CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761024Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA 761024

Submission Date(s): November 25, 2015

Applicant: Amgen, Inc.

Product: ABP 501; Amjevita (adalimumab-atto)

Reviewer: Keith M Hull, MD, PhD

Date of Review: September 22, 2016

Covered Clinical Study (Name and/or Number): 217, 262, 263

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 779		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators. The applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, Amgen requested statements of financial interests from a total of 142 Principal Investigators and 637 sub-investigators for the following studies:

- Study 217
- Study 262
- Study 263

A total of 140 principal investigators and 633 sub-investigators reported no financial information to disclose. Three sub-investigators did not provide financial disclosure information due to leaving their position prior to collection of financial disclosure information.

Two principal investigators and one sub-investigator disclosed financial arrangements/interests that could potentially introduce bias:

- (b) (6), MD (Principal Investigator, Study Site# (b) (6) enrolled (b) (6) subject):
    - Dr. (b) (6) participates in Amgen Speakers Bureau ~10 to 15 times per year at a rate of $1000-$2000 per speaking engagement
- (b) (6), MD (Principal Investigator, Study Site# (b) (6), enrolled (b) (6) subjects):
    - Ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria (>$25,000) cumulatively. Research ongoing for another Amgen study
- (b) (6) MD (Sub-investigator, Study Site# (b) (6), enrolled (b) (6) subjects):
    - Significant financial interest in Amgen due to stock ownership

Overall, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study. In all cases, the applicant took steps to minimize potential bias which primarily consisted of excluding the investigator from the selection process of subjects, blinding to study drug, and exclusion from the knowledge and analysis of results. Review of the documents does not raise concerns regarding the integrity of the submitted data to the current application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NIKOLAY P NIKOLOV
09/22/2016
This is an addendum to the primary clinical review entered on behalf of Dr. Keith Hull.

Medical Officer Review
Division of Gastroenterology and Inborn Errors Products of BLA 761024

Application Type:	351(k) BLA 761,024
Drug:	ABP 501 (adalimumab-xxxx[1], a proposed biosimilar to US-licensed Humira (adalimumab)
Applicant:	Amgen, Inc.
Route of Administration:	Injection for Subcutaneous use
Pharmacologic Class:	TNF-α antagonist
DGIEP Division Director:	Donna J. Griebel, MD
DGIEP Team Leader:	Anil Rajpal, MD, MPH
DGIEP Clinical Reviewer:	Aisha P Johnson, MD, MPH, MBA
Review Completion Date:	14 September 2016

Proposed Indications

Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.

Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.

Adult Crohn's Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6- mercaptopurine (6-MP). The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers.

[1] A four letter suffix for the nonproprietary name for ABP 501 has not been determined. FDA is using "-xxxx" as a placeholder for the suffix. Since the proper name for ABP 501 has not yet been determined, ABP 501 is used throughout this review in place of the nonproprietary name for this product.

Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

Executive Summary:

The Division of Gastroenterology and Inborn Errors Products concludes that the data submitted provide adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data, including clinical data from the studied populations (rheumatoid arthritis and plaque psoriasis), to support approval of ABP 501 for the inflammatory bowel disease indications (ulcerative colitis and Crohn's disease).

The Division concludes that the totality of the evidence provided by the Applicant supports a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in terms of safety, purity and potency.

Introduction:

On November 25, 2015, Amgen, Inc. submitted a biologics license application (BLA) under section 351(k) of the Public Health Service (PHS) Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab). Humira received marketing approval in the US on 31 December 2002.

In support of the current BLA, the Applicant provided clinical trial data collected from healthy subjects and patients with rheumatoid arthritis (RA) and plaque psoriasis (PsO). See Table 1 below.

The inflammatory bowel disease (IBD) indications were not directly studied in the ABP 501 clinical program. For additional information on the indications evaluated (i.e., RA and PsO), please refer to the clinical reviews from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), the Division of Dermatology and Dental Products (DDDP) and the Cross-Discipline Team Leader (CDTL) review.

Table 1. Overview of ABP 501 Clinical Program

Study	Design	Objectives	Subjects	Treatments	Endpoints
PK Similarity Study					
20110**217**	R, PG, SD, 3-way PK bridging	PK, safety, and immunogenicity	203 Healthy Subjects	40 mg SC: • ABP 501 • US-Humira • EU-Humira	Cmax, AUCt and AUCinf
Comparative Clinical Studies					
20120**262**	26 Weeks, R, DB, PG	Efficacy, safety, immunogenicity, PK	526 RA Patients	40 mg SC Q2W+MTX: • ABP 501 • US-Humira	ACR20
20120**263**	R, DB, PG (Week 1-16)	Efficacy, safety, immunogenicity, PK	350 PsO Patients	80 mg SC Day 1, then 40 mg SC Q2W from Wk2: • ABP 501 • EU-Humira	% PASI
	Single transition from EU-Humira to ABP 501 (Week 16 to 48)	Safety, immunogenicity, PK	Patients on EU-Humira arm re-randomized to transition to ABP 501	40 mg SC Q2W: • ABP→ABP • EU-Humira→ABP • EU-Humira→EU Humira	Safety, Immunogenicity

Electronically copied and reproduced from the FDA AC Meeting Backgrounder, Slide #5, Introductory Remarks by Nikolay P Nikolov, MD.

Extrapolation of Existing Data to Support Biosimilarity to IBD Indications:

The Applicant studied their product in patients with RA and PsO, and also seeks licensure for the same indications as approved for US-licensed Humira (b) (4) The FDA has clarified that extrapolation to non-studied indications of a reference product is possible if specific criteria are met (see the excerpt from the FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015).

> *If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the* (b) (4)

> *reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.*[3]

The scientific justification for extrapolation should address the following issues that are described in the FDA Guidance:[4]

- The mechanism(s) of action (MOA) in each condition for which licensure is sought;
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations;
- The immunogenicity of the product in different patient populations;
- Differences in expected toxicities in each condition of use and patient population; and
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Each of the issues outlined will be briefly discussed.

Mechanism of Action

The primary mechanism of action of adalimumab is direct binding and blocking of TNF-α receptor-mediated activities. Adalimumab blocks both TNFR1 and TNFR2 receptors by binding both soluble(s) and transmembrane(tm) TNF-α. In addition, adalimumab has efficacy mechanisms involving the Fc region of the antibody which are thought to be plausible mechanisms involved in the efficacy of adalimumab for the treatment IBD. Similar to the studied indications (RA and PsO), TNF-α plays a central role in the pathology experienced by patients with IBD. In addition, TNF-α inhibition plays an important role in treating these diseases as evidenced by the efficacy of the TNF-α inhibitor class of medications in treating IBD.

The Product Quality reviewers have concluded that the Applicant has provided data to support a demonstration that ABP 501 is highly similar to the reference product not

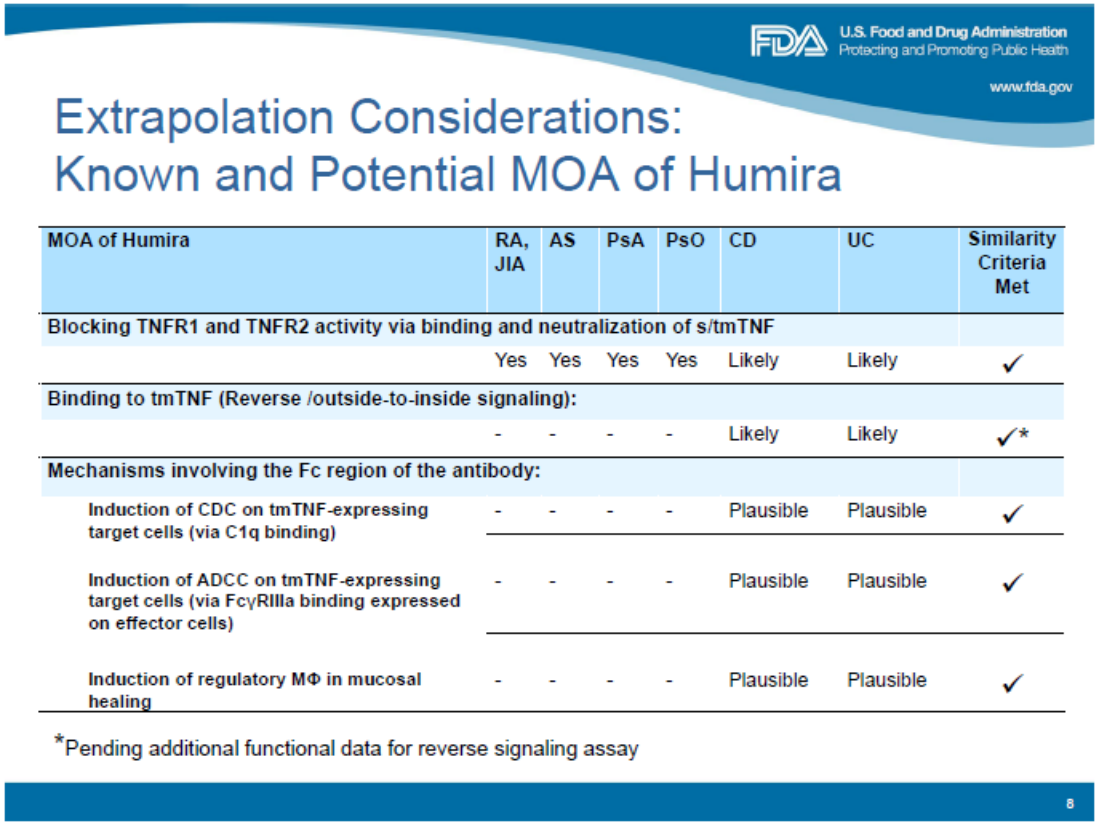
[3] FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

[4] Id.

withstanding minor differences in clinically inactive components. The Applicant has adequately addressed each of the known and potential mechanisms of action of US-licensed Humira as outlined in Table 2. The Applicant provided data to demonstrate s/tmTNF-α binding, blocking TNFR1 and TNFR2 activity, and Fc region-mediated potential are similar between ABP 501 and US-licensed Humira. These data support a demonstration that ABP 501 and US-licensed Humira utilize the same mechanism or mechanisms of action, to the extent such mechanism or mechanisms of action are known for US-licensed Humira.

DGEIP MO Review
BLA 761,024

Table 2. Mechanisms of Action, US-Licensed Humira



U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Extrapolation Considerations: Known and Potential MOA of Humira

MOA of Humira	RA, JIA	AS	PsA	PsO	CD	UC	Similarity Criteria Met
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF							
	Yes	Yes	Yes	Yes	Likely	Likely	✓
Binding to tmTNF (Reverse /outside-to-inside signaling):							
	-	-	-	-	Likely	Likely	✓*
Mechanisms involving the Fc region of the antibody:							
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible	✓
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible	✓
Induction of regulatory MΦ in mucosal healing	-	-	-	-	Plausible	Plausible	✓

*Pending additional functional data for reverse signaling assay

8

Electronically copied and reproduced from the FDA Arthritis Advisory Committee Meeting Backgrounder July 12, 2016, Slide #8, Considerations for Extrapolation by Nikolay P Nikolov, MD.

Pharmacokinetics (PK)

The Applicant submitted three PK studies. Study 217 was the key PK study while Studies 262 (conducted using US-licensed Humira) and 263 (conducted using EU-approved Humira) were regarded as supportive. The clinical pharmacology reviewers concluded that the results of the studies showed that PK similarity was demonstrated between ABP 501, US-licensed Humira, and EU-licensed Humira. PK similarity between ABP 501 and EU-approved Humira justifies the relevance of comparative data generated using EU-approved Humira. Because PK similarity was demonstrated between ABP 501 and US-licensed Humira, a similar PK profile would be expected for ABP 501 in patients with IBD.

Safety and Immunogenicity

In general, the incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.[5]

Small differences in efficacy between the Neutralizing antibody (Nab) positive patients of the ABP 501 and Humira groups (US-licensed and EU-approved Humira) were seen in the RA and PsO studies. However, the DPARP reviewer stated that these data may not be generalizable given the small number of patients and the fact that no differences in PK or other safety outcomes were observed. Immunogenicity was otherwise similar between ABP 501, US-licensed Humira, and EU-approved Humira in RA and PsO, using two approved dosing regimens with and without concomitant immunosuppression.

The DPARP reviewer concluded that the immunogenicity results support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira. Safety outcomes were similar between patients treated with ABP 501 and the reference product. No new safety signals were identified.

The safety and immunogenicity results support a demonstration that there are no clinically meaningful differences between ABP 501 and the US-licensed Humira.

Conclusion:

[5] Prescribing information for US-licensed Humira (site accessed 13 September 2016). http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125057s397lbl.pdf

Consistent with the principles of the FDA Guidance outlined above, the Division of Gastroenterology and Inborn Errors Products concludes that the data submitted provide adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data, including data from the studied populations (rheumatoid arthritis and plaque psoriasis), to the proposed inflammatory bowel disease indications (ulcerative colitis and Crohn's disease). The submitted data and information thus support approval of ABP 501 for the inflammatory bowel disease indications (ulcerative colitis and Crohn's disease).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AISHA P JOHNSON
09/14/2016

ANIL K RAJPAL
09/14/2016

DONNA J GRIEBEL
09/15/2016

CLINICAL REVIEW

Application Type	351(k) BLA
Application Number(s)	761024
Priority or Standard	Standard
Submit Date(s)	November 24, 2015
Received Date(s)	November 24, 2015
PDUFA Goal Date	September 24, 2016
Division / Office	DPARP – lead division Collaborative review with DDDP and DGIEP
Reviewer Name(s)	Keith M Hull, MD, PhD, for DPARP Denise Cook, MD, for DDDP
Review Completion Date	August 10, 2016
Nonproprietary Name	ABP 501 (adalimumab-xxxx)[1]
(Proposed) Trade Name	Amjevita
Therapeutic Class	TNF-inhibitor
Applicant	Amgen
Formulation	Subcutaneous injection
Indications Sought	• Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA • Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older • Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. • Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS • Adult Crohn's Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and

[1] In this document, FDA generally refers to Amgen's proposed product by the Amgen descriptor "ABP 501." FDA has not yet designated a nonproprietary name for Amgen's proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products). The placeholder for a distinguishing suffix is designated as "xxxx".

	symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to adalimumab. • Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF blockers. • Plaque Psoriasis (PsO): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
Dosing Regimens	• Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis: 40 mg every other week • Juvenile Idiopathic Arthritis: 15 kg to <30 kg: 20 mg every other week ≥30 kg: 40 mg every other week • Plaque Psoriasis: 80 mg initial dose then one week later 40 mg every other week • Crohn's disease and Ulcerative Colitis: 160 mg initial dose, 80 mg two weeks later, then 40 mg every other week

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This biologic licensing application (BLA 761024) seeks approval of the product ABP 501 (proposed trade name: Amjevita) which is a proposed biosimilar to US-licensed Humira (active ingredient adalimumab, a TNFα-inhibitor). The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed 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 proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

From a clinical standpoint, the data submitted to the 351(k) BLA from the clinical development program of ABP 501 support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira in pharmacokinetic parameters and in the indications studied, i.e., rheumatoid arthritis (RA) and plaque psoriasis (PsO). A demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components together with the clinical data discussed in this review, will support licensure of ABP 501 as a biosimilar to US-licensed Humira under section 351(k) of the PHS Act.

1.2 Risk Benefit Assessment

Brief Overview of the Clinical Program

The following three controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between ABP 501 and US-licensed Humira:

- **Study 20110217 (Study 217):** a single-dose pharmacokinetic (PK) study providing a 3-way comparison of ABP 501, US-licensed Humira, and EU-approved Humira intended to (i) support PK similarity of ABP 501 and US-licensed Humira and (ii) provide PK bridge to support the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP 501 to US-licensed Humira.

- **Study 20120262 (Study 262):** a comparative clinical study between ABP 501 and US-licensed Humira in patients with RA to support a demonstration of no clinically meaningful differences in terms of safety, purity, and potency. This was a 26-week, randomized, double-blind, parallel group study conducted in 526 patients with moderate to severely active RA on background methotrexate (MTX), who were randomized 1:1 to ABP 501 or US-licensed Humira at a dose of 40 mg every other week (Q2W) subcutaneously (SC).

- **Study 20120263 (Study 263):** a second comparative clinical study intended to assess efficacy, safety, and immunogenicity between ABP 501 and EU-approved Humira in patients with plaque psoriasis (PsO), and safety and immunogenicity in patients undergoing a single transition from EU-approved Humira to ABP 501. This was randomized, double-blind, parallel-group study conducted outside the US in 350 patients with moderate to severe plaque psoriasis who were randomized 1:1 to ABP 501 or EU-approved Humira at a dose of 80 mg on Day 1, then 40 mg Q2W starting one week later. At Week 16, subjects who achieved at least a 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 to

provide a descriptive comparative assessment of safety and immunogenicity between these re-randomized cohorts.

Clinical Efficacy Overview

Study 217

Study 217 compared the PK, safety, tolerability, and immunogenicity of single 40 mg subcutaneous dose of either ABP 501, US-licensed Humira, or EU-approved Humira in healthy subjects. The pairwise comparisons of ABP 501, US-licensed Humira, and EU-approved Humira met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%), thus establishing the PK similarity and providing the PK bridging data in addition to the analytical bridging data, to justify the relevance of the comparative data generated using EU-approved Humira. Further PK support of similarity was demonstrated by similar trough concentrations for ABP 501 and US-licensed Humira in patients with RA in Study 262 and for ABP 501 and EU-approved Humira in patients with PsO.

Overall, the clinical pharmacology studies support the demonstration of PK similarity between ABP 501 and US-licensed Humira and did not raise any new uncertainties in the assessment of biosimilarity of ABP 501 to US-licensed Humira.

Study 262

Study 262 enrolled 526 subjects, 264 randomized to the ABP 501 arm and 262 randomized to the US-licensed Humira arm and all randomized patients received ≥1 dose of study product. Subjects were enrolled in Europe, North America, and Latin America. The primary endpoint was the proportion of patients who remained in the study and achieved an American College of Rheumatology 20% (ACR20) response at Week 24. Approximately 71% of patients randomized to ABP 501 and 72% of patients

randomized to US-licensed Humira were ACR20 responders, for an estimated absolute difference between treatments of -0.4% (90% confidence interval [CI]: -6.8%, +6.1%). The 90% CI successfully ruled out the similarity margin of ±12% that the Agency has determined reasonable. ACR20, ACR50, and ACR70 responses over time, in addition to mean changes from baseline in the components of the ACR composite endpoint, and the disease activity score (DAS28-CRP), were also similar between the treatment arms. These data demonstrate similar efficacy between ABP 501 and US-licensed Humira in patients with RA.

Study 263

Study 263 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 Psoriasis Area Severity Index (PASI) from Week 1 to Week 16. The pre-specified similarity margin for the confidence interval for the difference in means was ±15%. The mean percent improvement in PASI score was similar on the ABP 501 and EU-approved Humira arms (81% vs. 83%) and the corresponding 90% confidence interval for the difference of (-6.6, 2.2) was within the pre-specified margin of ±15%. The results on the secondary endpoints were supportive of the results of the primary endpoint analysis.

Clinical Safety Overview

Analysis of the safety and immunogenicity data using two dosing regimens (40 mg Q2W SC on the background of MTX, or a loading dose of 80 mg on Day 1, followed by 40 mg Q2W SC starting one week late as monotherapy), in two distinct patient populations, are adequate to support the demonstration of no clinically meaningful differences between ABP 501 and US-approved Humira in patients with RA and PsO. The safety database submitted for ABP 501 is adequate to provide a reasonable descriptive comparison

between the two products. The safety risks identified are consistent with the known adverse event profile of US-licensed Humira. The analysis of the data indicates a safety profile of ABP 501, similar to that of US-licensed Humira. There were no notable differences between ABP 501 and EU-approved Humira in treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events leading to discontinuations, or deaths between the treatment groups. No cases of drug-induced liver injury meeting Hy's law criteria were reported in the ABP 501 clinical program. The safety data support the demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the populations studied. In addition, transitioning of non-treatment naïve patients, i.e., patients previously treated with EU-approved Humira, to ABP 501 does not appear to result in an increase of clinically significant adverse reactions.

Clinical Efficacy and Safety Overview Conclusions

Overall, the safety and efficacy data from clinic studies 217, 262, and 263 support a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira.

Extrapolation to Non-studied Indications

Amgen seeks licensure for the following indications for which US-licensed Humira is licensed (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, UC, and PsO). The ABP 501 clinical program however, provides clinical efficacy and safety data primarily from clinical studies in patients with RA and PsO.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference

product is licensed, based on data from a clinical study(ies) performed in another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: *"Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009"*, if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed.[2] The Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA), if known or can reasonably be determined, in each condition of use for which licensure is sought,
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations,
- The immunogenicity of the product in different patient populations,
- Differences in expected toxicities in each condition of use and patient population,
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. Consistent with the principles outlined in the above FDA guidance, Amgen has provided a justification for the proposed extrapolation of clinical data from studies in RA and PsO to each of the other indications approved for

[2] Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

US-licensed Humira for which Amgen is seeking licensure, as summarized in this section.

First, Amgen believes that its extensive analytical characterization data support a demonstration that ABP 501 is highly similar to US-licensed Humira, and that the data support a demonstration there are no clinically meaningful differences between ABP 501 and US-licensed Humira based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in two indications, RA and PsO.

Further, the additional points considered in the scientific justification for extrapolation of data to support biosimilarity in the indications for which Amgen is seeking licensure (JIA in patients 4 years of age and older, PsA, AS, adult CD, and UC) include:

- The PK of ABP 501 is comparable across the various studied populations including healthy subjects and patients with RA and PsO.[3] Further, the observed trough concentrations in Studies 262 and 263 were within the range of steady state trough concentrations for US-licensed Humira in PsA, UC, CD, RA and PsO.[4] The pharmacokinetics of US-licensed Humira in patients with AS were similar to those in patients with RA.[5] Additionally, the steady-state trough concentrations were similar between pediatric patients with JIA or CD compared to adult patients following the administration of US-licensed Humira.[6] Since similar PK was demonstrated between ABP 501 and US-licensed Humira as discussed above, together with the demonstration that ABP 501 is highly similar to US-licensed Humira, as assessed by the CMC review team, a similar PK profile would be expected for ABP 501 in patients across the indications being sought for licensure.

[3] FDA-approved Humira labeling
[4] FDA-approved Humira labeling
[5] FDA-approved Humira labeling
[6] FDA-approved Humira labeling

- In general, immunogenicity of the US-licensed Humira was affected primarily by the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used.[7] In RA, PsA, and AS, the recommended dose is 40 mg Q2W SC. Adalimumab is used without MTX in PsO and may be used with or without concomitant immunosuppression in PsA, CD and UC.[8] These usage scenarios were assessed in Amgen's RA Study 262 (concomitant use of methotrexate) and Amgen's PsO Study 263 (use with a loading dose of 80 mg SC on Day 1, followed by 40 mg Q2W SC starting one week later, but without concomitant immunosuppressive therapy). There are sufficient data to indicate similar immunogenicity between ABP 501, EU-approved Humira, and US-licensed Humira. Accordingly, similar immunogenicity would be expected between ABP 501 and US-licensed Humira in patients with JIA, PsA, AS, adult CD, and UC.

- The mechanism(s) of action (MOA; Table 1) relevant to the extrapolation of data to support biosimilarity in specific indications are discussed below.

[7] FDA-approved Humira labeling
[8] FDA-approved Humira labeling

Table 1. Known and Potential (Likely or Plausible) Mechanisms of Actions of US-licensed Humira in the Conditions of Use Sought for Licensure of ABP 501

MOA of Humira	RA, JIA	AS	PsA	PsO	CD	UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; JIA: juvenile idiopathic arthritis; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF						

Source: FDA summary of existing published literature on the topic of mechanisms of action of TNF inhibitors[9,10, 11]

Extrapolation of Data to Support Biosimilarity in JIA, PsA, AS

The primary MOA of adalimumab is direct binding and blocking of TNF receptor-mediated biological activities (see Table 1 above). Adalimumab binds to both soluble(s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The published scientific literature indicates that this MOA is the primary MOA in RA, JIA, PsA, AS, and PsO. The data provided by Amgen showed similar TNF binding and potency to neutralize TNF-α, supporting the demonstration of analytical similarity pertinent to this MOA. Therefore, based on the above considerations, it is reasonable to extrapolate conclusions regarding similar efficacy and safety of ABP 501 and US-licensed Humira in RA and PsO to JIA, PsA and AS.

[9] Oikonomopoulos A et al., Current Drug Targets, 2013, 14, 1421-1432.
[10] Tracey D et al., , Pharmacology & Therapeutics 117 (2008) 244–279.
[11] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

Extrapolation of Data to Support Biosimilarity in Inflammatory Bowel Disease (IBD) Indications

TNF plays a central role in the pathogenesis of the IBD indications (Crohn's Disease and ulcerative colitis), and TNF inhibition is important in treating the diseases, as evidenced by the efficacy of the approved TNF monoclonal antibodies, but the detailed cellular and molecular mechanisms involved have not been fully elucidated.[12] However, the available scientific evidence suggests that for TNF inhibitors in IBD, in addition to binding and neutralization of sTNF, other MOA, listed in Table 1 may play a role.[13] Binding to sTNF and tmTNF involves the Fab region of the antibody, while the other plausible mechanisms of action involve the Fc region of the molecule.

Amgen provided experimental data supporting a demonstration that ABP 501 and US-licensed Humira are highly similar based on extensive structural and functional analytical characterization.

Therefore, based on the totality of the data demonstrating analytical high similarity, PK similarity, and no clinically meaningful differences in RA and PsO between ABP 501 and Humira comparator products, similar PK, safety, and immunogenicity profiles are expected between ABP 501 and US-licensed Humira in patients with JIA, PsA, AS, adult CD, and UC.

In aggregate, the based on the above considerations, it is reasonable to extrapolate data to support a demonstration that there are no clinically meaningful differences for JIA, PsA, AS, adult CD, and UC between ABP 501 and US-licensed Humira to support licensure of ABP 501 for the indications being sought.

[12] Oikonomopoulos A et al., "Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?", Current Drug Targets, 2013, 14, 1421-1432
[13] Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", Pharmacology & Therapeutics 117 (2008) 244–279

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No clinical postmarket risk evaluation and mitigation strategies are anticipated at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements and commitments are anticipated at the time of this review.

2 Introduction and Regulatory Background

2.1 Product Information

ABP 501 is a proposed biosimilar to US-licensed Humira (adalimumab). ABP 501 is an IgG1 kappa monoclonal antibody with a high affinity and avidity for the soluble and membrane-bound forms of TNF-α. The analytical similarity assessment of ABP 501 with US-licensed Humira supports a demonstration that ABP 501 is highly similar to US-licensed Humira except for minor differences in clinically inactive components.

2.2 Tables of Currently Available Treatments for Proposed Indications

Rheumatoid Arthritis

Many effective therapies are approved for the treatment of patients with RA including nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, disease modifying anti rheumatic drugs (DMARDs) and biologics. Currently approved DMARDs and biologic therapies are listed in Table 2 and Table 3, respectively.

Table 2. Small Molecule DMARDs Approved for RA in the United States

Product Name (Trade Name) [Applicant]	Mechanism of Action in RA	Year of First Approval for RA
Sulfasalazine (AZULFIDINE) [Pfizer]	Anti-inflammatory and antimicrobial	1950
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	Anti-metabolite	1953
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	Interference with antigen processing (?)	1955
Azathioprine (IMURAN) [Prometheus Labs]	Cytostatic	1968
Penicillamine (CUPRIMINE) [Alton]	Unknown	1970
Auranofin (RIDAURA) [Prometheus Labs]	Unknown	1985
Cyclosporine (NEORAL) (SANDIMMUNE) [Novartis]	T-cell activation inhibitor	1995, 1990
Leflunomide (ARAVA) [Sanofi-Aventis]	Anti-metabolite	1998
Tofacitinib (XELJANZ) [Pfizer]	*JAK kinase inhibitor*	2012

Table 3. Biologic DMARDs Approved for RA in the United States

Product Name (Trade Name) [Applicant] {year} *	Presentation and *ROA* †	Description and *MOA* §
Etanercept (ENBREL)+ [Immunex/Amgen] {1998}	Vial 25 mg Prefilled syringe 25 or 50 mg/mL SureClick Autoinjector 50 mg/mL *SC injection*	Fusion protein consisting of TNF-R and human IgG1 Fc *TNF inhibitor*
Infliximab (REMICADE) [Centocor] {1999}	Vial 10 mg/mL *IV infusion*	Chimeric IgG1 k mAb *TNF inhibitor*
Anakinra (KINERET) [Amgen] {2001}	Prefilled syringe 10 mg *SC injection*	Recombinant polypeptide *IL-1 receptor antagonist*
Adalimumab (HUMIRA) + [Abbott] {2002}	Prefiled syringe 40 mg/0.8 mL Humira Pen 40 mg/0.8 mL *SC injection*	Human IgG1 k mAb *TNF inhibitor*
Abatacept (ORENCIA) + [Bristol Myers Squibb] {2005}	Lyophilized powder 250 mg/vial *IV infusion*	Fusion protein consisting of CTLA-4 and human IGg1 Fc *T cell activation inhibitor*
Rituximab (RITUXAN) [Genentech and Biogen] {2006}	Vial 10 mg/mL *IV infusion*	Chimeric murine/human IgG1 k mAb *Anti CD20, B cell depletor*
Golimumab (SIMPONI) [Centocor] {2009}	Prefilled syringe 50 mg/0.5 mL SmartJect Autoinjector 50 mg/0.5 mL *SC injection*	Humanized IgG1 k mAb *TNF inhibitor*
Certolizumab Pegol (CIMZIA) [UCB Inc] {2009}	Lyophilized powder 200 mg/vial *SC injection*	Humanized Fab fragment *TNF inhibitor*
Tocilizumab (ACTEMRA) + [Genentech/Roche] {2010}	Vial 20 mg/mL *IV infusion*	Humanized IgG1 k mAb *IL-6 receptor inhibitor*

*Year = Year of first approval for RA †ROA = Route of administration §MOA= Mechanism of action +Approved for treatment of JIA

Psoriatic Arthritis

The first-line therapy for the treatment of psoriatic arthritis is typically the off-labeled use of small molecular immunomodulators (commonly referred to as disease modifying anti-rheumatic drugs [DMARDs]), e.g., methotrexate (MTX), sulfasalazine, and leflunomide. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are also frequently used. Currently approved biologic drugs for treatment of adult patients with psoriatic arthritis are listed in Table 4.

Table 4. Biologics Approved for Psoriatic Arthritis in the United States

Product Name (Trade Name) [Applicant]	Class
Infliximab (REMICADE)	TNFα-blocker
Etanercept (ENBREL)	TNFα-blocker
Adalimumab (HUMIRA)	TNFα-blocker
Golimumab (SIMPONI)	TNFα-blocker
Certolizumab (CIMZIA)	TNFα-blocker
Ustekinumab (STELARA)	interleukin-12 and -23 antagonist
Secukinumab (COSENTYX)	Interleukin-17 antagonist

Ankylosing Spondylitis

There are four biologic TNF-inhibitors that are approved in the United States for the treatment of AS as listed in Table 5

Table 5. Approved Products for the Treatment of AS in the United States

Product	BLA (Applicant)	Date of approval for AS‡	Characteristic	ROA
Etanercept (Enbrel)	103795 (Immunex)	7/24/03	Fusion protein (TNF-inhibitor)	SC
Infliximab (Remicade)	103772 (Centocor)	12/17/04	Monoclonal antibody (TNF-inhibitor)	IV
Adalimumab (Humira)	125057 (Abbott)	8/28/06	Monoclonal antibody (TNF-inhibitor)	SC
Golimumab (Simponi)	125289 (Centocor)	4/24/09	Monoclonal antibody (TNF-inhibitor)	SC
Secukinumab (Cosentyx)	BLA 125504 (Novartis)	1/15/16	Interleukin-17 antagonist	SC

Abbreviations: BLA=Biologics License Applications; ROA=route of administration; SC=subcutaneous; IV=intravenous; RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis
† NSAIDs (e.g., celecoxib, diclofenac, indomethacin, naproxen, sulindac) and steroids (e.g., betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, and triamcinolone) are also approved for the treatment of AS
‡ Etanercept was originally approved in 1998 for RA, infliximab was originally approved in 1998 for Crohn's Disease, adalimumab was originally approved in 2002 for RA, and golimumab was approved for RA, PsA, and AS concurrently

Plaque Psoriasis

The products in the tables below (Table 6 & Table 7) could be considered as therapeutic options for the applicant's target population. These include systemic small molecule therapies, biologics and phototherapy.

Table 6. Small Molecules Approved for Plaque Psoriasis in the United States

Product Name (Trade Name) [Applicant]	Class
Acitretin	retinoid
Methotrexate	folate antagonist
Cyclosporine	IL-2 inhibitor
Apremilast (OTEZLA)	phosphodiesterase 4 inhibitor

Table 7. Approved Biologic Therapies for Plaque Psoriasis in the United States

Product Name (Trade Name) [Applicant]	Class
Infliximab (REMICADE)	TNFα-blocker
Etanercept (ENBREL)	TNFα-blocker
Adalimumab (HUMIRA)	TNFα-blocker
Ustekinumab (STELARA)	Interleukin-12 and -23 antagonist
Secukinumab (COSENTYX)	Interleukin-17 antagonist

Phototherapy: This therapy involves exposures to UVB (including narrowband) or to UVA in combination with the photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA.

2.3 Availability of Proposed Active Ingredient in the United States

ABP 501 is not currently marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The safety program for ABP 501 was designed based on the well-characterized safety profile of US-licensed Humira.[14] Potential risks based on class of drug (TNFα) and of the drug substance were considered. Potential risks associated with immunomodulating biologic therapies may include infections, cardiovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, injection site reactions and immunogenicity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

ABP 501 was developed globally with regulatory input from the FDA, European Medicines Agency, (b) (4) The major clinical regulatory activity with the FDA was as follows:

- August 24, 2011
  - Type B meeting to discuss the development program for ABP 501 as a proposed biosimilar to US-licensed Humira
- May 9, 2013
  - BPD Type 2 meeting to review Study 20110217 PK data and the acceptability of proposed phase 3 study design in subjects with RA
- January 29, 2014

[14] FDA-approved Humira labeling

  - BDP Type 2 meeting to discuss the data requirements related to the device aspects of the ABP 501 pre-filled syringe and autoinjector to be presented in the BLA

- January 26, 2015
  - BPD Type 2 meeting to discuss the acceptability of the proposed structure and format of the statistical data presentation to support the BLA
- June 10, 2015
  - BPD Type 4 meeting to discuss the structure, format, and content of a proposed BLA

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were good. The amount of missing data was small and did not impact the overall conclusions on safety and efficacy. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

OSI Inspection

The Office of Scientific Investigations (OSI) was consulted to conduct routine applicant/monitor inspection for four clinical sites that contributed to the data for Study 262 (three in Poland and one in the US) as well as the Applicant. The inspections showed the clinical sites to be in compliance with Good Clinical Practices and were without deficiencies. The OSI investigators concluded that the data submitted were acceptable to support the current BLA.

3.2 Compliance with Good Clinical Practices

All studies were conducted by Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters form for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

Written informed consent was obtained prior to the subject entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. The applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

In accordance with 21 CFR part 54 Financial Disclosures by Clinical Investigators, Amgen requested statements of financial interests from a total of 142 Principal Investigators and 637 sub-investigators for the following studies:

- Study 217
- Study 262
- Study 263

A total of 140 principal investigators and 633 sub-investigators reported no financial information to disclose. Three sub-investigators did not provide financial disclosure information due to leaving their position prior to collection of financial disclosure information.

Two principal investigators and one sub-investigator disclosed financial arrangements/interests that could potentially introduce bias:

- [redacted], MD (Principal Investigator, Study Site# [redacted], enrolled [redacted] subject):
    - Dr. [redacted] participates in Amgen Speakers Bureau ~10 to 15 times per year at a rate of $1000-$2000 per speaking engagement

- [redacted], MD (Principal Investigator, Study Site# [redacted], enrolled [redacted] subjects):
    - Ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria (>$25,000) cumulatively. Research ongoing for another Amgen study

- [redacted], MD (Sub-investigator, Study Site# [redacted], enrolled [redacted] subjects):
    - Significant financial interest in Amgen due to stock ownership

Overall, the number of subjects enrolled at the individual investigator sites were small compared to the total number of subjects enrolled in the overall study. In all cases, the applicant took steps to minimize potential bias which primarily consisted of excluding the investigator from the selection process of subjects, blinding to study drug, and exclusion from the knowledge and analysis of results. Review of the documents does not raise concerns regarding the integrity of the submitted data to the current application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The ABP 501 product has been evaluated and compared to US-licensed Humira and EU-approved Humira in a variety of structural, physicochemical, and functional assays. The assessment also included assays that addressed each potential mechanism of action, either directly or indirectly. The evidence submitted supports a demonstration that ABP 501 is highly similar to US-licensed Humira. The amino acid sequences of ABP 501 and US-licensed Humira are identical. TNF-α binding and neutralization activities, reflecting the primary mechanism of action of US-licensed Humira, are similar between ABP 501 and US-licensed Humira, supporting a demonstration that ABP 501 has the same mechanism of action as US-licensed Humira. Additional data evaluating reverse signaling as one of the potential mechanisms of action in IBD is pending at the time of this document; however, if these data are determined to be adequate, they would further support a demonstration that ABP 501 is highly similar to US-licensed Humira. Further, it would support the demonstration that ABP 501 and US-licensed Humira have the same mechanisms of action for the indications sought for licensure, to the extent that the mechanisms of action are known or can reasonably be determined.

In aggregate, the analytical data (i.e., the extensive structural characterization, functional data in support of effector function, binding to membrane-bound TNF-α, activation of regulatory macrophages) support a demonstration that ABP 501 is highly similar to US-licensed Humira. Furthermore, a comparison of the secondary and tertiary structures of ABP 501 and US-licensed Humira support a demonstration that the two products are highly similar. The impurity profile of ABP 501 is acceptable and was shown to be similar to US-licensed Humira.

Some tests indicate that slight changes in quality attributes are observed, including

glycosylation pattern and charge variant profile; however, these slight differences do not preclude a demonstration of high similarity between ABP 501 and US-licensed Humira. When ABP 501 is compared to US-licensed Humira, the biological functions that these subtle differences might impact are nevertheless within the quality range of US-licensed Humira and do not preclude a demonstration that ABP 501 is highly similar to US-licensed Humira.

The Product Quality review team concluded that Amgen provided a sufficiently robust analysis for the purposes of establishing the analytical component of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical studies that used EU-approved Humira, to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira.

For a detailed review and analysis of the CMC data, refer to the review by the Product Quality review team.

4.2 Clinical Microbiology

No issues have been identified by the CMC review team regarding clinical microbiology at the time of this review.

4.3 Preclinical Pharmacology/Toxicology

Two nonclinical studies of ABP 501 were submitted in support of the BLA: a toxicokinetic study in cynomolgus monkeys comparing ABP 501 vs. US-licensed Humira and a toxicity/toxicokinetic study in cynomolgus monkeys comparing ABP 501 vs. US-licensed Humira. The results of the two studies were considered comparable to that of US-licensed Humira in cynomolgus monkeys and there was no evidence to indicate potential clinical safety concerns associated with ABP 501 administration.

The nonclinical pharmacokinetic and repeat-dose toxicity data submitted support the demonstration of biosimilarity (i.e., comparable systemic exposure and safety profile) between ABP 501 and US-licensed Humira. There were no outstanding issues from the nonclinical Pharmacology and Toxicology perspective and the results of these animal studies can be taken together with the data from the analytical bridging studies (refer to the CMC section of this document for details) to support a demonstration that ABP 501 is biosimilar to US-licensed Humira. No residual uncertainties have been identified by this discipline.

Please refer to the review by the Pharmacology/Toxicology review team for a detailed analysis of the pharmacology/toxicology results of the ABP 501 development program.

4.4 Clinical Pharmacology

The objectives of clinical pharmacology program were to evaluate the pharmacokinetic similarity between ABP 501 and US-licensed Humira, and to support the scientific bridge between ABP 501, US-licensed Humira and EU-approved Humira in order to justify the relevance of comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP 501 to US-licensed Humira. The Applicant submitted PK data from three studies. The pivotal PK similarity study (Study 217) was conducted in healthy subjects comparing ABP 501, US-licensed Humira, and EU-approved Humira. Similarities in PK between ABP 501 and both US-licensed and EU-approved Humira were then confirmed in the two clinical comparative studies. The trough concentration was collected in study 262 to compare ABP 501 and US-licensed Humira in RA patients (with concomitant use of methotrexate), and study 263 in plaque psoriasis patients to compare ABP 501 and EU-approved Humira (administered as monotherapy).

Pharmacokinetic (PK) similarity of ABP 501 to US-licensed Humira was evaluated in a pivotal 3-way PK similarity study 217 that compared the PK, safety, tolerability, and immunogenicity of single 40 mg subcutaneous dose of either ABP 501, US-licensed

Humira, or EU-approved Humira in healthy subjects. In this study, the pairwise comparisons of ABP 501, US-licensed Humira, and EU-approved Humira met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUC_{inf}, AUC_{last}, and C_{max}, within the interval of 80% to 125%), thus establishing the PK similarity and providing the PK bridging data in addition to the analytical bridging data, to justify the relevance of the comparative data generated using EU-approved Humira. The data from Study 217 also demonstrated that the observed small differences in key glycans between ABP 501, US-licensed Humira, and EU-approved Humira, described in the section on Analytical Similarity above, did not have an impact on PK similarity.

In addition, similar trough concentrations were demonstrated for ABP 501 and US-licensed Humira in patients with RA (with concomitant use of methotrexate, Study 262), and for ABP 501 and EU-approved Humira in patients with PsO (administered as monotherapy, Study 263).

Overall, the submitted clinical pharmacology studies support the demonstration of PK similarity between ABP 501 and US-licensed Humira and did not raise any new uncertainties in the assessment of biosimilarity of ABP 501 to US-licensed Humira.

Refer to the clinical-pharmacology review for a detailed analysis of the pharmacokinetic and pharmacodynamics aspects related to this application.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Key design features of the ABP 501 clinical studies are summarized in Table 8.

Table 8. Clinical Development: Controlled Studies

Study	Patient Population	Design/Objectives	Duration	Sample size Randomization	Treatment arms
217	HV	R, SB, SD, 3-arm, PG, 3-way PK bridging	Single dose	N=203 1:1:1	ABP 501 EU-Humira1 US-Humira2
262	RA	R, DB, PG Comparative Clinical Study	26 weeks	N=526 1:1	ABP 501 US-Humira
263	PsO	R, DB, PG Comparative Clinical Study	52 weeks	N=347 1:1	ABP 501 EU-Humira

[1]EU-approved Humira [2]US-licensed Humira
R–Randomized, SB-Single blind, DB-Double blind, HV-Healthy Volunteers, PG-Parallel-group, PK-Pharmacokinetics, SD-Single dose, MTX– Methotrexate, IR-Inadequate Responders

5.2 Review Strategy

The clinical development program for ABP 501 consists of three controlled clinical studies, listed in Table 8. These three studies provide the primary evidence to support the determination of no clinically meaningful differences between ABP 501 and US-licensed Humira. Additional long-term safety and immunogenicity data for patients who transitioned from EU-approved Humira to ABP 501 or continued to receive ABP 501 were provided in Study 263.

Assessment of comparative clinical efficacy to support the demonstration of no clinically meaningful differences between ABP 501 and Humira are provided in the comparative

clinical studies 262 and 263 that enrolled patients with RA and PsO, respectively. All clinical studies are included in the safety review.

Additional supportive clinical safety and efficacy data were derived from the single dose PK study (Study 217), which provided a 3-way comparison of ABP 501, US-licensed Humira, and EU-approved Humira intended to support PK similarity of ABP 501 and US-licensed Humira as well as to provide a PK bridge to support the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP 501 to US-licensed Humira.

All endpoints used are validated endpoints used in the approval of other drugs in RA and PsO and represent clinically meaningful endpoints.

The safety analysis included in this review includes data from all three clinical studies and represents the Agency's primary safety analysis. The efficacy analysis presented in this review here will concentrate on the results of the multiple repeat dose Studies 262 and 263 in RA and PsO and describe the results from the single dose Study 217 in healthy subjects. Detailed review of the efficacy analyses of Studies 217 can be found in the reviews by the clinical pharmacology review team.

Of note, the Studies 217 and 262 were conducted based on discussions with FDA; however, Study 263 was conducted without input from the Agency. In general, the overall clinical program is adequate to provide the evidence to support the demonstration of no clinically meaningful differences in the studied indications of RA and PsO.

5.3 Discussion of Individual Studies/Clinical Studies

Study 217: PK Similarity Study

Study 217, entitled *"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" was conducted between July 3, 2012 and October 26, 2012 at two centers in two countries (US and UK). The study was designed as a randomized, double-blind, three-arm, parallel-group study following a single 40 mg/0.8 mL SC injection via PFS to compare the PK, safety, tolerability, and immunogenicity of ABP 501, US-licensed Humira, and EU-approved Humira in healthy subjects.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
    - Male or female subjects aged 18 to 45 years
    - Body mass index (BMI) between 18 and 30 kg/m^2
    - Normal or clinically acceptable physical examination, clinical laboratory values, ECG, and vital signs at screening and baseline.
    - Females of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study
- Major Exclusion Criteria
    - History or evidence of a clinically significant disorder, condition, or disease that would have posed a risk to subject safety or would have interfered with the study evaluation, procedures, or study completion in the opinion of the investigator.
    - Evidence of any bacterial, viral, parasitic, systemic fungal infections, or infections due to other opportunistic pathogens within the 30 days prior to investigational product administration
    - Evidence of a recent (≤ 6 months) infection requiring in-patient hospitalization or intravenous antibiotics
    - Known positive tuberculin skin test, exposure to an individual with tuberculosis, or positive QuantiFERON® test or local equivalent consistent with previous exposure to TB prior to or during screening
    - Tuberculosis or fungal infection seen on available chest x-ray taken within 6 months of screening

- History of malignancy of any type, other than surgically excised non-melanomatous skin cancers, within 5 years prior to investigational product administration
- Positive test for HIV antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies at screening
- Received live vaccines ≤3 months prior to investigational product administration
- Women who were pregnant or nursing
- Use of any protocol-prohibited medications

The primary PK endpoints evaluated in the study included AUC_{inf}, $AUC_{0\text{-}last}$, and C_{max}.

All AEs recorded during the study were coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), Version 15.0, and presented by subject in the data listings. Adverse events leading to study discontinuation, serious AEs (SAEs), and deaths were listed separately.

A treatment-emergent AE was defined as an AE that was not present prior to treatment with investigational product, but appeared following treatment or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the subject was on treatment was a TEAE. The overall incidence of TEAEs, AEs, and SAEs as well as the number of events, was summarized by treatment.

For the incidence at the subject level by SOC and PT, if a subject experienced ≥1 event within the same SOC and PT, only one occurrence was included. For the incidence at the subject level by SOC, PT, and severity, if a subject experienced more than 1 event within the same SOC and PT, only the most severe occurrence was included.

Observed and change from baseline vital signs data were listed and summarized descriptively by treatment and scheduled time point. Observed and change from baseline 12-lead ECG data were listed with all associated comments and summarized descriptively by treatment and scheduled time point. Antidrug antibody results were listed and summarized by treatment.

A total of 196 (97%) subjects completed the study while seven (3%) discontinued from the study due to missed visits (n=5), dermoid cyst (n=1), and early withdrawal from the study (n=1).

All randomized subjects were included in the Safety and Intent-to-Treat populations and no data were excluded.

There were a total of 45 protocol deviations reported with 41 (91%) related to deviations in the timing of PK blood draws. Two subjects were included despite being outside the specified BMI values; one subject took prenatal vitamins within 30 days of dosing, and one subject self-administered metronidazole for a suspected sinus infection. These protocol deviations are not expected to impact the analysis and interpretation of the results for Study 217.

Overall, the baseline demographics were similar between treatment arms with the average patient being approximately 29 years of age, White (85%), and a slightly higher proportion of males than females (57% vs. 43%, respectively).

Study 262: Comparative Clinical Study in RA

Study 262, entitled “A Randomized, Double-blind, Phase 3 Study of ABP 501 Efficacy and Safety Compared to Adalimumab in Subjects with Moderate to Severe Rheumatoid Arthritis”, was conducted between October 24, 2013 and November 19, 2014 at 92 centers in 12 countries. The study was designed as a randomized, double-blind, active

comparator-controlled, 26-week study in subjects with moderate to severe RA who had an inadequate response to MTX. Subjects were randomized 1:1 to receive ABP 501 or US-licensed Humira at 40 mg SC injection every 2 weeks (Q2W).

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
    - Male or female subjects aged 18 to 80 years
    - Diagnosed with RA as determined by meeting 2010 ACR/EULAR classification criteria for RA for ≥3 months
    - Active RA defined as ≥6 swollen joints and ≥6 tender joints (based on 66/68 joint count excluding distal interphalangeal joints) at screening and baseline and ≥1 of the following at screening:
        - ESR ≥ 28 mm/hr
        - serum CRP > 1.0 mg/dL
        - Positive rheumatoid factor or anti-cyclic citrullinated peptide (CCP) at screening
    - Subjects must be taking MTX for ≥12 weeks and on a stable dose of 7.5 to 25 mg/week for >8 weeks prior to receiving the study drug
    - Stable doses of NSAIDs or low potency analgesics for ≥2 weeks prior to screening
    - Stable doses of oral corticosteroids, (≤10 mg prednisone or equivalent) for ≥4 weeks prior to screening
    - No known history of active tuberculosis and a negative test for tuberculosis during screening

- Major Exclusion Criteria
    - Active infection or history of infection
    - Known history of HIV, HbsAg, or HCV antibody positivity
    - Uncontrolled, clinically significant systemic disease such as diabetes

mellitus, cardiovascular disease including moderate to severe heart failure, renal disease, liver disease or hypertension

- Malignancy within 5 years except treated and cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma history of neurologic symptoms suggestive of central nervous system demyelinating disease
- Major chronic inflammatory disease or connective tissue disease other than RA
- Laboratory abnormalities at screening, including any of the following:
  - hemoglobin < 9 g/dL
  - platelet count < 100,000/mm^3
  - white blood cell count < 3,000 cells/mm^3
  - AST and/or ALT ≥2.0 x the upper limit of normal
  - creatinine clearance <50 mL/min
- Any of the following within 28 days prior to first dose of study drug:
  - Intra-articular (IA) hyaluronic acid injections
  - IA, intramuscular (IM), or IV corticosteroids, including ACTH
  - Non-biologic DMARDs other than MTX within 28 days prior to first dose of study drug except as noted in protocol
- Prior use of ≥2 biologic therapies for RA
- Live vaccines ≥3 month of study drug
- Women who were pregnant or breast feeding
- Sexually active subjects of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study

The primary endpoint of the study was the proportion of patients achieving an ACR20 response at Week 24. An ACR20 response was defined as at least 20% improvement from baseline in both the tender and swollen joint counts, in addition to at least 20% improvement in at least three of the following: patient assessment of pain on a visual

analog scale (VAS), patient global assessment of disease status (VAS), physician global assessment of disease status (VAS), Health Assessment Questionnaire Disability Index (HAQ-DI), and serum C-reactive Protein concentration. Secondary efficacy endpoints included the components used to define ACR20 response, the Disease Activity Score in 28 joints with CRP (DAS28-CRP), ACR50 response, and ACR70 response. Most were evaluated at Weeks 2, 4, 8, 12, 18, and 24.

The primary analysis was based on a log-binomial regression model adjusting for region and prior biologic use in which the null hypothesis would be rejected if the 90% confidence interval (CI) for the ratio in ACR20 response proportions was contained within the similarity margin of (0.738, 1/0.738). The last observation carried forward (LOCF) approach was used to impute missing data for patients who discontinued treatment early, or had missing or incomplete data for the evaluation of ACR20 at Week 24. The primary analysis was carried out in both the full analysis set (FAS) and the per-protocol population. The FAS consisted of all randomized patients and the per-protocol population consisted of patients who completed the treatment period and did not have a protocol violation that would affect evaluation of the primary objective of the study.

The Applicant also carried out a supportive analysis that FDA suggested during regulatory interactions, in which the difference in ACR20 response proportions was recommended as the main metric with a similarity margin of ±12%, and patients who withdrew early were treated as non-responders. The analysis was based on a binomial regression model with identity-link function adjusting for region and prior biologic use.

All AEs recorded during the study were coded by SOC and PT using MedDRA, Version 17.1, and presented by subject in the data listings. Adverse events leading to study discontinuation, SAEs and deaths were listed separately.

A treatment-emergent AE was defined as an AE that was not present prior to treatment with investigational product, but appeared following treatment or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the subject was on treatment was a TEAE. The overall incidence of TEAEs, AEs, and SAEs as well as the number of events, was summarized by treatment.

For the incidence at the subject level by SOC and PT, if a subject experienced ≥1 event within the same SOC and PT, only one occurrence was included. For the incidence at the subject level by SOC, PT, and severity, if a subject experienced more than 1 event within the same SOC and PT, only the most severe occurrence was included.

Observed and change from baseline vital signs data were listed and summarized descriptively by treatment and scheduled time point. Observed and change from baseline 12-lead ECG data were listed with all associated comments and summarized descriptively by treatment and scheduled time point. Antidrug antibody results were listed and summarized by treatment.

A total of 526 (n=264 ABP 501, n=262 US-licensed Humira) subjects were randomized in Study 262. Of these, 494 (94%) subjects completed the study (n=243 ABP 501, n=251 US-licensed Humira). A total of 32 (6%) subjects discontinued the study: 17 subjects withdrew consent, 10 subjects discontinued due AEs, four subjects were lost to follow-up, and one subject discontinued due to protocol violations. All randomized subjects were included in the Safety and Intent-to-Treat populations and no data were excluded.

There were a total of 55 protocol deviations reported during Study 262 (n=25 ABP 501, n=30 US-licensed Humira). The most common protocol violation was mis-stratification at randomization due to incorrect designation to prior biological use category. All other protocol violations occurred in <2% of subjects. The types and frequencies of protocol

violations were balanced between treatment groups and are not expected to impact the analysis and interpretation of the results for Study 262.

The baseline demographics and disease characteristics were similar between treatment arms with the average patient being approximately 56 years of age, White (95%), and largely female (81%). On average subjects had been diagnosed with RA for 9 years and had 14 swollen joints and 24 tender joints and an average DAS28-CRP; scale: 0 - 10 of 5.7 at the time of randomization.

Study 263 Comparative Clinical Study in PsO

Study 263, entitled *"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"*, was conducted between October 18, 2013 and March 18, 2015 at 49 centers in 6 countries. The study was designed as a randomized, double-blind, active comparator-controlled study of ABP 501 and EU-approved Humira in subjects with moderate to severe PsO. Subjects were randomized 1:1 to ABP 501 or EU-approved Humira with an initial loading dose of 80 mg SC on Day 1 followed one week later by 40 mg SC Q2W and the primary efficacy endpoint was assessed at Week 16.

To study the potential safety of subjects transitioning from EU-approved Humira to ABP 501, subjects at Week 16 who achieved a PASI 50 response were re-randomized in a blinded manner such that all subjects initially randomized to ABP 501 continued treatment with ABP 501 (ABP 501/ABP 501) and subjects initially randomized to EU-approved Humira were re-randomized (1:1) to either continue treatment with EU-approved Humira (Humira/Humira) or were started on ABP 501 (Humira/ABP 501). All subjects continued with their assigned treatment until week 48. Subjects without a PASI 50 response at week 16 or who missed the week 16 visit were discontinued from the study.

Major inclusion and exclusion criteria were as follows:

- Major Inclusion Criteria
    - Male or female subjects aged ≥ 18 and ≤ 75 years
    - Subject had stable moderate to severe plaque psoriasis for ≥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)

- Major Exclusion Criteria
    - Subject diagnosed with erythrodermic PsO, pustular PsO, guttate PsO, medication-induced PsO, 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 PsO
    - Subject has an active infection or history of infections as follows:
    - any active infection for which systemic anti-infectives were used within 28 days prior to first dose of study drug
    - a serious infection, defined as requiring hospitalization or intravenous antiinfectives within 8 weeks prior to the first dose of investigational product recurrent or chronic infections or other active infection
    - Known history of HIV, HbsAg, or HCV antibody positivity
    - Uncontrolled, clinically significant systemic disease such as diabetes mellitus, cardiovascular disease including moderate to severe heart failure, renal disease, liver disease or hypertension
    - Malignancy within 5 years except treated and cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma

- Has neurologic symptoms suggestive of central nervous system demyelinating disease
- Subject has moderate to severe heart failure (New York Heart Association [NYHA] class III/IV)
- Subject has used ustekinumab ≤3 months before screening; etanercept ≤1 month or other anti-TNF agents ≤3 months prior to screening
- Prior use of ≥2 biologics for treatment of PsO
- Live vaccines ≥3 month of study drug
- Women who were pregnant or breast feeding
- Sexually active subjects of child-bearing potential were required to use a medically-reliable method of contraception throughout their participation in the study

The primary endpoint was the percent improvement in PASI from baseline to Week 16. 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 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 percent improvement in PASI at Week 16 was 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. Although the protocol for Study 263 specified 95% confidence intervals for the primary endpoint, FDA also analyzed the

data using 90% confidence intervals to be consistent with the analyses in the Applicant's comparative clinical study in rheumatoid arthritis subjects (Study 262).

All AEs recorded during the study were coded by SOC and PT using MedDRA, Version 17.1, and presented by subject in the data listings. Adverse events leading to study discontinuation, SAEs and deaths were listed separately.

A treatment-emergent AE was defined as an AE that was not present prior to treatment with investigational product, but appeared following treatment or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the subject was on treatment was a TEAE. The overall incidence of TEAEs, AEs, and SAEs as well as the number of events, was summarized by treatment.

For the incidence at the subject level by SOC and PT, if a subject experienced ≥1 event within the same SOC and PT, only one occurrence was included. For the incidence at the subject level by SOC, PT, and severity, if a subject experienced more than 1 event within the same SOC and PT, only the most severe occurrence was included.
Observed and change from baseline vital signs data were listed and summarized descriptively by treatment and scheduled time point. Observed and change from baseline 12-lead ECG data were listed with all associated comments and summarized descriptively by treatment and scheduled time point. Antidrug antibody results were listed and summarized by treatment.

A total of 350 (n=175 ABP 501, n=175 EU-approved Humira) subjects were randomized in Study 263. Of these, 326 (95%) subjects completed the study (n=167 ABP 501, n=165 EU-approved Humira) through Week 16. Of the 18 subjects who discontinued the study: nine subjects discontinued due to AE, five subjects withdrew consent, three subjects had protocol violations and one subject was lost to follow-up. A total of 308

(88%) subjects were re-randomized at Week 16. From baseline to the end of study, a total of 275 (79%) subjects completed the study. The most common reasons for subjects discontinuing study drug after re-randomization included AE, protocol-specific criteria, and withdrawal of consent. In general, the reasons and proportions of subjects who discontinued the study were balanced between treatment arms.

From baseline to Week 16 there were a total of 35 subjects who had protocol violations reported during Study 263 (n=17 ABP 501, n=18 EU-approved Humira). The most common protocol violation was mis-stratification at randomization due to incorrect designation to prior biological use category. All other protocol violations occurred in <2% of subjects. The types and frequencies of protocol violations were balanced between treatment groups and are not expected to impact the analysis and interpretation of the results for Study 263.

The baseline demographics and disease characteristics were similar between treatment arms with the average patient being approximately 45 years of age, White (93%), and a greater proportion of men (65%). On average subjects had been diagnosed with PsO for 20 years with an average baseline PASI score of 20.1 and average baseline BSA of 26.9%. On the sPGA, 59.9% of subjects had a baseline score of moderate and 40.1% had a baseline score of severe or very severe at randomization.

6 Review of Efficacy

Efficacy Summary

Three controlled studies provide the primary evidence to support the determination of no clinically meaningful differences between ABP 501 and the US-licensed Humira:

- **Study 20110217 (Study 217):** a single-dose pharmacokinetic (PK) study providing a 3-way comparison of ABP 501, US-licensed Humira, and EU-approved Humira intended to (i) support PK similarity of ABP 501 and US-licensed Humira and (ii) provide PK bridge to support the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP 501 to US-licensed Humira.

- **Study 20120262 (Study 262):** a comparative clinical study between ABP 501 and US-licensed Humira in patients with RA to support a demonstration of no clinically meaningful differences in terms of safety, purity, and potency. This was a 26-week, randomized, double-blind, parallel group study conducted in 526 patients with moderate to severely active RA on background MTX, who were randomized 1:1 to ABP 501 or US-licensed Humira at a dose of 40 mg ever Q2W SC.

- **Study 20120263 (Study 263):** a second comparative clinical study intended to assess efficacy, safety, and immunogenicity between ABP 501 and EU-approved Humira in patients with PsO, and safety and immunogenicity in patients undergoing a single transition from EU-approved Humira to ABP 501. This was randomized, double-blind, parallel-group study conducted outside the US in 350 patients with moderate to severe plaque psoriasis who were randomized 1:1 to ABP 501 or EU-approved Humira at a dose of 80 mg on Day 1, then 40 mg Q2W starting one week later. At Week 16, subjects who achieved at least a 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 to provide a descriptive comparative assessment of safety and immunogenicity between these re-randomized cohorts.

Study 217 compared the PK, safety, tolerability, and immunogenicity of single 40 mg subcutaneous dose of either ABP 501, US-licensed Humira, or EU-approved Humira in healthy subjects. The pairwise comparisons of ABP 501, US-licensed Humira, and EU-approved Humira met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%), thus establishing the PK similarity and providing the PK bridging data in addition to the analytical bridging data, to justify the relevance of the comparative data generated using EU-approved Humira. Further PK support of similarity was demonstrated by similar trough concentrations for ABP 501 and US-licensed Humira in patients with RA in Study 262 and for ABP 501 and EU-approved Humira in patients with PsO. Overall, the clinical pharmacology studies support the demonstration of PK similarity between ABP 501 and US-licensed Humira and did not raise any new uncertainties in the assessment of biosimilarity of ABP 501 to US-licensed Humira.

Study 262 enrolled 526 subjects, 264 randomized to the ABP 501 arm and 262 randomized to the US-licensed Humira arm and all randomized patients received ≥1 dose of study product. Subjects were enrolled in Europe, North America, and Latin America. The primary endpoint was the proportion of patients who remained in the study and achieved an American College of Rheumatology 20% (ACR20) response at Week 24. Approximately 71% of patients randomized to ABP 501 and 72% of patients randomized to US-licensed Humira were ACR20 responders, for an estimated absolute difference between treatments of -0.4% (90% confidence interval [CI]: -6.8%, +6.1%).

The 90% CI successfully ruled out the similarity margin of ±12% that the Agency has determined reasonable. ACR20, ACR50, and ACR70 responses over time, in addition to mean changes from baseline in the components of the ACR composite endpoint, and the disease activity score (DAS28-CRP), were also similar between the treatment arms. These data demonstrate similar efficacy between ABP 501 and US-licensed Humira in patients with RA.

Study 263 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 Psoriasis Area Severity Index (PASI) from Week 1 to Week 16. The pre-specified similarity margin for the confidence interval for the difference in means was ±15%. The mean percent improvement in PASI score was similar on the ABP 501 and EU-approved Humira arms (81% vs. 83%) and the corresponding 90% confidence interval for the difference of (-6.6, 2.2) was within the pre-specified margin of ±15%. The results on the secondary endpoints were supportive of the results of the primary endpoint analysis.

6.1 Indication

The proposed therapeutic indications for ABP 501 are listed below:

Rheumatoid Arthritis (RA):

> Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Juvenile Idiopathic Arthritis (JIA):

> Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.

Psoriatic Arthritis (PsA):

Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS):

Reducing signs and symptoms in adult patients with active AS

Adult Crohn's Disease (CD):

Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to adalimumab.

Ulcerative Colitis (UC):

Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis (PsO):

The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

6.1.1 Methods

In the context of a biosimilar development program, the objective of the clinical development program of a proposed biosimilar is to help resolve any residual uncertainties that arise after a robust analytical similarity is established between the proposed biosimilar and the reference product. As such, the clinical development program of ABP 501 was designed to compare efficacy and safety of ABP 501, and Humira in select conditions of use.

Similarity in clinical efficacy was assessed in Studies 262 and 263 comparing ABP 501 with US-licensed Humira in patients with RA and EU-approved Humira in patients with PsO. Thus, this review focuses on the two large, randomized, double-blind controlled Studies 262 and 263 in RA and PsO patients, respectively.

To demonstrate therapeutic similarity between ABP 501 and comparator adalimumab, the applicant chose the indications of RA and PsO as both have been well-studied among the anti-TNF indications. Further, use of adalimumab has been well-characterized including PK & PD profiles, safety and efficacy in these patient populations.[15] We agree with the applicant's rationale that the study populations are sensitive in the assessment of no clinically meaningful differences in the context of a proposed biosimilar development.

6.1.2 Demographics

Study 262: Comparative Clinical Study in RA

The treatment groups in Study 262 were balanced with respect to demographics and baseline characteristics. The study was conducted in Europe, North America, and Latin America. The population enrolled was consistent with the population of moderate-to-severe RA with average baseline swollen and tender joint counts of 14 and 24, respectively, and an average disease activity score (DAS28-CRP; scale: 0 - 10) was 5.7.

[15] FDA-approved Humira labeling

Study 263: Comparative Clinical Study in PsO

Treatment groups in Study 263 were generally balanced with respect to demographics and baseline characteristics. The study was conducted in Europe, Canada, and Australia. The population enrolled was consistent with the population of moderate-to-severe plaque psoriasis with an average baseline PASI score of 20.1 and average baseline BSA of 26.9%. On the sPGA, 59.9% of subjects had a baseline score of moderate and 40.1% had a baseline score of severe or very severe.

6.1.3 Subject Disposition

Subject disposition for each of the clinical studies used to evaluate efficacy are included in the discussion of the individual studies (Section 5.3). Each of the studies had a high proportion (>90%) of subjects completing the study. For the small number of subjects that did discontinue from the studies, the numbers of subjects and reasons for discontinuation were similar between treatment arms with the most frequent reasons reported as due to AEs or withdrawal of consent. On the whole, the patterns of patient disposition did not appear to favor or disfavor ABP 501.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Study 262: Comparative Clinical Study in RA

Primary Endpoint: ACR20 response

Study 262 met the pre-specified similarity criterion for the primary endpoint of ACR20 response at Week 24 (Table 9). For the Applicant's primary analysis in the FAS population, the 90% confidence interval for the ratio in ACR20 response was within the pre-specified margin of (0.738, 1/0.738). Missing data was imputed using LOCF.

Table 9. Applicant-pre-specified Primary Analysis on ACR20 Response at Week 24 (FAS/LOCF), Study 262

	ABP 501 (N=264)	US-licensed Humira (N=262)
Responder[1]	194/260 (74.6%)	189/261 (72.4%)
	Ratio: 1.039 (90% CI: 0.954, 1.133)[2]	

[1] Defined by meeting ACR20 response criteria after applying LOCF method for missing ACR20 data at Week 24; Patients who did not have post-baseline ACR measures were excluded from the analysis.
[2] Ratio between ABP 501 and US-licensed Humira and CI based on a generalized linear model adjusted for geographic region and prior biologic use for RA as covariates in the model
Source: Applicant's analysis of data from Amgen 351(k) BLA submission

Study 262 also met the FDA-suggested similarity criterion for the primary endpoint of ACR20 response at Week 24. For the analysis in the FAS population, the 90% confidence interval for the difference in ACR20 response rates was within the FDA-suggested margin of ±12%. Patients who discontinued treatment were considered non-responders (NRI) in this analysis (Table 10).

Table 10. FDA-suggested Primary Analysis on ACR20 Response at Week 24 (FAS/NRI), Study 262

	ABP 501 (N=264)	US-licensed Humira (N=262)
Responder[1]	188/264 (71.2%)	189/262 (72.1%)
	Difference: -0.4% (90% CI: -6.8%, 6.1%)[2]	

[1] Defined by remaining in the study through Week 24, and meeting ACR20 response criteria at Week 24
[2] Difference between ABP 501 and US-licensed Humira and CI based on a generalized linear model adjusted for geographic region and prior biologic use for RA as covariates in the model
Source: FDA analysis of data from Amgen 351(k) BLA submission

In a supportive analysis of ACR20 response in the subset of patients who completed the study and adhered to the protocol (per-protocol population), the 90% confidence interval for the difference in ACR20 response rates was within the FDA-suggested margin of ±12% (Table 11).

Table 11. Per-Protocol Analysis on ACR20 Response at Week 24, Study 262

	ABP 501 (N=230)	US-licensed Humira (N=233)
Responder[1]	176/230 (76.5%)	178/233 (76.4%)
	Difference: 0.4% (90% CI: -6.0%, 6.9%)[2]	

[1] Defined by meeting ACR20 response criteria at Week 24
[2] Difference between ABP 501 and US-licensed Humira and CI based on a generalized linear model adjusted for geographic region and prior biologic use for RA as covariates in the model
Source: Applicant's analysis of data from Amgen 351(k) BLA submission

For further details on the statistical considerations for the analysis of the efficacy endpoints, the reader is referred to DPARP statistical team review.

6.1.4.2 Study 263: Comparative Clinical Study in PsO

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, the 95% confidence interval for the difference in mean percent improvement in PASI was within the pre-specified margin of ±15%. Correspondingly, the 90% confidence interval also fell within the ±15% margin. Because the lower 90% confidence bound was -6.6, the study would meet the similarity criteria for margins of ±7% or larger. Missing data was imputed using LOCF (Table 12).

Table 12. Percent Improvement in PASI at Week 16 (FAS/LOCF), Study 263

	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: FDA analysis of data from Amgen 351(k) BLA submission

For further details on the statistical considerations for the analysis of the efficacy endpoints, the reader is referred to DDDP statistical team review.

6.1.5 Analysis of Key Secondary Endpoints(s)

6.1.5.1 Study 262: Comparative Clinical Study in RA

The secondary endpoints were ACR50/70 responses and DAS28-CRP. The proportions of patients remaining in the study and achieving ACR20 responses at Weeks 2, 4, 8, 12, 18, and 24, in addition to ACR50 and ACR70 response probabilities over time, were similar between the treatment arms (data not shown). Mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28-CRP) were also similar between the arms in all randomized patients who completed the study (Table 13). In particular, the 95% CI of (-0.20, 0.21) and the 90% CI of (-0.18, 0.17) for the estimated mean difference in Week 24 DAS28-CRP change ruled out the margin of ±0.6 proposed by the Applicant. Empirical distribution functions with worst possible values assigned for dropouts were also comparable between the treatment arms for DAS28-CRP (data not shown). Overall, the results for the secondary endpoints support the demonstration of similarity between ABP 501 and US-licensed Humira.

Table 13. Mean Changes from Baseline in the ACR Components and DAS28-CRP at Week 24 in Study Completers, Study 262

	ABP 501 (N=264)		US-licensed Humira (N=262)		Difference (95% CI)[2]
	N[1]	Mean	N[1]	Mean	
Swollen Joint Count	246	-10.5	253	-10.3	-0.2 (-1.1, 0.7)
Tender Joint Count	246	-15.4	253	-14.8	-0.7 (-2.2, 0.9)
HAQ Score	246	-0.44	253	-0.47	0.03 (-0.06, 0.12)
Patient Pain	246	-31.7	253	-30.9	-0.8 (-4.6, 3.1)
Patient Global	246	-3.00	253	-2.96	-0.04 (-0.41, 0.33)
Physician Global	246	-4.37	253	-4.27	-0.10 (-0.40,0.21)
CRP	243	-5.97	251	-6.03	0.05 (-1.67, 1.78)
DAS28-CRP	243	-2.25	251	-2.26	0.01 (-0.20, 0.21)

[1] Number of patients with complete data included in analysis
[2] Mean difference between ABP 501 and US-licensed Humira and CI based on a linear regression model adjusted for baseline value, geographic region and prior biologic use for RA as covariates in the model
Source: FDA analysis of data from Amgen 351(k) BLA submission

6.1.5.2 Study 263: Comparative Clinical Study in PsO

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. These secondary endpoints plus percent improvement in PASI were also assessed at Weeks 32 and 50 in the second treatment period. Subjects with at least PASI 50 response at Week 16 were to continue to the second treatment period, where subjects originally treated with EU-approved Humira were randomized to continue EU-approved Humira or undergo a single transition to ABP 501. Subjects originally randomized to ABP 501 continued treatment with ABP 501. Descriptive statistics were provided for the secondary endpoints. The estimated treatment effects (ABP 501 – EU-approved Humira) at Week 16 for the secondary endpoints of PASI 75, sPGA response, and reduction in BSA were -7.7%, -7.4%, and -1.9 (Table 14). Although the point estimates for these secondary endpoints trended towards a lower response on the ABP 501 arm relative the EU-approved Humira arm, we believe that these results are likely confounded by the variability in distribution being magnified by dichotomized outcomes such as PASI 50, 75, and 90, which dichotomize the percent improvement in PASI. The same distribution in responses can result in larger or smaller differences in dichotomized endpoints depending on where the cut-off point is chosen, as can be seen with the range of the treatment effect estimates for PASI 75 (-7.7%) and for PASI 90 (+0.3%). Further, there are no analytical, pharmacokinetic, or immunogenicity differences between ABP 501 and EU-approved Humira to account for the observed trends in the secondary endpoints in Study 263.

Table 14. Secondary Endpoints at Week 16 (FAS/LOCF), Study 263

	ABP 501 N=172	EU-approved Humira N=173	Difference[a]	90% Conf. Int.
Week 16 Endpoints				
PASI 75	74.4%	82.7%	-7.7%	(-15.2, -0.3)
PASI 50	92.4%	94.2%	-2.7%	(-7.0, 1.6)
PASI 90	47.1%	47.4%	0.3%	(-8.4, 9.0)
sPGA (clear/almost clear)	58.7%	65.3%	-7.4%	(-15.6, 0.9)
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)

[a] Model estimate adjusted for prior biologic use, region, and baseline PASI
Source: FDA analysis of data from Amgen 351(k) BLA submission

During the second treatment period, the percent improvement in PASI remained relatively constant among the re-randomized subjects from Week 16 to Week 50 (Table 15).

Table 15. Percent Improvement in PASI after Re-randomization (Observed Cases), Study 263

	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: FDA analysis of data from Amgen 351(k) BLA submission

6.1.7 Subpopulations

For further details on the subpopulation analyses the reader is referred to statistical teams' reviews.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The reader is referred to statistical teams' reviews.

6.1.10 Additional Efficacy Issues/Analyses

The applicant's sensitivity analysis for key primary and secondary efficacy endpoints to account for missing data demonstrated results consistent with primary analysis. FDA's analysis of key primary and secondary efficacy endpoints was consistent with the applicant's analysis. For further details on the additional supportive analyses the reader is referred to statistical teams' reviews.

7 Review of Safety

Safety Summary

The submitted safety and immunogenicity data and analyses using two dosing regimens (40 mg Q2W SC on the background of MTX, or a loading dose of 80 mg on Day 1, followed by 40 mg Q2W SC starting one week later as monotherapy), in two distinct patient populations, are adequate to support the demonstration of no clinically meaningful differences between ABP 501 and US-approved Humira in patients with RA and PsO. The safety database submitted for ABP 501 is adequate to provide a reasonable descriptive comparison between the two products. The safety risks identified are consistent with the known adverse event profile of US-licensed Humira. The analysis of the data indicates a safety profile of ABP 501, similar to that of US-licensed Humira. There were no notable differences between ABP 501 and US-licensed or EU-approved Humira in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, or deaths between the treatment groups. No cases of drug-induced liver injury meeting Hy's law criteria were reported in the ABP 501 clinical program. The safety data support the demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the populations studied. In addition, transitioning of non-treatment naïve patients, i.e., patients previously treated with EU-approved Humira, to ABP 501 does not appear to result in an increase of clinically significant adverse reactions.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data were derived from the two comparative clinical studies in RA (Study 262) and in PsO (Study 263). In Study 263, at Week 16, a total of 77 subjects underwent a single transition from EU-approved Humira to ABP 501 to assess additional risks, if any, in safety and immunogenicity resulting from a single transition

from EU-approved Humira to ABP 501 to address the safety of the clinical scenario where non-treatment naïve patients transition to ABP 501. Supportive safety and immunogenicity information was also provided from the single dose PK study in healthy subjects (Study 217). Of note, some of the safety data are derived from a clinical study using the EU-approved Humira (Study 263); however, Amgen has provided robust comparative analytical data and clinical PK bridging data (Study 217) between the US-licensed and EU-approved Humira to justify the relevance of comparative data, including safety data generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP 501 to US-licensed Humira.

The safety population for ABP 501 is comprised of 1076 subjects who were treated with ABP 501 or Humira (US-licensed or EU-approved) and includes 526 subjects from the 26-week long comparative clinical study in RA (Study 262); 347 subjects from the 52-week comparative clinical study in PsO (Study 263); and 203 healthy subjects from the single-dose PK similarity study (Study 217). A total of 582 subjects were treated with ABP 501 across all three studies. The safety and immunogenicity were reviewed for each individual study (Table 8).

Overall, the safety database is adequate to provide a reasonable comparative safety assessment, using two approved dosing regimens in two distinct patient populations, to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

7.1.2 Categorization of Adverse Events

An AE was defined as any untoward medical occurrence in a clinical trial subject including worsening of a pre-existing medical condition, clinically significant laboratory finding, symptom, or disease in a patient enrolled in the study regardless of its causal relationship to study drug. Adverse events in the individual studies were coded to the appropriate SOC and preferred term using the Medical Dictionary for Regulatory

Activities (MedDRA). Safety parameters were selected based on the known safety profile of the US-licensed Humira.

Adverse event analyses were reported using the actual study treatment received. In the case of Study 263 where a subgroup of subjects underwent a single transition from EU-approved adalimumab to ABP 501, AEs were attributed to the study period through Week 16 if an AE occurred before the date of the first study drug administration following re-randomization, and to the post-Week 16 period if the AE occurred after the date of the first study drug administration. Safety analyses were performed by treatment group before and after re-randomization, and also included those subjects who did not continue post re- randomization at Week 16.

7.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence

All reported AEs are presented per individual study without integrating data across studies and indications. The Applicant provided sufficient analyses to allow review by individual studies and across all studies and indications.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety population, defined as patients exposed to at-least on dose of study drug, is comprised of a total of 1076 subjects of which 582 subjects were administered ABP 501 (Table 16). In Study 263, a total of 77 subjects underwent a single transition from EU-approved Humira to ABP 501 while the remainder of subjects continued in their initial treatment arm following re-randomization.

Table 16. Overall Extent of Exposure to Study Treatment

Study	Number of Subjects Administered ≥1 dose of Study Drug			
	ABP 501 only	Humira only	Humira/ABP 501	Total

217	67	136[1]	N/A	203
262	264	262	N/A	526
263	174	96	77	347
Total	505	494	77	1076

[1]67 subjects exposed to EU-approved Humira and 69 subjects exposed to US-licensed Humira.
Source: Summary of Clinical Safety, Table 2.

Study 217

Study 217 enrolled 203 healthy volunteers who all received a single 40 mg dose of ABP 501 US-licensed Humira, or EU-approved Humira of Study Day 1. Each dose of study drug was administered as a single 0.8 mL SC injection by PFS.

Study 262

Study 262 enrolled 526 subjects with active RA who were randomized to receive ABP 501 or US-licensed Humira 40 mg EOW administered as a 0.8 mL SC injection by PFS. Subjects received a mean (±SD) dose of 456 mg (±75) of study drug over the course of the study with similar median doses between treatment arms: ABP 501-treated subjects (449 mg ±90) compared to US-licensed Humira (463 mg ±56). The mean (±SD) duration of exposure was also similar between treatment arms (147 days ±31 vs. 151 days ±19, respectively).

Study 263

Study 263 enrolled 350 subjects with active PsO of whom 347 received study drug. Subjects received an initial loading dose of ABP 501 or EU-approved Humira 80 mg SC on Study Day 1 followed by 40 mg SC EOW beginning on Week 2 as a 0.8 mL SC injection by PFS. The mean (±SD) dose received by subjects through Week 16 was 350 mg (±33) and was similar between treatment arms. The mean duration of exposure was 90 days (±13) for ABP 501-treated subjects and 90 days (±9) for EU-approved Humira-treated subjects.

After Week 16, a total of 308 subjects were administered at least one dose of study drug following re-randomization with 152 subjects continuing to receive ABP 501 (ABP 501/ABP 501), 79 subjects continuing to receive EU-approved Humira (EU-approved Humira/EU-approved Humira), and 77 subjects undergoing single transition from EU-approved Humira to ABP 501 (EU-approved Humira/ABP 501). The total mean (±SD) dose of study drug received by subjects was 631 mg (±132) with similar mean doses between treatment arms. The mean (±SD) duration of exposure was also similar between treatment arms (212 days ±44 vs. 209 days ±51 vs. 211 days ±46, respectively).

The overall exposure of patients was balanced between the two treatment arms (ABP 501 and EU-approved Humira) throughout the controlled and extension studies.

7.2.2 Explorations for Dose Response

Given that the dose and dosing regimen of ABP 501 is identical to the US-licensed Humira, dose-exploration studies were not conducted.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to the current BLA.

7.2.4 Routine Clinical Testing

Not applicable to the current BLA.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance and interaction workup studies were conducted for this application. For further details, please refer to Clinical Pharmacology team review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

ABP 501 is a proposed biosimilar to US-licensed Humira. The safety profile of ABP 501 was assessed in the context of the known adverse event profile of US-licensed Humira as well as conventional DMARDs and biologics.

7.3 Major Safety Results

A summary of AEs across the controlled studies is found Table 17. Similar trends in safety were noted for the extension studies (data not shown).

Table 17. Summary of TEAEs: Controlled Studies

	Rheumatoid Arthritis Study 262		**Plaque Psoriasis Study 263**		**Healthy Subjects Study 217**		
	ABP 501 40 mg (n=264)	US-ADA 40 mg (n=262)	ABP 501 40 mg (n=174)	EU-ADA 40 mg (n=173)	ABP 501 40 mg (n=67)	US-ADA 40 mg (n=69)	EU-ADA 40 mg (n=67)
AEs, n (%)	132 (50)	143 (55)	117 (67)	110 (64)	39 (58)	33 (48)	46 (69)
SAEs, n (%)	10 (4)	13 (5)	6 (3)	5 (3)	0	0	1 (2)
Withdrawal due to AEs, n (%)	5 (2)	2 (1)	7 (4)	5 (3)	0	0	1 (2)
Infections, n (%)	61 (23)	68 (26)	59 (34)	58 (34)	9 (13)	4 (6)	9 (13)
Malignancies, n (%)	1 (<1)	1 (<1)	1 (1)	1 (1)	0	0	0
Liver Enzyme Elevations, n (%)	13 (5)	10 (4)	4 (2)	2 (1)	0	0	4 (6)
Injection site reactions, n (%)	6 (2)	13 (5)	3 (2)	26 (5)	1	0	1
Anaphylaxis, n	0	0	1	0	0	0	0
Death, n	0	0	0	0	0	0	0

Source: FDA analysis of data from Amgen 351(k) BLA submission
US-ADA: US-licensed Humira; EU-ADA: EU-approved Humira; AE: adverse event; SAE: serious adverse event

No new safety signals were identified in the ABP 510 treatment arm compared to the known adverse event profile of adalimumab. Overall, there were no major differences in AEs, SAEs, AEs leading to discontinuations, and deaths between the two treatment groups. Infections were the most common adverse event in all treatment groups. No deaths were reported in the ABP 501 development program.

7.3.1 Deaths

No deaths were reported in the ABP 501 development program.

7.3.2 Nonfatal Serious Adverse Events

Study 217

A single SAE was reported during Study 217 involving a 28-year-old woman who developed acute abdominal pain due to a dermoid cyst that required a laparoscopic ovarian cystectomy. The subject was subsequently discontinued from the study.

Study 262

A total of 27 SAEs were reported for 23/526 (4%) subjects enrolled in Study 262 with similar proportions of subjects in the ABP510 (10/264 subjects, 4%) and US-licensed Humira (13/262 subjects, 5%) treatment arms. Sepsis was reported as a SAE in two ABP510-treated subjects and was the only SAE to be reported in more than 1 subject. Single cases of perforated appendicitis, cardiopulmonary failure, cerebrovascular accident, enterocolitis, humerus fracture, hypersensitivity, hypertension, lymphadenopathy, meniscus injury, peritoneal abscess, pneumonia, and venous thrombosis of the limb accounted for the remainder of SAEs in ABP 510-treated subjects. A total of 13 subjects treated with US-licensed Humira reported single cases of acute myocardial infarction, bacterial arthritis, congestive cardiac failure, corneal graft rejection, foot deformity, gastroenteritis, large intestine obstruction, myocardial infarction, osteoarthritis, fungal pneumonia, pseudarthrosis, thoracic vertebral fracture, and Wolff-Parkinson-White syndrome.

Study 263

Twelve SAEs were reported for 11/347 (3%) subjects who received study drug from baseline to Week 16. A total of 6/174 (3%) ABP 501-treated subjects reported an SAE compared to 5/173 (3%) of subjects treated with EU-approved Humira. No SAE occurred in more than one subject. Reported SAEs for the ABP 501-treatment arm included acute myocardial infarction, appendicitis, arrhythmia, chronic obstructive pulmonary disease, hypersensitivity, lentigo maligna, and postoperative abscess. EU-approved Humira-treated subjects reported one case each of bronchitis, metrorrhagia, osteoarthirits, patellofemoral pain syndrome, and syncope.

Fourteen SAEs were reported for 12/308 (4%) subjects after Week 16 to the end of the study including 4/152 (3%) in the ABP 501/501 treatment arm (cerebral ischemia, coronary artery disease, diverticulitis, drug-induced liver injury, dyslipidemia, rotator cuff syndrome), 4/79 (5%) subjects in the EU-approved Humira/EU-approved Humira arm (depression, headache, intervertebral disc protrusion, migraine), and 4/77 (5%) subjects in the EU-approved Humira/ABP 501 treatment arm (ophthalmic herpes zoster, ovarian cyst, transient ischemic attack, urinary tract infection). No SAE was reported in more than one subject.

Overall, the clinical development program for ABP 501 demonstrated a small number of SAEs that were consistent in the type and frequencies of SAEs reported for US-licensed and EU-approved Humira. The proportion of subjects who experienced at least one SAE was similar in all three studies between the two treatment arms. Additionally, and the types of SAEs reported spanned across the system organ classes and showed a similar distribution with minor numerical differences between each group. There was no notable difference in the incidence of SAEs following transition from EU-approved Humira to ABP 501 in subjects with PsO compared to the other treatment arms.

7.3.3 Dropouts and/or Discontinuations

Study 217

One subject was discontinued from Study 217 at Day 18 due to a SAE of a dermoid cyst (discussed in Section 7.3.2).

Study 262

A total of 7/264 (2%) ABP 501-treated subjects and 2/262 (1%) of subjects from the US-licensed Humira treatment arm experienced 11 AEs that led to discontinuation from the Study 262. The types of AEs were varied and did not occur in more than one subject. ABP 501-treated subjects reported AEs of abdominal pain, cerebrovascular accident, depression, hypersensitivity, lymphadenopathy, peritoneal abscess, pneumonia, rash,

and sepsis. Subjects from the US-licensed Humira treatment arm reported one case each of congestive cardiac failure and corneal graft rejection.

Study 263

From baseline to Week 16, a total of 12/247 (4%) subjects randomized to the ABP 501 treatment arm and 5/173 (3%) of subjects from the US-licensed Humira treatment arm experienced an AE that led to discontinuation from the study. The only AEs reported in more than one subject were psoriasis (ABP 501, n=1; US-licensed Humira, n=2) and increased hepatic enzymes (ABP 501, n=2). The remainder of AEs included arrhythmia, erectile dysfunction, hypersensitivity, latent T, lentigo maligna, psoriatic arthropathy, and rash.

A total of 7/308 (2%) subjects reported an AE that led to discontinuation from the study after Week 16 through the end of study, including 4/152 (3%) subjects from the ABP 501/ABP 501 treatment arm, 1/79 (1%) subjects from the US-licensed Humira/ US-licensed Humira arm, and 2/77 (3%) subjects who made a single transition from US-licensed Humira/ABP 501. Psoriasis was the only AE reported in more than one subject.

Overall, the proportion of subjects who were discontinued from a clinical study due to an AE was small. The types and frequencies of AEs were similar in all three studies between the two treatment arms and there were no obvious safety signals among the types of AEs that lead to subject withdrawal. There was no notable difference in the incidence of AEs leading to discontinuation following transition from EU-approved Humira to ABP 501 in Ps subjects.

7.3.4 Significant Adverse Events

Adverse events of special interest (AESI)

In the context of the known adverse-event profile of US-licensed Humira, the following risks were characterized as adverse events of special interest. (AESI):

1. Infections
2. Malignancies
3. Hypersensitivity/anaphylaxis as per Sampson's criteria (Sampson et.al, 2006)
4. Demyelination
5. Hematological reactions
6. Heart Failure
7. Lupus-like syndromes
8. Liver Enzyme Elevations
9. Injection Site Reactions

The Applicant provided an integrated safety summary with a pooled analysis of AESI for Studies 262 and 263. In the two controlled studies, the incidence rates of AESI were similar between the two treatment groups across both studies with a few exceptions that were driven by small numerical imbalances. The safety results from Studies 262 and 263 were overall consistent with the safety observed with US-licensed Humira.

Infections

An infection-related AE was defined as any AE in the SOC Infections and Infestations. The known safety profile of US-licensed Humira includes an increased risk of infection and certain patient populations may be at greater risk, e.g., patients greater than 65 years old, comorbid medical conditions, and concomitant medications. Therefore, to limit the risk of infection-related AEs, subjects were excluded from the phase 3 clinical studies if they had a known history of active TB; active infection or history of infection within 28 days of baseline; serious infection requiring hospitalization within eight-weeks of baseline; recurrent or chronic infections; known history of infection with HIV; or hepatitis B surface antigen or hepatitis C antibody positivity.

Study 262

Infection AEs were reported in 129/526 (25%) of subjects treated in Study 262 with similar frequencies in the ABP 501 and US-licensed Humira treatment arms, 23% and 26%, respectively. The most commonly reported infections (≥2% of subjects) were nasopharyngitis, upper respiratory tract infection, and bronchitis. All other infection AEs were reported with a frequency <2% of subjects. Five subjects reported eight infection SAEs all of which were reported as single events in single subjects except for sepsis that was reported for two subjects in the ABP 501 treatment arm. There was a single case of an opportunistic infection, reported as cytomegalovirus, in the ABP 501 treatment arm. No cases of active of TB were reported.

Study 263

A total of 117/347 (34%) of subjects from baseline through Week 16 reported an infection-related AE with similar frequencies in the ABP 501 (34%) and EU-approved Humira (34%) treatment arms. The most frequently reported infections (≥2% of subjects) were nasopharyngitis, upper respiratory tract infection, and rhinitis. All other infection AEs were reported with a frequency <2% of subjects. Three subjects experienced an infection-related SAE, all of which were reported as single events, and included appendicitis and postoperative abscess (ABP 501) and bronchitis (EU-approved Humira). No opportunistic infections were reported during the first 16-weeks of the study and no cases of active of TB were reported.

After Week 16 and through the end of study the applicant reported 133/308 (43%) of subjects experienced an infection AE with relatively similar frequencies between the ABP 501/ABP 501 (67/152, 44%), EU-approved Humira/EU-approved Humira (29/79, 37%), and EU-approved Humira/ABP 501 (37/77, 48%) treatment arms. The most

commonly reported infections (≥2% of subjects) were nasopharyngitis, upper respiratory tract infection, and sinusitis.

Three subjects experienced an infection-related SAE, all of which were reported as single events, and included diverticulitis (ABP 501/ABP 501), and ophthalmic herpes zoster and urinary tract infection (EU-approved Humira/ABP 501). No opportunistic infections were reported during the first 16-weeks of the study.

Overall, the types and frequency of infections were consistent with those reported for US-licensed and EU-approved Humira.

Malignancies

A greater number of malignancies have been observed in adults treated with TNF-inhibitors, including US-licensed Humira. More cases of lymphoma have been observed in TNF-inhibitor-treated subjects compared to control-treated subject during the controlled portions of clinical trials in adults. Additionally, postmarketing cases of acute and chronic leukemia have been reported in association with the use of TNF-inhibitors in RA and other indications.

Malignancy AEs were determined using the search strategy for the MedDRA SMQ malignancies. Subjects were excluded from the phase 3 studies if they had any malignancy within the previous five years except for subjects considered to be fully treated for cutaneous squamous carcinoma, basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.

Study 262

Three malignancies were reported in two subjects that were classified as nonmelanoma skin cancers. One subject from the ABP 501 treatment arm was diagnosed with two skin cancers (basal cell and squamous cell carcinoma) and one US-licensed Humira-treated subject was diagnosed with a squamous cell carcinoma. All skin cancers were treated and

Study 263

Two cases of malignancy were reported from baseline through Week 16. One ABP 501-treated subject was diagnosed with lentigo maligna on Day 78 and resolved on Day 93. This event was reported as a SAE and led to the subject's discontinuation from the study. One subject in the EU-approved Humira treatment arm was diagnosed with Bowen's disease that was reported on Day 22 and resolved on Day 40 following surgical excision.

Following Week 16, a single case of malignancy was reported as squamous cell carcinoma that occurred in a subject from the ABP 501/ABP 501 treatment arm.

Overall, the types and frequency of malignancies were consistent with those reported for US-licensed and EU-approved Humira.

Hypersensitivity, Including Anaphylaxis

US-licensed Humira is known to cause allergic reactions such as rash, anaphylaxis, fixed drug reaction, non-specific drug reaction, and urticaria. The term "hypersensitivity" is often used as an umbrella term to capture a large number of conditions related to an exaggerated response of the body to a foreign agent.

Hypersensitivity treatment-emergent adverse events were determined using the search strategy for the MedDRA SMQ hypersensitivity. The aim of this SMQ is to support database searches for potential drug related hypersensitivity/allergic reactions and is designed to retrieve all types of cases possibly related to hypersensitivity/allergic reactions.

Study 262

Thirty-one cases of hypersensitivity were reported in 24/526 (5%) subjects with 18 of the events occurring in 14/264 (5%) ABP 501-treated subjects and 13 of the events occurring in 10/262 (4%) of subjects treated with US-approved Humira. The most commonly reported (≥1% of subjects) hypersensitivity-related AE was rash (2% and <1%, respectively). All other hypersensitivity-related AEs occurred in <1% of subjects. Hypersensitivity AEs that occurred in more than one subject included rash, erythematosus rash, allergic dermatitis, and urticaria. Three events (ABP 501, n=2; US-approved Humira, n=1) resulted in discontinuation of study drug and were reported as rash a hypersensitivity NOS (ABP 501) and injection site eczema (US-licensed Humira).

Study 263

Seventeen hypersensitivity AEs were reported in 15/347 (4%) subjects with 8/174 (5%) ABP 501-treated subjects and 7/173 (4%) EU-approved Humira-treated subjects. The most frequently reported (≥1% of subjects) hypersensitivity-related AEs were eczema, allergic conjunctivitis, contact dermatitis, and rash. One AE in the ABP 501 treatment arm led to the discontinuation from study.

After Week 16 and through the end of the study, 16 AEs of hypersensitivity in 13/208 (4%) subjects were reported in the ABP 501/ABP 501 (8/152, 5%), EU-approved Humira/EU-approved Humira (2/79, 2%), and EU-approved Humira/ABP 501 (3/77, 4%) treatment arms. None of the events were reported as serious or led to study discontinuation.

A single case of anaphylaxis meeting the Sampson criteria (2006) was identified in a ABP 501-treated subject. The subject was a 47-year-old man with an ongoing history of asthma, hypertension, diabetes mellitus, obesity, and elevated liver enzymes. On Day 93, the subject developed acute dyspnea and facial pruritis approximately six hours after receiving his SC injection of study drug. The subject was brought emergently to the hospital and found to have an oxygen saturation of 84% on room air. A CT scan demonstrated pneumonia and pulmonary infarct and a pulmonary embolism could not be ruled out. The subject received appropriate treatment and recovered on Day 95 and was discontinued from the study.

Overall, there was a low frequency of hypersensitivity reactions, which in general, were consistent in the type and frequencies of hypersensitivity-related AEs reported for US-licensed and EU-approved Humira. There was only a single case of anaphylaxis reported in the ABP 501 development program that may have been confounded by underlying comorbidities. There was no notable difference in the incidence of hypersensitivity reactions following transition from EU-approved Humira to ABP 501 in Ps subjects compared to the other treatment arms.

Demyelinating Diseases

No demyelinating disease-related AEs were reported for subjects in Studies 262 or 263.

Hematological Reactions

Cases of clinically significant cytopenias, including rare reports of pancytopenia and aplastic anemia, have been reported with TNF-inhibitors, including US-licensed Humira. Hematologic-related AEs were determined based on the search strategy for the MedDRA SMQ hematopoietic cytopenias. Subjects were excluded from the phase 3

studies if they had hematological laboratory abnormalities of hemoglobin < 90 g/L, platelet count <100 x 109/L, or white blood cell count <3 x 109/L.

Study 262

A total of ten hematologic-related AEs were reported in Study 262 occurring in 5/264 (2%) ABP 501-treated subjects and 5/262 (2%) subjects of the US-licensed Humira treatment arm. The most frequently reported (≥1% of subjects) AE was leucopenia. Other hematologic AEs occurred as single cases and included neutropenia (ABP 501), and thrombocytopenia and decrease in white blood cell count (US-approved Humira).

Study 263

The incidence of hematologic reactions in the Study 263 was low. Five AEs, primarily neutropenia (1.2%), through Week 16 were reported in three subjects, all occurring in the EU-approved Humira treatment arm. None of the AEs were reported as serious.

Following Week 16, four hematologic AEs were reported in 2/308 (1%) subjects with two AEs occurring in the EU-approved Humira continued treatment arm and two AEs occurring in patients who underwent a transition from the EU-approved Humira to ABP 501. None of the AEs were reported as serious.

Overall, the types and frequency of infections were consistent with those reported for US-licensed and EU-approved Humira and there was no notable difference in the incidence of hematologic AEs following transition from EU-approved Humira to ABP 501 in Ps subjects compared to the other treatment arms.

Heart Failure

Cases of new or worsening congestive heart failure, myocardial infarction, and cerebrovascular accidents have been reported in patients treated with US-licensed

and/or EU-approved Humira. Heart failure AEs were determined based on the search strategy for the MedDRA SMQ cardiac failure. Subjects with New York Heart Association Grade 3 or 4 heart failure were excluded from participating in the phase 3 studies.

Study 262

Four reports of cardiac failure were identified in 3/526 (1%) subjects (ABP 501, n=1; US-approved Humira, n=2). A single case of cardiopulmonary failure (ABP 501) and congestive cardiac failure (US-approved Humira) were reported as SAEs. The subject with Grade 4 cardiopulmonary failure had resolution of symptoms following treatment and did not require discontinuation for the study or study drug.

Study 263

No AEs related to heart failure were reported for subjects during Study 263.

Lupus-like Syndrome

No lupus-like syndrome AEs were reported for subjects in Studies 262 or 263.

Liver Enzyme Elevations

A comprehensive search SMQ using drug related hepatic disorders was used to identify liver enzyme elevation-related AEs. Subjects with AST and/or ALT values ≥2 times the upper limit of normal at baseline were excluded from the phase 3 studies.

Study 262

A total of 31 liver enzyme elevation AEs were reported in 23/526 (4%) subjects with 18 AEs reported in 13/264 (5%) of ABP 501-treaeted subjects and 13 AEs reported in 10/262 (4%) subjects treated with US-licensed Humira (Table 18). None of the 31 AEs

were associated with bilirubin that would cause concern regarding drug-induced liver injuries according to Hy's law.

Table 18. Study 262: Liver Enzyme Elevation AEs by Preferred Term

	Rheumatoid Arthritis	
	Study 262	
Preferred Term	ABP 501 (N=264) n (%)	US-ADA (N=262) n (%)
All Liver Enzyme Elevations AEs	13 (5)	10 (4)
ALT increased	7 (3)	3 (1)
GGT increased	3 (1)	2 (1)
AST increased	3 (1)	1 (<1)
Transaminases increased	1 (<1)	3 (1)
Hepatic enzyme increased	1 (<1)	1 (<1)
ALT abnormal	1 (<1)	0
AST abnormal	1 (<1)	0
GGT abnormal	0	1 (<1)
Liver function test abnormal	0	1 (<1)

Source: FDA analysis of data from Amgen 351(k) BLA submission
US-ADA: US-licensed Humira; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase

Study 263

Six events related to liver enzyme elevations were identified in 6/347 (2%) subjects consisting of 4/174 (2%) ABP 501-treated subjects and 2/173 (1%) subjects in the EU-approved Humira treatment arm. One subject from each treatment arm experienced a grade 3 elevated liver enzymes AE, while the remaining events were reported as grade 1 or 2. Two ABP 501-treated subjects with reported increased hepatic enzymes were discontinued from the study. None of liver enzyme elevations met the criteria for an SAE.

Seventeen elevated liver enzyme AEs were reported after Week 16 in 13/308 (4%) subjects (Table 19). A total of 9/152 (6%) subjects from the ABP 501/ABP 501 treatment arm, 2/79 (3%) subjects from the EU-approved Humira/EU-Humira treatment

arm, and 2/77 (3%) subjects from the EU-approved Humira/ABP 501 treatment arm. One subject randomized to the ABP 501/ABP 501 treatment arm experienced an SAE reported as drug-induced liver injury and was subsequently discontinued from the study. The subject had reported increases in ALT and AST levels but no changes in bilirubin. All other reported increased liver enzyme AEs were reported as grade 1 or 2.

Table 19. Study 263 post-Week 16: Liver Enzyme Elevation AEs by Preferred Term

	Plaque Psoriasis		
	Study 263 post-week 16		
Preferred Term	ABP 501/ABP 501 (N=152) n (%)	EU-ADA/EU-ADA (N=79) n (%)	EU-ADA/ABP 501 (N=77) n (%)
All Liver Enzyme Elevations AEs	9 (6)	2 (3)	2 (3)
ALT increased	5 (3)	0	1 (1)
GGT increased	4 (3)	0	0
AST increased	2 (1)	0	0
Drug-induced liver injury	1 (1)	0	0
Hepatic enzyme increased	0	0	1 (1)
Hepatic function abnormal	0	1 (1)	0
Non-alcoholic steatohepatitis	1 (1)	0	0
Transaminases increased	0	1 (1)	0

Source: FDA analysis of data from Amgen 351(k) BLA submission
EU-ADA: EU-approved Humira; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase

Overall, the types and frequency of liver enzyme elevation AEs were consistent with those reported for US-licensed and EU-approved Humira and there was no notable difference in the incidence of elevated liver enzyme-related AEs following transition from EU-approved Humira to ABP 501 in Ps subjects compared to the other treatment arms.

Injection Site Reactions

Any AE that occurred at or around the site of an injected study drug was considered an injection site reaction. All terms from the high level term of Injection Site Reactions, plus

other selected terms from other categories, were used in the search for the injection site reaction adverse events.

Study 262

A total of 48 AEs of injection site reactions were identified in 19/526 (4%) subjects. Of these, nine events occurred in 6/264 (2%) subjects enrolled in the ABP 501 treatment arm and 39 events occurred in 13/262 (5%) in the US-licensed Humira treatment arm. None of injection site reactions were reported as serious and one AE in a subject treated with US-licensed Humira developed injection site eczema and was discontinued from the study drug. The most frequent (≥1% of subjects) types of injection site reactions included injection site erythema, injection site reaction, and injection site pruritis (data not shown).

Study 263

Thirty events of injection site reactions were identified in 12/347 (4%) of subjects with four of the events reported in 3/174 (2%) ABP 501-treated subjects and 26 events in 9/173 (5%) of subjects in the EU-approved Humira treatment arm. The most frequent AE related to injection site reactions during the period was injection site pain all of which occurred in the EU-approved Humira arm. The leading cause of injection site reactions for ABP 501 subjects was injection site erythema. None of the reported AE were serious and no event led to discontinuation from the study drug or study.

Following Week 16, a total of eight injection site reaction AEs were reported in 5/308 (2%) of subjects. Two of these eight events occurred in 2/152 (1%) subjects in the ABP 501/ABP 501 treatment arm, six events in 3/79 (4%) occurred in the EU-approved Humira/EU-approved Humira treatment arm, and no events occurred in the subjects who underwent transition in the EU-approved Humira/ABP 501 treatment arm. None of the reported AE were serious and no event led to discontinuation from the study drug or study.

Overall, the types and frequency of injection site reaction-related AEs were consistent with those reported for US-licensed and EU-approved Humira and there was no notable difference in the incidence of injection site reactions following transition from EU-approved Humira to ABP 501 in Ps subjects compared to the other treatment arms.

Summary of AESI

Overall, the incidence of AESI between the ABP 501, US-licensed Humira, and EU-approved Humira treatment arms was similar across the controlled and transition studies in the RA and Ps populations. Non-clinically significant numerical imbalances were noted in several AESI categories, however, the number of subjects identified in each case was small and there was no consistent pattern of types or frequency of AEs occurring in any one treatment arm.

Evaluation and review of the safety data did not identify any new safety signals with the administration of ABP 501. The safety risks identified are well within the known adverse event profile of US-licensed Humira. Most common adverse events include infection, and infusion-related reactions. The safety data support the demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira in the populations studied. Transitioning of non-treatment naïve patients, i.e., patients previously treated with EU-approved Humira, to ABP 501 does not appear to result in an increase of clinically significant adverse reactions.

7.3.5 Submission Specific Primary Safety Concerns

Please refer to adverse events of special interest.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 217

As shown in Table 20, 118/203 (58%) subjects experienced a TEAE. The most frequently reported TEAE reported in ≥5% of subjects by preferred term were headache, oropharyngeal pain, sinus congestion, nasopharyngitis, and nausea.

Table 20. Study 217: TEAEs in ≥5% of Subjects in any Treatment Arm

	Study 20110217		
Preferred Term	ABP 501 (N=67) n (%)	US-ADA (N=69) n (%)	EU-ADA (N=67) n (%)
Subjects with any TEAE	38 (58)	33 (48)	46 (69)
Headache	19 (28)	16 (23)	13 (19)
Oropharyngeal pain	6 (9)	6 (9)	3 (5)
Sinus congestion	6 (9)	6 (9)	0
Nasopharyngitis	4 (6)	0	7 (10)
Nausea	5 (8)	2 (3)	4 (6)
Diarrhea	1 (2)	1 (1)	8 (12)
Vomiting	1 (2)	2 (3)	5 (8)
Back Pain	1 (2)	1 (1)	5 (8)
Dizziness	1 (2)	1 (1)	4 (6)
Dysmenorrhea	1 (2)	4 (6)	1 (2)
Nasal congestion	1 (2)	4 (6)	0

Source: FDA analysis of data from Amgen 351(k) BLA submission
US-ADA: US-licensed Humira; EU-ADA: EU-approved Humira

Study 262

A total of 275/526 (52%) of subjects enrolled in Study 262 experienced TEAEs with similar frequencies and types of events between treatment arms (Table 21). Nasopharyngitis was the only TEAE that was reported in greater than five percent of subjects, followed by headache, arthralgia, cough, and upper respiratory tract infection. Most AEs were mild or moderate in severity. A total of 6/262 (2%) ABP 501-treated-subjects experienced grade 3 AEs and three subjects experienced grade 4 AEs including 2 cases of sepsis and single events of perforated appendicitis, peritoneal

abscess, meniscus injury, and cardiopulmonary failure. Sixteen US-licensed Humira-treated subjects reported grade 3 AEs and one grade 4 AE of myocardial infarction.

Table 21. Study 262: TEAEs in ≥2% of Subjects in any Treatment Arm

	Study 20120262	
Preferred Term	ABP 501 (N=264) n (%)	US-ADA (N=262) n (%)
Subjects with any TEAE	132 (50)	143 (55)
Nasopharyngitis	17 (6)	19 (7)
Headache	12(5)	11 (4)
Arthralgia	8 (3)	9 (3)
Cough	7 (3)	8 (3)
Upper respiratory tract infection	4 (2)	10 (4)
Hypertension	6 (2)	5 (2)
Bronchitis	6 (2)	5 (2)
Back pain	5 (2)	6 (2)
ALT increase	7 (3)	3 (1)
Diarrhea	6 (2)	4 (2)
Rheumatoid arthritis	4 (2)	6 (2)
Pharyngitis	2 (1)	7 (3)

Source: FDA analysis of data from Amgen 351(k) BLA submission
US-ADA: US-licensed Humira

Study 263

Through Week 16 of the study, 227/347 (65%) subjects experienced a TEAE with similar frequency and types of AEs observed between treatment arms (Table 22). TEAEs reported in more than five percent of subjects included nasopharyngitis, headache, and upper respiratory tract infection. The majority of AEs were mild or moderate in severity. Five ABP 501-treated subjects experienced grade 3 events and three subjects experienced grade 4 events including appendicitis, arrhythmia, and hypersensitivity. Five subjects in the EU-approved Humira treatment arm experienced grade 3 events and no grade 4 events.

Table 22. Study 263: TEAEs in ≥2% of Subjects in any Treatment Arm through Week 16

	Study 20120263 Baseline through Week 16	
Preferred Term	ABP 501 (N=174) n (%)	EU-ADA (N=173) n (%)
Subjects with any TEAE	117 (67)	110 (64)
Nasopharyngitis	25 (14)	27 (16)
Headache	12 (7)	18 (10)
Upper respiratory tract infection	9 (5)	9 (5)
Arthralgia	5 (3)	7 (4)
Pruritis	3 (2)	6 (4)
Rhinitis	3 (2)	6 (4)
Back pain	7 (4)	1 (1)
Toothache	2 (1)	5 (3)
Nausea	3 (2)	4 (2)
Injection site pain	0	5 (3)
Dyspnea	1 (1)	4 (2)
Abdominal pain	1 (1)	4 (2)
Oropharyngeal pain	0	5 (3)

Source: FDA analysis of data from Amgen 351(k) BLA submission
EU-ADA: EU-approved Humira

Following Week 16, 214/308 (70%) of subjects were reported to have experienced a TEAE with similar rates across the three treatment arms. Table 23 shows reported TEAEs in greater than five percent of subjects in all treatment arms. The majority of AEs were mild or moderate in severity. Seven, two, and three subjects each experienced a grade 3 AE in the ABP 501/ABP 501, EU-approved Humira/EU-approved Humira, and EU-approved Humira/ABP 501 treatment arms, respectively. No grade 4 AEs were reported.

Table 23. Study 263: TEAEs in ≥5% of Subjects in any Treatment Arm Post Week 16

	Study 20120263 Post Week 16

Preferred Term	ABP 501/ABP 501 (N=152) n (%)	EU-ADA/EU-ADA (N=79) n (%)	EU-ADA/ABP 501 (N=77) n (%)
Subjects with any TEAE	57 (38)	33 (42)	36 (48)
Nasopharyngitis	25 (16)	14 (18)	18 (23)
Upper respiratory tract infection	9 (6)	6 (8)	7 (9)
Psoriasis	10 (7)	5 (6)	4 (5)
Headache	5 (3)	8 (10)	2 (3)
Diarrhea	3 (2)	4 (5)	8 (10)
Arthralgia	4 (3)	5 (6)	2 (3)
Back pain	5 (3)	5 (6)	1 (1)
Source: FDA analysis of data from Amgen 351(k) BLA submission US-ADA: US-licensed Humira; EU-ADA: EU-approved Humira			

In summary, the incidence and types of common adverse events were similar between the treatment arms and were consistent with the known safety profile of US-licensed Humira and EU-approved Humira. No new safety signals have been identified further supporting the demonstration that there are no clinically meaningful differences between APB501 and US-licensed Humira in the indications studied.

7.4.2 Laboratory Findings, Vital Signs and Electrocardiograms (ECGs)

The distribution of laboratory findings, vital signs and electrocardiogram (ECGs) findings was balanced between the APB501, US-licensed Humira, and EU-approved Humira arms. No new or unexpected laboratory findings were reported in the ABP 501 clinical program.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies with ABP 501 have been submitted in the BLA.

7.4.6 Immunogenicity

An application submitted under section 351(k) of the PHS Act contains, among other things, information demonstrating that the biological product is biosimilar to a reference

product based upon data derived from "a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product."[16] Immune responses against therapeutic biological products are a concern because they can negatively impact the drug's pharmacokinetics, safety, and efficacy. Unwanted immune reactions to therapeutic biological products are mostly caused by antibodies against the drug (anti-drug antibodies; ADA). Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of ADA (including neutralizing antibodies, NAb) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the ABP 501 clinical studies, all samples were screened with a two-tiered approach (screening and specificity) for binding ADA activity using a sensitive and drug-tolerant bridging immunoassay. Samples were also analyzed to detect drug-specific ADA; thus, all samples were tested for binding ADA against ABP 501, US-licensed Humira, and EU-approved Humira. Samples that tested positive in either assay were considered positive for the immunogenicity assessment. Positive samples for binding ADAs were then tested for neutralizing activity and titers against ABP 501 using a validated method.

[16] Section 351(k)(2)(A)(i)(I) of the PHS Act.

Immunogenicity Results

Study 217

No pre-existing ADAs were detected in subject samples at baseline. Table 24 shows the incidence of ADAs throughout the study following a single dose of 40 mg SC of study drug. Importantly, the rate of neutralizing ADA was similar between all three treatment arms at 18%, 22%, and 21%, respectively.

Table 24. Summary of Binding Antidrug Antibody Results, Study 217

	Study 217 in Healthy Subjects		
Timepoint	ABP 501 (N=67) n (%)	US-licensed Humira (N=69) n (%)	EU-approved Humira (N=67) n (%)
Day 1, Predose	0	0	0
Day 16	12 (18%)	12 (17%)	23 (35%)
Day 29	21 (32%)	27 (42%)	27 (42%)
End of Study	29 (43%)	34 (50%)	34 (51%)
Source: FDA analysis of data from Amgen 351(k) BLA submission			

Study 262

The incidence of subjects developing ADAs for the ABP 501 and US-licensed Humira treatment arms was 101/254 (38%) and 100/262 (38%), respectively. The incidence of neutralizing ADAs was similar between treatment arms at 9% and 11%, respectively. Overall, the incidence rates of ADA and neutralizing ADA were similar between ABP 501 and US-licensed Humira.

Study 263

At baseline, prior to receiving study drug, 3/347 (1%) of subjects (ABP 501, n=1; EU-approved Humira, n=2) were found to be ADA-positive but no neutralizing ADAs were detected. Through Week 16, of subjects who were negative for ADAs at baseline, 99/174 (55%) ABP-501-treated subjects developed binding ADAs and 110/173 (64%) of subjects randomized to EU-approved Humira. Of these, 17/174 (10%) treated with ABP

501 were positive for neutralizing ADAs and 24/173 (14%) treated with EU-approved Humira.

Overall, as summarized in Table 25, in studies 262 in RA and 263 in PsO patients, following repeat dosing the rates of immunogenicity, assessed as the proportion of binding and neutralizing ADA-positive patients at any time, were similar between the ABP 501 and US-licensed Humira (Study 262) and EU-approved Humira (Study 263) treatment groups for the duration of the studies. The rates of binding and neutralizing ADA positivity were also similar between patients who underwent a single transition from EU-approved Humira to ABP 501 and those who remained on EU-approved Humira in Study 263 in PsO patients. Further, the titers of neutralizing antibodies were similar between the treatment groups (data not shown).

Table 25. Summary of Binding and Neutralizing ADAs Following Repeat Dosing in Study 262 and Study 263

	Rheumatoid Arthritis Study 262		**Plaque Psoriasis Study 263**				
			Through Week 16		Week 16 to EOS		
	ABP 501 40 mg (n=264)	US-ADA 40 mg (n=262)	ABP 501 40 mg (n=174)	EU-ADA 40 mg (n=173)	ABP 501/ ABP 501 40 mg (n=152)	EU-ADA/ EU-ADA 40 mg (n=79)	EU-ADA/ ABP 501 40 mg (n=77)
Binding ADA-positive, n (%)	101 (38)	100 (38)	96 (55)	110 (64)	104 (68)	59 (75)	56 (73)
Neutralizing ADA-positive, n (%)	24 (9)	29 (11)	17 (10)	24 (14)	21 (14)	16 (20)	19 (25)

Source: FDA analysis of data from Amgen 351(k) BLA submission
US-ADA: US-licensed Humira; EU-ADA: EU-approved Humira; EOS: end of study

Assessment of the Impact of Immunogenicity

The development of anti-drug antibodies, including neutralizing ADAs, may have implications for both safety and efficacy.

To investigate the potential impact of the ADA on PK in healthy subjects, the FDA clinical pharmacology review team examined the relationship between ADA and exposure parameters in the PK similarity study 217. Following the single SC injection of 40 mg, the overall exposure (AUC) was approximately 20% to 30% lower for all 3 treatments in ADA-positive subjects compared to ADA-negative subjects, as summarized in **Table 26**. While the development of ADAs appears to increase clearance of the products, the impact of ADAs appeared to influence PK similarly following treatment with ABP 501, US-licensed Humira, and EU-approved Humira.

Table 26. Summary of PK Parameters in Study 217 by the Binding ADA Status

Parameter	C_{max} (ng/ml) GM [n] (GeoCV%)	AUC_{last} (µg.h/mL) GM [n] (GeoCV%)	AUC_{inf} (µg.h/mL) GM [n] (GeoCV%)
ADA positive			
ABP 501	3237 [36] (31.5%)	1726[36] (36.7%)	1831 [33] (27.3%)
US-licensed Humira	3214 [38] (33.0%)	1759 [38] (40.9%)	1782 [36] (41.6%)
EU-approved Humira	3333 [45] (31.8%)	1846 [44] (41.9%)	1874 [42] (42.9%)
ADA negative			
ABP 501	3311 [31] (29.1%)	2488 [31] (31.4%)	2627 [25] (36.9%)
US-licensed Humira	3172 [31] (32.8%)	2157 [31] (44.4%)	2114 [25] (34.8%)
EU-approved Humira	3059 [22] (28.1%)	2360 [22] (26.8%)	2502 [17] (32.6%)

Source: FDA analysis of data from Amgen 351(k) BLA submission
Abbreviations: ADA = antidrug antibody; GeoCV% = geometric mean coefficient of variation; GM = geometric mean; n = number of nonmissing observations

To investigate the potential impact of the ADA on PK in RA and PsO patients, the FDA clinical pharmacology review team examined the relationship between ADA and trough concentrations in Study 262 and Study 263. The overall steady-state trough concentrations by ADA status were evaluated at the closest comparable time points (i.e., week 12 [Study 262] and week 16 [Study 263]). While the development of ADAs appears to increase clearance of adalimumab products and decrease the serum concentrations of adalimumab, the impact of binding ADAs or neutralizing ADAs

appeared to influence PK similarly following treatment with ABP 501 versus treatment with US-licensed in Study 262 and EU-approved Humira in Study 263 (data not shown). The trough concentrations for ADA-negative and ADA-positive subgroups were consistent between ABP 501 and US-licensed Humira and EU-approved Humira treated groups in each study. In addition, the trough concentrations were consistent between studies (Study 262 and Study 263) with similar variability.

To investigate the potential impact of the ADA and the NAbs on comparative clinical outcomes, the FDA review team examined the relationship between ADA, primary efficacy endpoints, and select relevant safety outcomes such as hypersensitivity reactions and injections site reactions as summarized in Table 27 for Study 262 and in Table 28 for Study 263. We acknowledge that such analyses are exploratory in nature and limited by the small sample sizes within subgroups and the non-randomized nature of comparisons, as ADA status is a post-randomization variable and observed differences (or lack thereof) could be attributable to ADA formation or to other confounding variables.

Within each ADA subpopulation there were no notable differences between ABP 501 and US-licensed Humira (Study 262), and ABP 501 and EU-approved Humira (Study 263) in hypersensitivity and injection site reactions.

Table 27. Incidence of Clinical Responses and Safety Outcomes of Interest by ADA and Neutralizing ADA Status in Study 262 in RA at Week 24

	ABP 501 n/N (%)	US-licensed Humira n/N (%)	Difference (95% CI)
Binding ADA positive			
ACR20 response	74/101 (73)	69/100 (69)	4.3% (-8.2%, 16.8%)
Hypersensitivity reactions	7/101 (7)	1/100 (1)	5.9% (0.6%, 11.3%)
Injection site reactions	2/101 (2)	7/100 (7)	-5.0% (-10.7%, 0.7%)
Binding ADA negative			
ACR20 response	114/160 (71)	120/160 (75)	-3.8% (-13.5%, 6.0%)
Hypersensitivity reactions	7/160 (4)	9/160 (6)	-1.3% (-6.0%, 3.5%)
Injection site reactions	4/160 (3)	6/160 (4)	-1.3% (-5.1%, 2.6%)
Neutralizing ADA positive			
ACR20 response	15/24 (63)	21/29 (72)	-9.9% (-35.2%, 15.4%)
Hypersensitivity reactions	2/24 (8)	2/29 (7)	1.4% (-13.0%, 15.8%)
Injection site reactions	0/24 (0)	1/29 (3)	-3.4% (-10.1%, 3.2%)
Neutralizing ADA negative			
ACR20 response	173/237 (73)	168/231 (73)	0.3% (-7.8%, 8.3%)
Hypersensitivity reactions	12/237 (5)	8/231 (3)	1.6% (-2.1%, 5.3%)
Injection site reactions	6/237 (3)	12/231 (5)	-2.7% (-6.2%, 0.8%)
Source: FDA analysis of data from Amgen 351(k) BLA submission			

Table 28. Incidence of Clinical Responses and Safety Outcomes of Interest by ADA and Neutralizing ADA Status in Study 263 in PsO at Week 16

	ABP 501 Mean (SD) or n/N (%)	EU-approved Humira Mean (SD) or n/N (%)	Difference (95% CI)
Binding ADA positive	N=69	N=70	
% Improvement PASI	73.3 (24)	77.6 (22)	-5.3 (-13.1, 2.5)
Hypersensitivity reactions	3/69 (4%)	0/70 (0%)	4.3% (-0.5%), (9.2%)
Injection site reactions	1/69 (1%)	3/70 (4%)	-2.9% (-8.4%, 2.7%)
Binding ADA negative	N=97	N=97	
% Improvement PASI	89.2 (14)	91.6 (8)	-2.4 (-5.8, 0.9)
Hypersensitivity reactions	5/97 (5%)	5/97 (5%)	0% (-6.2%, 6.2%)
Injection site reactions	2/97 (2%)	6/97 (6%)	-4.1% (-9.7%, 1.4%)
Neutralizing ADA positive	N=17	N=24	
% Improvement PASI	48.5 (41)	61.9 (48)	-13.3 (-41.0, 14.4)
Hypersensitivity reactions	0/17 (0%)	0/24 (0%)	NA
Injection site reactions	1/17 (5%)	1/24 (4%)	1.7% (-12.0%, 15.5%)
Neutralizing ADA negative	N=155	N=149	
% Improvement PASI	84.5 (19)	86.5 (17)	-2.1 (-6.1, 1.9)
Hypersensitivity reactions	8/155 (5%)	7/149 (5%)	0.5% (-4.4%, 5.3%)
Injection site reactions	2/155 (1%)	8/149 (5%)	-4.1%, (-8.1%, -0.01%)
Source: FDA analysis of data from Amgen 351(k) BLA submission			

Of note, in the NAb positive subpopulations, the clinical responses were numerically lower in ABP 501 arms compared to comparator arms. In evaluating this observation, the FDA considered the following:

- The apparent differences in the treatment responses were seen also at Week 4, when the majority of the subjects were NAb negative indicating that these differences were not related to NAb status,
- There were no differences in NAb titers between ABP 501 and US-licensed Humira in Study 262, and between ABP 501 and EU-approved Humira in Study 263,
- The number of NAb positive subjects is small resulting in wide confidence intervals, and there were fewer NAb positive subjects on the ABP 501 arms,
- Exploratory post-hoc statistical models including the NAb by-treatment interaction were analyzed for both Studies and these analyses did not identify a statistically significant differential impact of NAb on efficacy between ABP 501 and comparator Humira products.

In light of these additional contextual pieces, the we not believe that the apparent numerical differences in clinical responses preclude a finding of no clinically meaningful differences between ABP 501, US-licensed Humira, and EU-approved Humira. Collectively, these data do not indicate that the ADA formation differentially impacts safety or efficacy between patients treated with ABP 501 and US-licensed Humira (Study 262) and EU-approved Humira (Study 263). Therefore, there are sufficient data supporting similar immunogenicity between ABP 501, EU-approved Humira, and US-licensed Humira and that immunogenicity data adds to the totality of the evidence to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable.

7.5.2 Time Dependency for Adverse Events

Not applicable.

7.5.3 Drug-Demographic Interactions

No significant safety signals were identified based on drug-demographic interactions.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable for this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Malignancies, including lymphoma, have been identified as potential risk with US-licensed Humira and other TNF-inhibitors as described in the Warnings and Precautions section of US-licensed Humira's USPI. There were a small number of malignancies reported in the ABP 501 clinical program that were similar in type of malignancies and balanced between the treatment arms as summarized in Section 7.3.4.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

7.7.1 120-day Safety Update

A 120-day safety update report was submitted on March 17, 2016 and provided additional information from the time of the NDA submission through September 10, 2015. There were limited data provided since the clinical studies included in this application were completed at the time of submission. However, the 120-day safety update included interim safety data of Study 20130258 (Study 258), which was an open-label, single-arm extension study of the parent Study 262.

Study 258 was conducted to evaluate the long term efficacy and safety of ABP 501 treatment for approximately 18 months in subjects who completed 6 months of treatment during Study 262 and transitioned from US-licensed Humira to ABP 501 or continued treatment with ABP 501. All data collected during the reporting period from April 23, 2014 through the last clinic visit on September, 10 2015 were included in the analysis. A total of 467 subjects were enrolled in the study and were included in the full analysis set. A total of 466 subjects received ≥1 dose of ABP 501. The median exposure of ABP 501 was 48 weeks (range: 0.1 to 68.3 weeks).

During the reporting period, the safety profiles seen in the original 26-week parent study were maintained in the open-label extension study up to 72 weeks, with a median ABP 501 exposure of 48 weeks. The safety profile of ABP 501 remained consistent with the known safety profile of US-licensed Humira and no new safety signals were identified.

8 Postmarket Experience

ABP 501 is not currently marketed; consequently, no postmarketing experience is available.

9 Appendices

9.1 Literature Review/References

FDA Guidance for Industry: "*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*."

FDA Guidance for Industry "*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.*"

Sampson HA et al., Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium *J Allergy Clin Immunol.* 2006 Feb;117(2):391-7

USPI Humira (adalimumab), June 2016

9.2 Labeling Recommendations

- Proprietary name
  The proposed proprietary names for ABP 501 are Amjevita and (b) (4) . These names have been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the names were acceptable.

- Non-proprietary/Proper name
  FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Amgren's ABP 501 product is necessary to distinguish this proposed product from US-licensed Humira (adalimumab). As explained in FDA's draft Guidance for Industry[17], Nonproprietary Naming of Biological Products, FDA

expects that a nonproprietary name that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance of biological products. FDA advised Amgen to provide proposed suffixes in accordance with the draft guidance. This information is pending at the time of this review.

- Physician Labeling

  At the time of this review, labeling discussions are ongoing.

9.3 Advisory Committee Meeting

As the first 351(k) BLA filed for a proposed biosimilar to US-licensed Humira, an Advisory Committee (AC) meeting was deemed necessary to obtain public input on issues related to analytical similarity assessment and extrapolation to non-studied indications. The AC meeting was held July 12, 2016. The committee agreed that (1) the analytical data are adequate to support a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, (2) that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the studied conditions of use (RA and PsO), and (3) that the Applicant provided sufficient scientific justification to support that there are no clinically meaningful differences for the additional indications sought for licensure. The committee members voted unanimously that, based on the totality of the evidence, ABP 501 should be licensed as a biosimilar product to US-licensed Humira for each of the following indications for which US-Humira is currently licensed and for which Amgen is seeking licensure (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, UC, and PsO).

[17] See the FDA draft guidance for industry on Nonproprietary Naming of Biological Products (August 2015). When final, this guidance will represent FDA's current thinking on this topic. The guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEITH M HULL
09/07/2016

NIKOLAY P NIKOLOV
09/07/2016
I concur.

DENISE COOK
09/07/2016

GORDANA DIGLISIC
09/07/2016

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

BLA 761024

ABP 501: Proposed Biosimilar to Adalimumab Filing Meeting

Internal Meeting

Clinical Team

January 7, 2016

Summary

- Sponsor: Amgen
- Product: ABP 501: Proposed Biosimilar to US-licensed Humira
- Proposed Indications: RA, JIA (≥4 yo), PsA, AS, CD, US, PsO (b) (4) (b) (4)
- Presentations:
  - PFS: 40 mg/0.8 mL
  - AI: 40 mg/0.8 mLAmgen preparing BLA for submission Q4 2015
- Recommendation
  - Fileable as a 351(k) BLA
- Clinical Review Focus (Collaborative Review)
  - Review of 3-way PK bridging suty
  - Review of Phase 3 RA comparability study
  - Review of single transition study
  - Extrapolation to non-studied indications

Regulatory History: Key Meetings

- August 2011
  - First meeting to discuss development program
- May 2013
  - Review PK data and acceptability of proposed RA study
- June 2013
  - Information amendment including CSR PK similarity study, RA study, statistical simulations, and request of Waiver of Peds studies
- Jan 2014
  - Discussed data requirements related to PFS and AI presented in BLA
- April 2014
  - Discussion of RA study with OLE; submission of SAP, discussion of Ps study
- August 2014
  - Submission of iPSP
- February 2015
  - Submission of revised iPSP (b) (4) (b) (4)
- June 2015
  - Pre-BLA meeting

Clinical Program Overview

- **PK Study**
  - 3-way PK similarity appears established
- **RA Study**
  - Study met its predefined similarity margin
  - ACR20 @ Wk 24
    - ABP: 75%
    - ADA: 72%
  - ACR70 @ Wk 24
    - ABP: 26%
    - ADA: 23%
- **Safety**
  - Database:
    - 1076 total subjects
      - 526 RA subjects (26-wks)
      - 360 Ps subjects (52-wks)
  - Overall safety and immunogenicity was similar between treatment arms
  - Similar safety and immunogenicity profile for subjects undergoing single transition from Humira to ABP 501

Study Number (status)	Subject Population	Number of Subjects	Type	Investigational Products
20110217 (Completed)	Healthy subjects	203 randomized	PK similarity, safety, tolerability, immunogenicity	ABP 501, adalimumab (US), adalimumab (EU)
20120262 (Completed)	Rheumatoid arthritis	526 randomized	Efficacy, safety, immunogenicity	ABP 501, adalimumab (US)
20120263 (Ongoing)	Plaque psoriasis	350 randomized	Efficacy, safety, immunogenicity	ABP 501, adalimumab (EU)

PK = pharmacokinetic; EU = European Union.

Extrapolation

- Proposed justification for extrapolation to all indications of US-licensed Humira:
  - Role of TNF-signaling in immune-mediated inflammatory diseases
    - TNFα is prominent inflammatory mediator in pathogenesis of these diseases
  - Mode of action of Humira in inflammatory arthropathies and psoriasis
    - Inhibition of TNFα induced and maintained inflammation in joints and skin
  - PK properties of Humira across indications
  - Analytical similarity of ABP501, US-Humira and EU-Humira
  - Supportive nonclinical data on similarity of ABP501 and Humira
  - Similar PK profile of ABP501 and EU-Humira
  - Similar efficacy of ABP501 and Humira in Phase 3 studies

Review of Labeling

- ABP501 (trade name TBD) draft label copy of US-licensed Humira® label
- Replaced [redacted] (b) (4) with "ABP-tradename" or "adalimumab" throughout label
- Indications:
- RA, JIA (≥4 yo), PsA, AS, CD, US, PsO [redacted] (b) (4)
- Section 6, Adverse Reactions, copy of Humira label*
- Section 14, Clinical Studies, copy of Humira label*

Filing and Planning

- Clinical Filing Checklist:
  - Completed, no omissions
- Advisory Committee:
  - To be scheduled
- OSI Audit:
  - Recommended for a new BLA
- Pediatric Development Plan:
  - Agreed iPSP is included in the BLA

Conclusions and Mid-cycle Deliverables

- Application is fileable, as a 351(k) BLA
- Mid-cycle deliverables:
- Complete review:
    - Comparative efficacy
    - Comparative safety
    - Adequacy of 3-way PK bridging
    - Adequacy of the justification of extrapolation to non-studied indications

DPARP CLINICAL FILING CHECKLIST FOR BLA 761024

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5. Are all documents submitted in English, or are English translations provided when necessary?	X			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	X			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	X			
9. Has the applicant submitted the integrated summary of safety (ISS)?	X			
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11. Has the applicant submitted a benefit-risk analysis for the product?	X			
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	351(k); biosimilar to Humira			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e*., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	N/A			
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 20120263 Indication: Plaque Psoriasis	X			
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?			X	
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	X			
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?			X	
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
27. Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
29. Are all datasets to support the critical safety analyses available and complete?	X			
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE				

33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter:

None.

Keith M Hull, MD, PhD

Reviewing Medical Officer

Nikolay Nikolov, MD

Clinical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEITH M HULL
02/01/2016

NIKOLAY P NIKOLOV
02/01/2016

DDDP CLINICAL FILING CHECKLIST FOR BLA 761024

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	Electronic CTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5. Are all documents submitted in English, or are English translations provided when necessary?	X			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	X			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	X			
9. Has the applicant submitted the integrated summary of safety (ISS)?	X			
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11. Has the applicant submitted a benefit-risk analysis for the product?	X			
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	Biosimilar to Humira; (b) (4) submitted under 351(k)			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	N/A			This product is a biosimilar and thus is using the already approved dose for the indication
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 20120263 Indication: Plaque Psoriasis	X			
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				Unable to locate this in the submission
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?	N/A			
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	X			This is the 1st marketing application for this biosimilar
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?	N/A			
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?	N/A			
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				Unable to locate this in the submission
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
27. Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
29. Are all datasets to support the critical safety analyses available and complete?	X			
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			

FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The sponsor should submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.

Reviewing Medical Officer

Clinical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DENISE COOK
01/08/2016

GORDANA DIGLISIC
01/08/2016