatment period, 10% of ABP 501 subjects and 14% of EU-approved Humira subjects developed neutralizing antibodies. Among the subjects who continued into the second treatment period, 20% of subjects on EU-approved Humira/EU-approved Humira arm, 25% on the EU-approved Humira/ABP 501 arm, and 14% on the ABP 501/ABP 501 arm developed neutralizing antibodies during the study.

Thus we conclude that the results on the ABP 501 and EU-approved Humira arms are similar and that Study 263 supports a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

2 Introduction

2.1 Overview

ABP 501 is being developed as a proposed biosimilar to US-licensed Humira (adalimumab) under Section 351(k) of the Public Health Service (PHS) Act. Section 351(i) of the PHS Act defines biosimilarity to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." As part of their development program, the applicant has conducted two comparative clinical studies of ABP 501 and a 3-way pharmacokinetic similarity study. Study 262 evaluated ABP 501 and US-licensed Humira in subjects with rheumatoid arthritis. Study 263 evaluated ABP 501 and EU-approved Humira in subjects with plaque psoriasis. Study 217 was a 3-way pharmacokinetic similarity study (ABP 501 vs. US-licensed Humira vs. EU-approved Humira) in healthy volunteers. This review will evaluate Study 263. The design details for Study 263 are summarized in Table 2.

Study 263 was conducted outside the US and the protocol was not submitted to the FDA prior to conducting the study. Although the details of Study 263 were not discussed with FDA, other components of the development program were discussed at Biosimilar Biological Product Development meetings held on August 24, 2011 and June 10, 2015.

Table 2 – Characteristics of Study 263

Study Number	20120263 (Study 263)
Study Design	Part 1:ABP 501 vs. EU-approved Humira (Week 1 to Week 16) Part 2: Subjects with PASI 50 continue in study. ABP 501 subjects continue treatment with ABP 501 through Week 52. EU-approved Humira subjects are randomized 1:1 to transition to ABP 501 or continue EU-approved Humira through Week 52.
Inclusion criteria	Subjects age 18-75 years with stable moderate to severe plaque psoriasis for at least 6 months Body Surface Area≥10%, PASI ≥ 12, and static Physician's Global Assessment (sPGA) ≥ 3.
Treatment regimen	80 mg at Week 1, 40 mg at Week 2 and every other week thereafter.
Primary endpoint	Percent reduction in PASI at Week 16
Secondary endpoints	PASI 75, sPGA response (0 or 1), change in BSA
Treatment arms and Sample Size	ABP 501 - 175 EU-approved Humira - 175
Study location	Australia, Canada, France, Germany, Hungary, Poland

2.2 Data Sources

This reviewer evaluated the applicant's clinical study report for Study 263, clinical summaries, and proposed labeling. The submission was in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The analysis datasets for Study 263 used in this review are archived at \\cdsesub1\evsprod\bla761024\0001\m5\datasets\20120263\ analysis\adam\datasets\ .

3 Statistical Evaluation

3.1 Data and Analysis Quality

The databases for Study 263 required minimal data management prior to performing the analyses, and no requests for information regarding the datasets for Study 263 were made to the applicant.

3.2 Evaluation of Efficacy

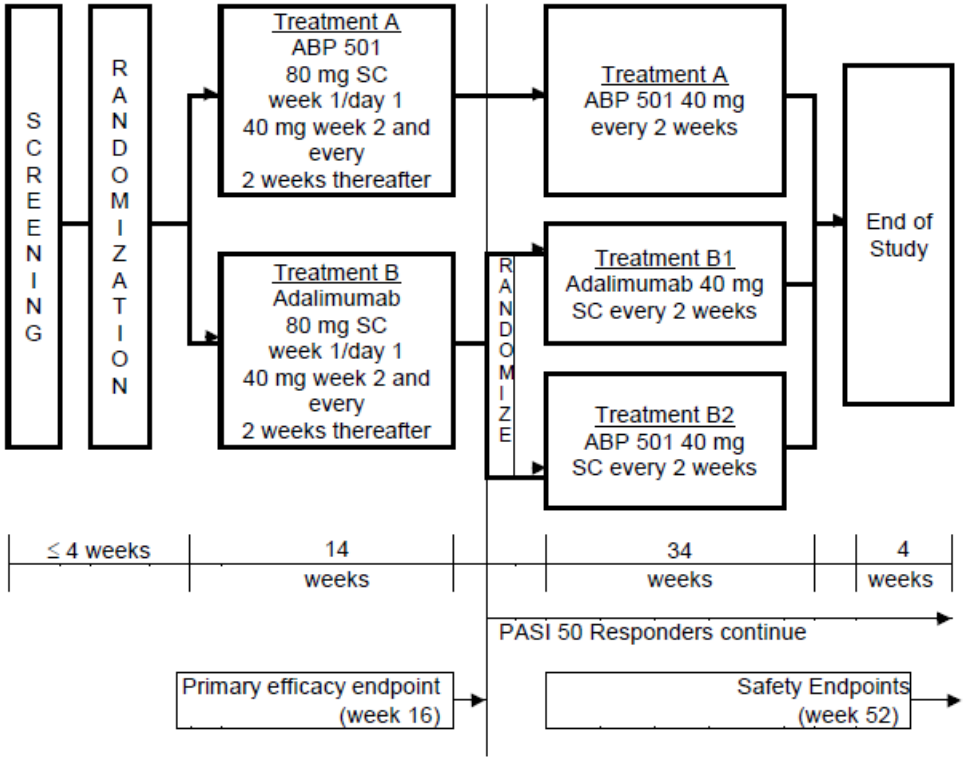
3.2.1 Study Design and Statistical Analysis

Study 263 was a randomized, double-blind comparative clinical study of ABP 501 and EU-approved Humira in subjects with moderate to severe plaque psoriasis. The study included data (including immunogenicity) on subjects transitioning from EU-approved Humira to ABP 501. The study enrolled subjects age 18 to 75 with stable moderate to severe plaque psoriasis for at least 6 months, involving at least 10% body surface area (BSA), PASI ≥ 12, and static Physician's Global Assessment (sPGA) ≥ 3 (moderate,

severe, or very severe). Subjects were to be candidates for systemic therapy or phototherapy and were to have previously failed, had inadequate response, intolerance to, or contraindication to at least one conventional anti-psoriatic systemic therapy.

The study enrolled 350 subjects, 175 randomized to the ABP 501 arm and 175 randomized to the EU-approved Humira arm, of which 347 received at least one dose of study product. Subjects were enrolled at 49 centers in 6 countries (Australia, Canada, France, Germany, Hungary, and Poland). Randomization was stratified by geographic region (Eastern Europe, Western Europe, Other) and prior biologic use for psoriasis (yes/no). Subjects received subcutaneous injection of 80 mg at Week 1, 40 mg at Week 2 and 40 mg every 2 weeks thereafter. The primary timepoint for efficacy assessment was Week 16 (15 weeks after treatment was initiated at Week 1). At Week 16, subjects who achieved at least PASI 50 response (at least 50% improvement from baseline) continued into the second treatment period. Subjects originally randomized to ABP 501 continued treatment with ABP 501 through Week 48. Subjects originally randomized to EU-approved Humira were re-randomized 1:1 to either continue treatment with EU-approved Humira or undergo a single transition to ABP 501 through Week 48. Subjects were followed through Week 52. See Figure 1.

Figure 1 – Design of Study 263



Source: pg. 17 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf.

Subjects were evaluated for efficacy at screening and Weeks 1, 4, 8, 12, 16, 32, and 50. Efficacy was assessed using the PASI scale, BSA, and sPGA. The PASI score is derived from assessments for erythema, plaque elevation, and scaling over four body regions

(head, trunk, upper limbs, and lower limbs). PASI scores can range from 0 to 72. The sPGA scale was a 6-point scale with 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe. The protocol states that the sPGA scale is used to measure the severity of disease in terms of induration, scaling, and erythema, but does not otherwise list any morphological descriptions for the categories of the sPGA scale.

The primary endpoint was the percent improvement in PASI from Week 1 to Week 16. The secondary endpoints were PASI 75 (at least 75% reduction from baseline in the PASI score), sPGA response (0 or 1; clear or almost clear), and change in BSA. Secondary endpoints were assessed at Weeks 16, 32, and 50.

The protocol specified that the percent improvement in PASI at Week 16 would be analyzed with a 95% confidence interval (CI) for the difference in means using estimates from an ANCOVA model adjusted for baseline PASI score and the stratification factors (geographic region and prior biologic use for psoriasis). The pre-specified similarity margin was ±15. Study 263 was conducted outside the US and the applicant did not discuss the study design with FDA prior to conducting the study. Accordingly, FDA did not provide any comments on the endpoints, margin, or analysis methods at the design stage. Although the protocol for Study 263 specified 95% confidence intervals for the primary endpoint, FDA also analyzed the data using 90% confidence intervals, as the FDA has generally recommended 90% confidence intervals (corresponding to a Type I error rate of 5%) for comparative clinical studies in biosimilarity development programs. Note also that FDA had advised the applicant to use a 90% confidence interval in their comparative clinical study in rheumatoid arthritis subjects (Study 262).

The primary analysis population was the full analysis set (FAS), defined in the protocol as all subjects initially randomized in the study. However, in their analyses, the applicant included in the FAS only subjects who had been randomized, dispensed medication, and who had at least one post-baseline efficacy assessment. In the study, 350 subjects were randomized, 347 received at least one dose of investigational product, and 345 had at least one post-baseline assessment. Analyses on the per protocol population were supportive. The per protocol population included subjects who completed the specified treatment period without protocol violations that affected the evaluation of the primary objective. For the second part of the study, the re-randomized analysis set included all subjects who were re-randomized at Week 16.

For the primary endpoint of percent improvement in PASI, missing data in the FAS were imputed using last observation carried forward (LOCF). An observed case analysis and the per protocol analysis were supportive. The protocol also stated that a sensitivity analysis would be conducted in which a number of covariates (age group, race, sex, disease duration, neutralizing antibody status, concomitant topical steroid use, and prior use of systemic or phototherapies) were included in the ANCOVA model and then assessed using backward selection. Percent improvement in PASI would also be analyzed using a repeated measures analysis using data from visits through Week 16.

Analyses for the secondary endpoints were considered descriptive. Confidence intervals for the difference in PASI 75 response and sPGA response were computed using estimates from a generalized linear model with the stratification factors (geographic region and prior biologic use for psoriasis) and baseline PASI score or baseline sPGA score, respectively, as covariates. Missing data for the FAS was handled with LOCF, non-responder imputation, or observed cases. Change in BSA was analyzed with an ANCOVA model with the stratification factors and baseline BSA as covariates.

3.2.2 Subject Disposition

Study 263 randomized 350 subjects, 175 each to the ABP 501 and EU-approved Humira arms. Three subjects were not dispensed treatment medication (1 on the ABP 501 arm and 2 on the EU-approved Humira arm). Two subjects had no post-baseline efficacy assessments (both on the ABP 501 arm). Approximately 5% of subjects on each arm discontinued treatment during the initial treatment period. The most common reasons for treatment discontinuation were adverse events and consent withdrawn. See Table 3. Most subjects continued into the second treatment period (152 (87%) of ABP 501 subjects and 156 (89%) of EU-approved Humira subjects), where subjects on the EU-approved Humira arm were randomized to continue EU-approved Humira or undergo a single transition to ABP 501 and subjects on the ABP 501 arm continued ABP 501. Approximately 90% of the subjects who entered Treatment Period 2 completed the study. See Table 4.

Table 3 - Disposition of Subjects in Treatment Period 1

	ABP 501	EU-approved Humira
Subjects Randomized	175	175
Subjects Treated	174 (99%)	173 (99%)
Discontinued treatment by Week 16	8 (5%)	10 (6%)
Adverse event	4 (2%)	5 (3%)
Consent withdrawn	3 (2%)	2 (1%)
Lost to follow-up	--	1 (<1%)
Protocol violation	1 (<1%)	2 (1%)
Completed efficacy assessments at Week 16[a]	165 (94%)	167 (95%)
Did not complete efficacy assessments at Week 16	10 (6%)	8 (5%)

[a] Day 92- 119

Source: pg 37-38 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis.

Table 4 – Disposition of Subjects in Treatment Period 2

	Treatment in Period 1		
	ABP 501 N=175	EU-approved Humira N=175	
Completed through Week 16	164 (94%)	162 (93%)	
Re-randomized at Week 16	152 (87%)	156 (89%)	
Not re-randomized at Week 16	23 (13%)	29 (11%)	
<PASI 50 at Week 16	11 (6%)	6 (3%)	
Missed Week 16 visit or discontinued study	12 (7%)	23 (13%)	
	Treatment in Period 2		
	ABP 501 N=152	EU-Hum N=79	ABP 501 N=77
Completed Treatment Period 2	138 (89%)	71 (90%)	69 (90%)
Discontinued Treatment Period 2	17 (11%)	8 (10%)	8 (10%)
Consent withdrawn	8 (5%)	3 (4%)	3 (4%)
Other	8 (5%)	4 (5%)	2 (3%)
Adverse event	*5 (3%)*	*1 (1%)*	*1 (1%)*
Lack of efficacy	*2 (1%)*	*3 (4%)*	*1 (1%)*
Non-compliance	*1 (<1%)*	--	--
Lost to follow-up	1 (<1%)	1 (1%)	2 (3%)
Physician decision	--	--	1 (1%)

Source: pg 40 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

Approximately 11% of subjects were excluded from the per protocol population. The most common reasons for being excluded from the per protocol population were not completing treatment through Week 16 and being mis-stratified at randomization. The rates were similar on the two arms. See Table 5.

Table 5 – Primary Reason for Per Protocol Population Exclusion

	ABP 501 N=175	EU-approved Humira N=175
Subjects excluded from Per Protocol Population	18 (10%)	22 (13%)
Did not complete treatment through Week 16	7 (4%)	8 (5%)
Did not have previous failure to psoriatic systemic therapy	--	1 (<1%)
Incorrect treatment received	1 (<1%)	2 (1%)
Mis-stratification at randomization	7 (4%)	6 (3%)
Prior use of 2 or more biologic therapies	--	4 (2%)
Prohibited medications during study	3 (2%)	1 (<1%)

Source: reviewer analysis.

3.2.3 Baseline Characteristics

The baseline demographics were generally balanced across the treatment groups in Study 263. The mean age was about 45 years, with about 6% of subjects age 65 and older. The majority of subjects were male (65%) and white (93%). The mean weight at baseline was 89 kg. Approximately 40% of subjects were enrolled in Eastern Europe, 25% in Western Europe, and 35% in Australia or Canada. See Table 6.

Table 6 – Baseline Demographics (Randomized Subjects)

	ABP 501 N=175	EU-approved Humira N=175
Age (years)		
Mean	45.1	44.0
Range	18-74	18-73
18 to 64 years	164 (94%)	163 (93%)
65 + years	11 (6%)	12 (7%)
Gender		
Female	63 (36%)	59 (34%)
Male	112 (64%)	116 (66%)
Race		
White	167 (95%)	157 (90%)
Black	--	2 (1%)
Asian	5 (3%)	8 (5%)
Other	1 (<1%)	5 (3%)
Unknown	2 (1%)	3 (2%)
Geographic Region		
Eastern Europe	71 (41%)	70 (40%)
Western Europe	43 (25%)	43 (25%)
Other	61 (35%)	62 (35%)
Weight (kg)	N=174	N=173
Mean (SD)	88.9 (23.6)	89.3 (19.4)
Range	48.0-200.6	52.9-166.1

Source: pg 45 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

To be enrolled in the study, subjects were to have stable moderate to severe plaque psoriasis for at least 6 months involving at least 10% body surface area (BSA), PASI ≥ 12, and static Physician's Global Assessment (sPGA) ≥ 3 (moderate, severe, or very severe). At baseline subjects had a mean PASI score of 20 and a mean BSA of 27%. Approximately 60% of subjects had an sPGA score of moderate. About 18% had prior use of a biologic for psoriasis. See Table 7.

Table 7 – Baseline Disease Characteristics (Subjects Randomized and Dispensed Medication)

	ABP 501 N=174	EU-approved Humira N=173
PASI		
Mean (SD)	19.7 (8.1)	20.5 (7.9)
Range	12.0 - 61.8	12.0 - 52.2
BSA		
Mean (SD)	25.3 (15.0)	28.5 (16.8)
Range	10 - 82	10 - 90
sPGA		
Moderate	106 (61%)	102 (59%)
Severe	61 (35%)	61 (35%)
Very Severe	7 (4%)	10 (6%)
Prior biologic use for psoriasis	N=175	N=175
Yes	33 (19%)	30 (17%)
No	142 (81%)	145 (83%)

Source: pg 46 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

3.2.4 Primary Efficacy Endpoint

The primary efficacy endpoint was the percent change in PASI from Week 1 to Week 16. The protocol specified that the percent improvement in PASI at Week 16 would be analyzed with a 95% confidence interval (CI) for the difference in means using estimates from an ANCOVA model adjusted for baseline PASI score and the stratification factors (geographic region and prior biologic use for psoriasis). The pre-specified similarity margin was ±15. The applicant also presented 90% confidence intervals. The primary analysis population was the full analysis set (FAS), defined in the protocol as all subjects initially randomized in the study. However, in their analyses, the applicant included in the FAS only subjects who had been randomized, dispensed treatment medication, and who had at least one post-baseline efficacy assessment. Missing data was handled with LOCF. Study 263 met the pre-specified similarity criterion for the primary endpoint of percent improvement in PASI at Week 16. For the applicant's primary analysis in the FAS population, both the 95% and 90% confidence intervals for the difference in mean percent improvement in PASI was within the pre-specified margin of ±15. See Table 8.

Table 8 – Percent Reduction in PASI at Week 16 (FAS/LOCF)

	ABP 501 N=172	EU-approved Humira N=173
Baseline (Week 1) PASI[a]	19.7 (8.1)	20.5 (7.9)
Week 16 PASI[a]	3.7 (5.1)	3.3 (5.8)
Percent Improvement[a]	80.9 (24.2)	83.1 (25.2)
Difference[b]	-2.2	
95% CI	(-7.4, 3.0)	
90% CI	(-6.6, 2.2)	

[a] Mean (SD)
[b] Model estimate adjusted for prior biologic use, region, and baseline PASI
Source: pg 52 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

The applicant conducted sensitivity analyses for the primary endpoint using the per protocol population and observed cases. The results of these analyses are similar to the analysis in the FAS population. See Table 9. FDA conducted additional sensitivity analyses for the handling of missing data. Although the applicant's FAS population was defined in the protocol as all randomized subjects, the applicant's analysis excluded two subjects who were dispensed medication but had no post-baseline efficacy assessments. Both subjects were on the ABP 501 arm and received both the Week 1 and Week 2 doses. Therefore, this reviewer conducted an additional sensitivity analysis including all subjects who were randomized and dispensed medication, using baseline observation carried forward for the subjects with no post-baseline assessments. The results of the sensitivity analysis are similar to the results of the applicant's primary analysis, but with a slightly larger estimated treatment difference of -3.1 and 90% confidence interval of (-7.5, 1.4).

This reviewer also conducted sensitivity analyses using alternate imputations for missing data for the percent improvement in PASI endpoint, where subjects with missing data on one arm are imputed assuming no improvement from baseline (0%) and subjects with missing data on the other arm are imputed assuming full improvement (100%). These results are also presented in Table 9. While these two imputations shift the estimated treatment difference to -6.3 and +2.3, the 90% confidence bounds for both sensitivity analyses remain within the bounds of -11 to +7 and thus the confidence bounds remain within the pre-specified margins of ±15 even under relatively extreme imputation assumptions. Thus the results of the sensitivity analyses for handling missing data are consistent with the primary analysis.

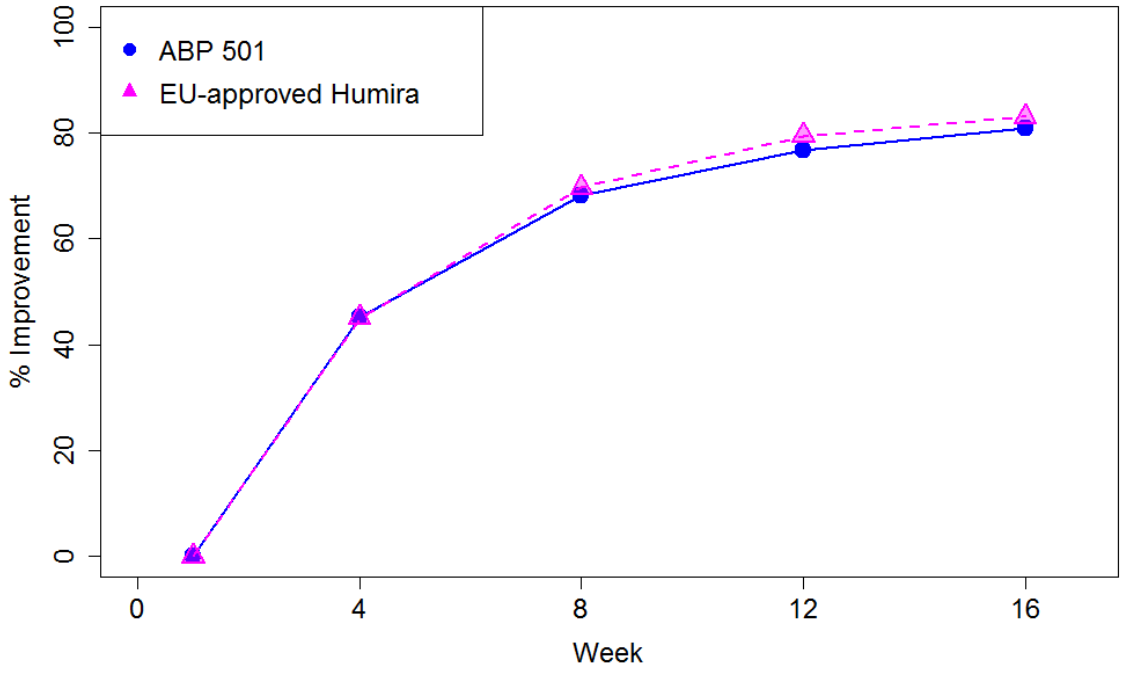
Table 9 - Sensitivity Analyses for the Percent Improvement in PASI at Week 16

	ABP 501	EU-approved Humira	Difference[a]	90% Conf. Int.
Applicant's sensitivity analyses				
Per protocol	N=155 82.6	N=152 85.3	-2.6	(-6.2, 0.9)
Observed Cases	N=165 82.6	N=167 84.1	-1.5	(-5.5, 2.6)
Reviewer's sensitivity analyses	N=174	N=173		
LOCF (including subjects with no post-baseline assessments)	80.0	83.1	-3.1	(-7.5, 1.4)
ABP 501 missing as 0%/ EU-approved Humira missing as 100%	78.3	84.6	-6.3	(-10.9, -1.8)
ABP 501 missing as 100%/ EU-approved Humira missing as 0%	83.5	81.1	2.3	(-2.0, 6.7)

[a] Model estimate adjusted for prior biologic use, region, and baseline PASI
Source: pg 274, 277 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

During the initial treatment period, PASI assessments were conducted at baseline (Week 1) and Weeks 4, 8, 12, and 16. The percent reduction in PASI over time for ABP 501 and EU-approved Humira were similar at each study visit. See Figure 2.

Figure 2 – Percent Improvement in PASI during Treatment Period 1 (FAS, LOCF)



Source: reviewer analysis

Subjects with at least PASI 50 at Week 16 were to continue into the second treatment period, where subjects originally randomized to ABP 501 continued on ABP 501 and subjects originally randomized to EU-approved Humira were randomized 1:1 to remain on EU-approved Humira or transition to ABP 501. During the second treatment period, the percent improvement in PASI remained relatively constant among the re-randomized subjects from Week 16 to Week 50. See Table 10.

Table 10 - Percent Improvement in PASI after Re-randomization (Observed Cases)

	ABP 501 / ABP 501		EU-Hum / EU-Hum		EU-Hum / ABP 501	
	N	Mean	N	Mean	N	Mean
Week 16	152	86.6	79	88.0	77	88.2
Week 32	143	87.6	72	88.2	71	87.0
Week 50	134	87.2	70	88.1	69	85.8

Source: pg 280-281 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

3.2.5 Secondary Endpoints

The secondary endpoints were PASI 75, sPGA response (clear or almost clear), and reduction in BSA. The applicant also assessed PASI 50 and PASI 90, though these analyses were not pre-specified in the protocol. The protocol stated that the secondary endpoints would be analyzed with descriptive statistics, including 95% confidence intervals for the treatment difference. The protocol did not specify margins for interpreting the confidence intervals. The response rates for PASI 75 and sPGA at Week 16 were each approximately 7-8% lower on the ABP 501 arm than on the EU-approved Humira arm. Similarly, the reduction from baseline in BSA was slightly lower on the ABP 501 arm than the EU-approved Humira arm. The 90% confidence intervals for the PASI 75 and BSA reduction endpoints do not include 0, but in both cases the 95% confidence intervals do. Both the 90% and 95% confidence intervals for sPGA response include 0. See Table 11.

Table 11 - Secondary Endpoints at Week 16 (FAS/LOCF)

	ABP 501 N=172	EU-approved Humira N=173	Difference[a]	90% Conf. Int.	95% Conf. Int.
PASI 75	74.4%	82.7%	-7.7%	(-15.2, -0.3)	(-16.6, 1.2)
sPGA (clear/almost clear)	58.7%	65.3%	-7.4%	(-15.6, 0.9)	(-17.2, 2.5)
Reduction in BSA					
Baseline (Week 1)	25.3	28.5			
Week 16	7.4	6.4			
Reduction	18.0	22.1	-1.9	(-3.8, -0.1)	(-4.1, 0.2)

[a] Model estimate adjusted for prior biologic use, region, and baseline score

Source: pg 354, 368, and 388 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

The PASI and sPGA scales are correlated as both scales measure the same underlying signs of erythema, scaling, and plaque elevation. Thus, it is not unexpected that endpoints based on these scales and BSA assessments would generally trend in the same direction. In addition, we would expect some variation in the magnitude of effect for different analyses when multiple analyses are conducted in a study. Because the 90% confidence interval for PASI 75 excluded 0 (although the 95% confidence interval included 0) and the fact that PASI 75 has been used as a primary endpoint in many clinical trials for psoriasis, this reviewer further evaluated the distribution of PASI scores and related endpoints (PASI 50, PASI 90, and absolute reduction in PASI). PASI 50 and PASI 90 response rates are presented in Table 12 along with the PASI 75 response rates at Week 16. Table 12 also presents the absolute reduction in PASI score from baseline to Week 16. When PASI 50 and PASI 90 are considered, the estimated treatment differences are smaller (-2.7% and +0.3%) than for PASI 75 (-7.7%). In addition the estimated treatment difference for the absolute reduction in PASI was less than 1 unit, with a narrow confidence interval that contains 0.

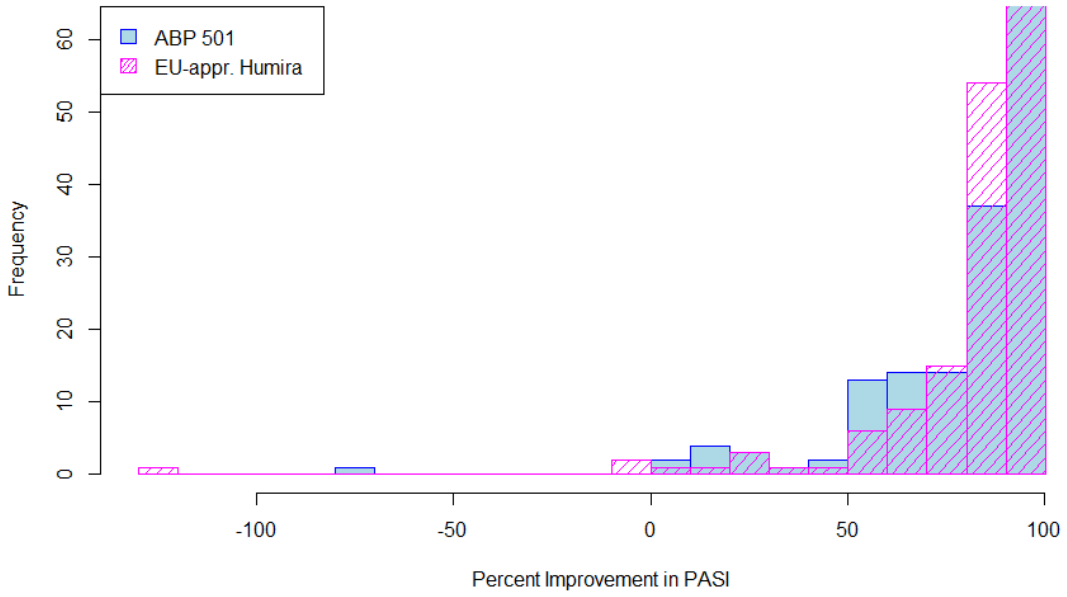
Table 12 –Supportive Endpoints based on PASI Score at Week 16 (FAS/LOCF)

	ABP 501 N=172	EU-approved Humira N=173	Difference[a]	90% Conf. Int.	95% Conf. Int.
PASI 50	92.4%	94.2%	-2.7%	(-7.0, 1.6)	(-7.8, 2.4)
PASI 75	74.4%	82.7%	-7.7%	(-15.2, -0.3)	(-16.6, 1.2)
PASI 90	47.1%	47.4%	0.3%	(-8.4, 9.0)	(-10.0, 10.7)
Reduction in PASI					
Baseline (Wk 1)	19.8 (8.1)	20.5 (7.9)			
Week 16	3.7 (5.1)	3.3 (5.8)			
Reduction	16.0 (8.1)	17.2 (9.2)	-0.58	(-1.5, 0.4)	(-1.7, 0.5)

[a] Model estimate adjusted for prior biologic use, region, and baseline PASI
Source: pg 343 and 439 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

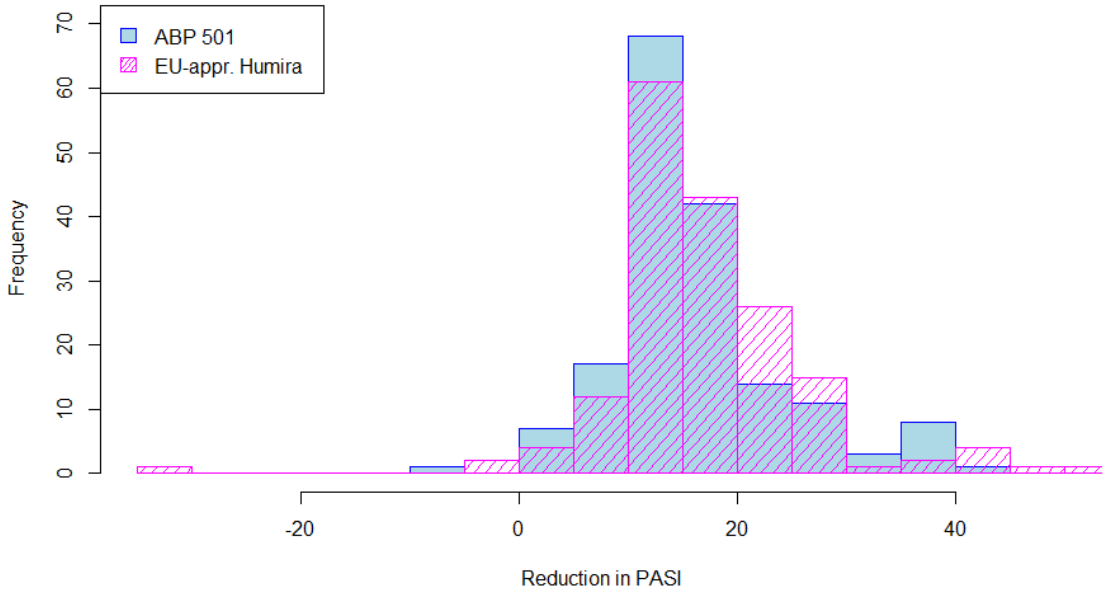
The overlaid histograms for the percent improvement and absolute reduction in PASI for ABP 501 and EU-approved Humira are presented in Figure 3 and Figure 4. The distribution of percent improvement in PASI is highly skewed with a few outliers, while the distribution for the absolute reduction in PASI is more symmetric. The slight difference in observed means for the two samples can be seen as a slight shift in location in each pair of histograms. The differences between the two samples appear to be magnified when dichotomizing the percent improvement in PASI using 75% improvement as the cutoff point, as opposed to other potential cutoff points. Thus, when considering the full distributions, the supportive PASI endpoints are consistent with the primary analysis of the mean percent improvement in PASI, and support the conclusion of the primary endpoint of no clinically meaningful differences between the treatments.

Figure 3 – Histogram of Percent Improvement in PASI at Week 16 (FAS/LOCF)



Source: reviewer analysis.

Figure 4 – Histogram of Absolute Reduction in PASI at Week 16 (FAS/LOCF)



Source: reviewer analysis.

3.2.6 Interpretation of Comparative Clinical Studies

Study 263 was a comparative clinical study of ABP 501 and EU-approved Humira; it did not include a placebo arm. Thus we need to evaluate whether the study has adequate assay sensitivity (the ability to detect meaningful differences if they were to exist) and have confidence that the pre-specified margin is appropriate. Three placebo-controlled trials of Humira have been published (Gordon (2006), Saurat (2008), and Menter (2008)). Each of these studies had PASI 75 as the primary endpoint, but all three also presented the percent improvement in PASI results at either Week 12 or Week 16. Note that for Study 263, baseline was defined as Week 1, while in the published studies baseline was defined as Week 0. Therefore for comparative purposes, the primary timepoint in Study 263 will be referred to as Week 15 in this section. The key design criteria and results for the published Humira studies are presented in Table 13. The Gordon study had less restrictive inclusion criteria (BSA ≥ 5, no requirement on PASI), but the Saurat and Menter studies had similar inclusion criteria to Study 263 (BSA ≥ 10, PASI ≥ 10 or 12, and sPGA ≥ Moderate). The percent improvement in PASI scores from Study 263 on the EU-approved Humira arm (83) was generally consistent with the percent improvement in PASI scores from the published Humira studies at Weeks 12-16 (70-81). Because the means for the percent improvement in PASI on the placebo arm (14-22) were generally much smaller than the means for the Humira arm, the assay sensitivity assumption appears reasonable for Study 263.

Table 13 – Study Characteristics and Results of Published Humira Studies

	Gordon (2006)	Saurat (2008)	Menter (2008)	Study 263
Selected inclusion criteria	BSA ≥ 5	BSA ≥ 10 PASI ≥ 10 sPGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 sPGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 sPGA ≥ Mod
Region/Country	US, Canada	Europe, Canada	US, Canada	Europe, Canada, Australia
Baseline PASI Mean *(Humira)*	PASI = 16.7	PASI = 20.2	PASI = 19.0	PASI = 20.5
% Imp. in PASI *Humira* *Placebo*	(Week 12) 70 14	(Week 16) 81 22	(Week 12) 76 15	(Week 15[a]) 83 --
PASI 75 *Humira* *Placebo*	(Week 12) 53% (n=50) 4% (n=52)	(Week 16) 80% (n=108) 19% (n=53)	(Week 16) 71% (n=814) 7% (n=398)	(Week 15[a]) 83% (n= 173) --

[a] 15 weeks after the baseline visit

Study 263 had a pre-specified similarity margin of ±15 for the primary endpoint of percent improvement in PASI. The applicant did not provide a rationale in their protocol

for the size of the proposed margin, and the margin was not discussed with FDA prior to conducting the study. While ideally the similarity margin would be selected based on a consensus of what magnitude of difference for the endpoint is not clinically meaningful, in practice sample sizes may be constrained by feasibility concerns. This reviewer took two approaches to assess the applicant's margin. The first approach computed the percent preservation of effect, to ensure that the test product would maintain at least some benefit relative to placebo. However, the goal of a comparative clinical study is to support the demonstration of no clinically meaningful differences. Therefore this reviewer also evaluated what margins would lead to an adequately powered study for a given sample size.

Although the Gordon, Saurat, and Menter studies included mean values for the percent improvement in PASI at either Week 12 or 16, none of the studies included standard deviations, which are needed to construct confidence intervals. Thus, alternate sources are needed to find reasonable estimates of the standard deviation for this endpoint. Two publications for studies of other TNF-α inhibitors (Enbrel and Remicade) presented standard deviations for the percent improvement in PASI endpoint (Table 14). Based on these publications, standard deviation estimates in the range of 20 to 30, may be a reasonable approximations for the purpose of constructing confidence intervals to aid in the evaluation the applicant's proposed margin.

Table 14 - Published Estimates of the Standard Deviation for the Percent Improvement in PASI Endpoint in Trials of Other TNF-α Inhibitors

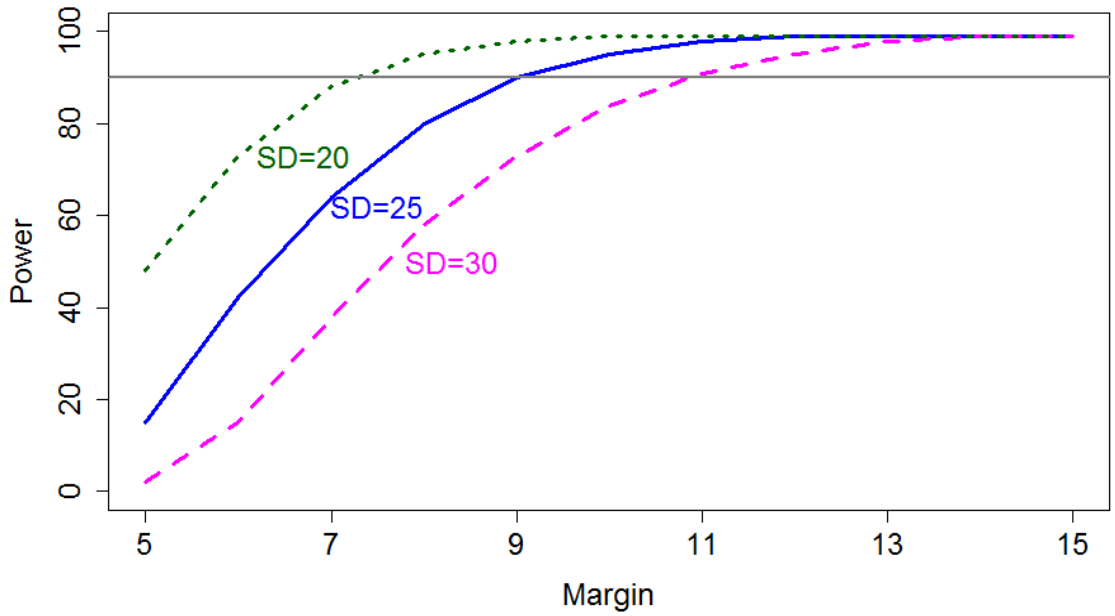
Study	Product	Week	N	Mean	Standard Deviation
Leonardi (2003)	Enbrel	12	164	64.2	30.7
Reich (2005)	Remicade	10	301	85.5	21.4

This reviewer calculated the percent preservation of the margin relative to the point estimate and an approximate lower 95% confidence bound for the treatment effect for the percent improvement in PASI. These calculations use the point estimate for percent improvement in PASI (61) and sample sizes ($n_1 = 814$, $n_2 = 398$) from the largest of the three Humira studies (Menter) and a standard deviation estimate in the upper end of the range observed in the Leonardi and Reich studies (SD=30). An approximate 95% confidence interval for the treatment effect for percent improvement in PASI for Humira would be $61 \pm 3.6 = (57.4, 64.6)$. Thus a lower bound margin of -15 maintains at least 75% of the expected treatment effect using the point estimate of 61 and at least 74% of the expected treatment effect using the lower 95% confidence bound of 57.4.

Although lower bound margin of -15 maintains a substantial portion of the expected treatment effect, because the estimated treatment effect relative to placebo is large, even retaining a substantial portion of the treatment effect relative to placebo could lead to clinically meaningful differences between treatments. Thus, the relationship between the study power and various margins for a given sample size is also of interest. Using the sample size originally proposed in the protocol of 340 subjects and the assumption that

the two treatments have the same effect, we can get a sense of what margins would lead to a design with adequate power. Figure 5 displays the relationship between study power and margin, assuming the true treatment difference is 0, total sample size of 340 subjects (170 per arm), symmetric margins, 90% confidence level, and standard deviations of 20, 25, and 30. Using the more conservative standard deviation estimate of 30, we see that a study of the proposed design and sample size would be powered at 90% for margins with magnitude of about ±11 or greater. We note that in Study 263, the 90% confidence interval for the percent improvement in PASI was (-6.6, 2.2), and the endpoint would have met the similarity criteria for margins with magnitude ±7 or greater. Thus the confidence interval for the primary endpoint of percent improvement in PASI is sufficiently narrow to conclude that the study met the criteria for demonstrating similarity.

Figure 5 – Study Power versus Margin Magnitude (Assuming True Treatment Difference = 0, N=340 and Symmetric Margins)



Source: reviewer analysis

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

The extent of exposure to study drug was similar for subjects randomized to ABP 501 and EU-approved Humira in the first treatment period, with approximately 90 days of drug exposure on each arm and approximately 87% of subjects receiving all 8 planned doses in the first treatment period. The mean total dose in the first treatment period was similar on both arms. All subjects received at least 2 doses. See Table 15. Exposure was also similar across the arms during the second treatment period. See Table 16.

Table 15 – Extent of Drug Exposure in Treatment Period 1

	ABP 501 N=174	EU-approved Humira N=173
Exposure Days		
Mean (SD)	89.5 (12.5)	89.9 (9.2)
Range	6-99	36-99
Total Dose Received (mg)		
Mean (SD)	349.9 (36.9)	350.8 (28.4)
Range	120 - 360	200-360
Number of Doses Administered		
1	--	--
2	3 (2%)	--
3	--	--
4	1 (<1%)	4 (2%)
5	1 (<1%)	--
6	3 (2%)	4 (2%)
7	13 (8%)	16 (9%)
8	153 (88%)	149[a] (86%)

[a] One subject received the initial 80 mg dose as two 40 mg doses two days apart for a total of 9 injections
Source: pg 457 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

Table 16 – Extent of Drug Exposure in Treatment Period 2

	ABP 501/ ABP 501 N=152	EU-appr. Hum./ EU-appr. Hum. N=79	EU-appr. Hum./ ABP 501 N=77
Exposure Days			
Mean (SD)	211.9 (43.8)	208.8 (51.1)	211.2 (45.5)
Range	13 - 233	1 - 232	15 – 232
Total Dose Received (mg)			
Mean (SD)	634.1 (124.6)	627.3 (146.4)	626.5 (131.0)
Range	80-720	40-720	80-680

Source: pg 459 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

3.3.2 Adverse Events

Similar rates of adverse events, serious adverse events, and study discontinuations due to adverse events occurred on the ABP 501 and EU-approved Humira arms. No deaths occurred during the study. See Table 17.

Table 17 – Summary of Adverse Events (Safety Population)

Treatment Period 1	ABP 501 N=174	EU-approved Humira N=173	
Any Adverse Events	117 (67%)	110 (64%)	
Serious Adverse Events	6 (3%)	5 (3%)	
Discontinued Study due to AE	7 (4%)	5 (3%)	
Treatment Period 2	**ABP 501/ ABP 501 N=152**	**EU-appr. Hum./ EU-appr. Hum. N=79**	**EU-appr. Hum./ ABP 501 N=77**
Any Adverse Events	108 (71%)	52 (66%)	54 (70%)
Serious Adverse Events	4 (3%)	4 (5%)	4 (5%)
Discontinued Study due to AE	4 (3%)	1 (1%)	2 (3%)

Source: pg 69-70 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

Adverse events of special interest were infections, malignancies, hypersensitivity, demyelinating diseases, hematological reactions, heart failure, lupus-like syndrome, liver enzyme elevations, and injection site reactions. No cases of demyelinating disease, heart failure, or lupus-like syndromes were reported during the study. Rates of observed adverse events of special interest were similar on the ABP 501 and EU-approved Humira arms. See Table 18.

Table 18 –Adverse Events of Special Interest (Safety Population)

Treatment Period 1	ABP 501 N=174	EU-approved Humira N=173	
Infections	59 (34%)	58 (34%)	
Hypersensitivity	8 (5%)	7 (4%)	
Injection site reactions	3 (2%)	9 (5%)	
Liver enzyme elevations	4 (2%)	2 (1%)	
Hematological reactions	--	3 (2%)	
Malignancies	1 (<1%)	1 (<1%)	
Treatment Period 2	**ABP 501/ ABP 501 N=152**	**EU-appr. Hum./ EU-appr. Hum. N=79**	**EU-appr. Hum./ ABP 501 N=77**
Infections	67 (44%)	29 (37%)	37 (48%)
Hypersensitivity	8 (5%)	2 (3%)	3 (4%)
Injection site reactions	2 (1%)	3 (4%)	--
Liver enzyme elevations	9 (6%)	2 (3%)	2 (3%)
Hematological reactions	--	1 (1%)	1 (1%)
Malignancies	1 (<1%)	--	--

Source: pg 88-90 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

3.3.3 Immunogenicity

During the initial treatment period, 17/174 (10%) ABP 501 subjects and 24/173 (14%) EU-approved Humira subjects developed neutralizing antibodies. Eleven of the ABP 501 subjects and 18 of the EU-approved Humira subjects with neutralizing antibodies continued into the second treatment period. Among the subjects who received EU-approved Humira in the first treatment period and were re-randomized in the second treatment period, 16/79 (20%) of subjects remaining on EU-approved Humira developed neutralizing antibodies during the study (9 in the first treatment period and 7 in the second treatment period) compared with 19/77 (25%) of subjects who transitioned to ABP 501 (9 in the first treatment period and 10 in the second treatment period). Among the subjects who remained in the study and received ABP 501 during both treatment periods, 21/152 (14%) developed neutralizing antibodies during the study (11 in the first treatment period and 10 during the second treatment period). See Table 19.

Table 19 – Neutralizing Antibodies (NAb)

Treatment in Period 1	ABP 501 N=174		EU-approved Humira N=173		
Treatment in Period 2	Not Re-randomized N=22	ABP 501 N=152	Not Re-randomized N=17	EU-appr. Humira N=79	ABP 501 N=77
First Positive Result for NAb in Treatment Period 1	6	11	6	9	9
Total	*17*		*24*		
First Positive Result for NAb in Treatment Period 2	7[a]	10	1[a]	7	10
Any Positive Result for NAb during Study	13	21	7	16	19

[a] For subjects not re-randomized, first positive result may have occurred during post-treatment follow-up
Source: pg 1413-1415 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

The mean percent improvement in PASI values at Week 16 were generally consistent across gender. The study enrolled too few non-white subjects and subjects over the age of 65 to have meaningful comparisons for these subgroups. Results were also generally consistent across geographic regions. Geographic region (Eastern Europe, Western Europe, and Other) was a stratification factor in the initial randomization. See Table 20.

Table 20 – Percent Improvement in PASI at Week 16 by Gender, Race, Age Group, and Geographic Region (FAS)

	ABP 501 N=172	EU-approved Humira N=173	Difference[a]	90% Conf. Int.
Gender				
Female	N=63	N=58		
	77.7 (31.9)	76.8 (36.4)	0.9	(-9.5, 11.23)
Male	N=109	N=115		
	82.8 (18.4)	86.2 (16.2)	-3.5	(-7.3, 0.3)
Race				
White	N=164	N=157		
	80.7 (24.7)	84.4 (23.8)	-3.7	(-8.1, 0.8)
Non-White	N=6	N=13		
	86.2 (12.2)	72.1 (29.7)	10.2	(-16.2, 36.5)
Age				
<65 years	N=161	N=161		
	81.2 (24.3)	83.1 (25.7)	-1.9	(-6.4, 2.7)
≥ 65 years	N=11	N=12		
	76.4 (24.7	83.3 (17.4)	-4.5	(-20.7, 11.8)
Geographic Region				
Eastern Europe	N= 71	N=70		
	84.4 (19.8)	88.4 (15.7)	-4.1	(-9.1, 0.9)
Western Europe	N=41	N=43		
	75.0 (32.3)	78.4 (22.5)	-3.0	(-13.1, 7.1)
Other	N=60	N=60		
	80.8 (22.2)	80.1 (33.8)	0.1	(-8.6, 8.8)

[a] Model estimate adjusted for prior biologic use, region, and baseline PASI
Source: pg 299-317 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

4.2 Other Special/Subgroup Populations

In addition to geographic region, the randomization was also stratified by prior use of biologics for psoriasis (yes/no). A relatively small proportion of subjects (18%) had prior biologic use. In general, the results were consistent across prior biologic use. See Table 21.

Table 21 – Percent Improvement in PASI at Week 16 by Prior Biologic Use

	ABP 501 N=172	EU-approved Humira N=173	Difference[a]	90% Conf. Int.
Prior Biologic Use				
Yes	N=32	N=30		
	79.5 (32.3)	76.0 (43.3)	3.3	(-12.8, 19.4)
No	N=140	N=143		
	81.2 (22.1)	84.5 (19.3)	-3.3	(-7.4, 0.7)

[a] Model estimate adjusted for prior biologic use, region, and baseline PASI
Source: pg 287 of \\cdsesub1\evsprod\bla761024\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5351-stud-rep-contr\20120263\02-csr-20120263-rpt-body.pdf and reviewer analysis

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The mean percent improvement in PASI at Week 16 was similar on the ABP 501 and EU-approved Humira arms and the confidence interval for the difference was within the pre-specified margin of ±15. In the applicant's full analysis set (FAS), defined as all subjects randomized and dispensed medication who had at least one post-baseline efficacy assessment, the mean percent improvement in PASI values on the ABP 501 and EU-approved Humira arms were 80.9 vs 83.1. Results on the per protocol population and an analysis population that includes all subjects randomized and dispensed medication whether or not they had post-baseline efficacy assessments were similar and also fell within the pre-specified margin.. See Table 22. The results of the secondary endpoints of PASI 75, clear or almost clear on the static Physician's Global Assessment, and reduction from baseline in body surface area were consistent with the primary endpoint.

Table 22 – Percent Improvement in PASI at Week 16

	ABP 501	EU-approved Humira	Difference[d]	90% Conf. Int.
Full Analysis Set[a] (LOCF)	N=172	N=173		
	80.9	83.1	-2.2	(-6.6, 2.2)
Sensitivity Analysis[b] (LOCF)	N=174	N=173		
	80.0	83.1	-3.1	(-7.5, 1.4)
Per protocol[c] (Observed)	N=155	N=152		
	82.6	85.3	-2.6	(-6.2, 0.9)

[a] Randomized, dispensed medication, and at least one post-baseline efficacy assessment
[b] Randomized, dispensed medication
[c] Completed the treatment period without protocol violations that affected the evaluation of the primary objective
[d] Model estimate adjusted for prior biologic use, region, and baseline PASI

Because Study 263 was conducted completely outside the US, the applicant did not discuss the proposed similarity margin with the FDA prior to conducting the study. The applicant did not provide a rationale for their choice of similarity margin in the protocol

or study report. Therefore, this reviewer evaluated the applicant's proposed margin using information from the literature on the percent improvement in PASI from published placebo-controlled studies of Humira and other TNF-α inhibitors. Based on this evaluation, we conclude that assumptions of consistency and assay sensitivity appear reasonable for Study 263, and that the confidence interval for the primary endpoint of percent improvement in PASI is sufficiently narrow to conclude that the study met the criteria for demonstrating similarity.

Adverse event rates were similar on both the ABP 501 and EU-approved Humira arms. During the initial treatment period, 10% of ABP 501 subjects and 14% of EU-approved Humira subjects developed neutralizing antibodies. Among the subjects who continued into the second treatment period, 20% of subjects on EU-approved Humira/EU-approved Humira arm, 25% on the EU-approved Humira/ABP 501 arm, and 14% on the ABP 501/ABP 501 arm developed neutralizing antibodies during the study.

5.2 Conclusions and Recommendations

We conclude that Study 263 met its objective for assessing clinical similarity and that Study 263 supports a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

References

Gordon KB et al, J Am Acad Dermatol. 2006 Oct; 55(4): 598-606
Saurat JH et al, Br J Dermatol. 2008; 158: 558-66
Menter A et al, J Am Acad Dermatol. 2008; 58(1): 106-15
Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22
Reich K et al, Lancet. 2005; 366:1367-74

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