



FDA Briefing Document
Arthritis Advisory Committee Meeting
July 12, 2016

BLA 761024
ABP 501, a proposed biosimilar to
Humira (adalimumab)

Amgen



DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the 351(k) BLA for ABP 501 with the Applicant's proposed indications to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.



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1 Introduction

Amgen has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for ABP 501¹, a proposed biosimilar to Humira (adalimumab). BLA # 125057 for Humira was initially licensed by FDA on December 31, 2002, and the BLA is currently held by AbbVie. Amgen is seeking licensure of ABP 501 for the following indications for which US-licensed Humira is licensed:²

- 1) 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.
- 2) Juvenile Idiopathic Arthritis (JIA):
 - Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- 3) Psoriatic Arthritis (PsA):
 - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- 4) Ankylosing Spondylitis(AS):
 - Reducing signs and symptoms in adult patients with active AS
- 5) 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.
- 6) 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.
- 7) 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.

The ABP 501 drug product was developed as a single-use pre-filled syringe and a single-use autoinjector in a strength approved for US-licensed Humira (i.e. 40 mg/0.8

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).

² FDA-approved Humira labeling

mL); it also has the same dosage form and route of administration as those approved for US-licensed Humira.

2 Background

Introduction to Regulatory Pathway

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product (the “reference product”). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated

development program is that a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and, once the applicant has established that the proposed biosimilar meets the analytical similarity prong of the biosimilarity standard the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

The ‘totality of the evidence’ submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

The Reference Product

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product.³ When an applicant’s proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product , the reference product), and the non-US-licensed comparator product) and is likely to also include bridging clinical PK and/or PD study data for all three products.

³ The BPCI Act defines the “reference product” as the single biological product licensed under section 351(a) of the PHS Act against which a proposed biosimilar product is evaluated in a 351(k) application (see section 351(i)(4) of the PHS Act).

3 Executive Summary

This is a 351(k) BLA submitted by Amgen, Inc. for ABP 501, a proposed biosimilar to Humira (adalimumab). Amgen is seeking licensure of ABP 501 for the above indications previously approved for US-licensed Humira. The application consists of:

- Extensive analytical data intended to support (i) a demonstration that ABP 501 and US-licensed Humira are highly similar, (ii) a demonstration that ABP 501 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet appropriate quality standards and (iii) a justification of the relevance of comparative data generated using the European Union (EU)-approved Humira to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira.
- A single-dose pharmacokinetic (PK) study (Study 217) 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.
- A comparative clinical study (Study 262) between ABP 501 and EU-approved 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).
- A second comparative clinical study (Study 263) 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, patients treated with EU-approved Humira were randomized to undergo a single transition to ABP 501 or continue on EU-approved Humira.
- A scientific justification for extrapolation of data to support biosimilarity in each of the additional indications for which Amgen is seeking licensure, specifically juvenile idiopathic arthritis in patients 4 years of age or older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, and ulcerative colitis.

Amgen submitted comparative analytical data on the ABP 501 lots used in clinical studies intended to support a demonstration of biosimilarity (“clinical product lots”) and on the proposed commercial product. Based on our review of the data provided, Amgen’s comparative analytical data for ABP 501 supports a demonstration that ABP 501 is highly similar to US-licensed Humira) notwithstanding minor differences in clinically inactive components.

Amgen used a non-US-licensed comparator (EU-approved Humira) in some studies intended to support a demonstration of biosimilarity to US-licensed Humira. Accordingly, Amgen provided scientific justification for the relevance of that data by establishing an adequate scientific bridge between EU-approved Humira, US-licensed Humira and ABP 501. Review of an extensive battery of test results provided by Amgen confirmed the adequacy of the scientific bridge and hence the relevance of comparative clinical and non-clinical data with EU-approved Humira to support a demonstration of biosimilarity to US-licensed Humira.

The results of the clinical development program indicate that Amgen’s data support a demonstration of “no clinically meaningful differences” between ABP 501 and US-Humira in terms of safety, purity, and potency in the indications studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included a spectrum of chronic dosing regimens of ABP 501 and EU-approved Humira (40 mg Q2W SC on the background of methotrexate, and 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 (RA and PsO), and a single dose of 40 mg SC in healthy subjects of ABP 501, EU-approved Humira, and US-licensed Humira, adequately support a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in RA and PsO. Further, the single transition from EU-approved Humira to ABP 501 during the second part of Study 263 in PsO did not result in different safety or immunogenicity profile. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to ABP 501.

In considering the totality of the evidence, the data submitted by Amgen support a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in terms of the safety, purity, and potency of the product to support the demonstration that ABP 501 is biosimilar to the US-licensed Humira in the studied indications of RA and PsO.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use and potential licensure of ABP 501 for each of the indications for which US-licensed Humira is currently licensed and for which Amgen is seeking licensure.

4 Draft Points to Consider

Discussion Point 1:

Does the Committee agree that the evidence supports a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components?

Discussion Point 2:

Does the Committee agree that the evidence supports a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the studied conditions of use (RA and PsO)?

Discussion Point 3:

Does the Committee agree that there is sufficient scientific justification to extrapolate data from the comparative clinical studies of ABP 501 in RA and PsO to support a demonstration of biosimilarity of ABP 501 for the following additional indications for which US-licensed Humira is licensed (JIA in patients 4 years of age and older, PsA, AS, adult CD, and UC)? If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

Voting Point 1:

Does the Committee agree that based on the totality of the evidence, ABP 501 should receive licensure as a biosimilar product to US-licensed Humira for each of the following indications for which US-licensed 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)?

5 Relevant Regulatory History

The first interaction with the FDA on the ABP 501 development program occurred at a Biosimilar Biological Product Development (BPD) meeting held on August 24, 2011 with follow up interactions to include a BPD Type 4 meeting held on June 10, 2015. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP). During the pre-submission interactions, FDA provided product quality, nonclinical, and clinical comments, including the recommendations to the Applicant regarding clinical development, such as:

- Design, endpoints and selection of similarity margin for the comparative clinical study in RA.
- Assessment of safety and immunogenicity in the setting of patients who undergo a single transition from comparator Humira to ABP 501 to provide a descriptive comparison with patients who continue on comparator Humira.
- Demonstration of PK similarity between ABP 501, US-licensed Humira and EU-approved Humira.
- Expectations for the scientific justification for extrapolation of biosimilarity.

Of note, Amgen conducted a second comparative clinical study in patients with plaque psoriasis outside the US. This study was conducted without advice from FDA, including on the design, endpoints, or selection of a similarity margin for the study.

At the BPD Type 4 meeting, general agreement was reached on the proposed format and content of the BLA, including the Agency’s expectation of the information needed to support a demonstration of biosimilarity and extrapolation of clinical data to support the demonstration of biosimilarity for each indication for which licensure is sought.

6 CMC

Executive summary

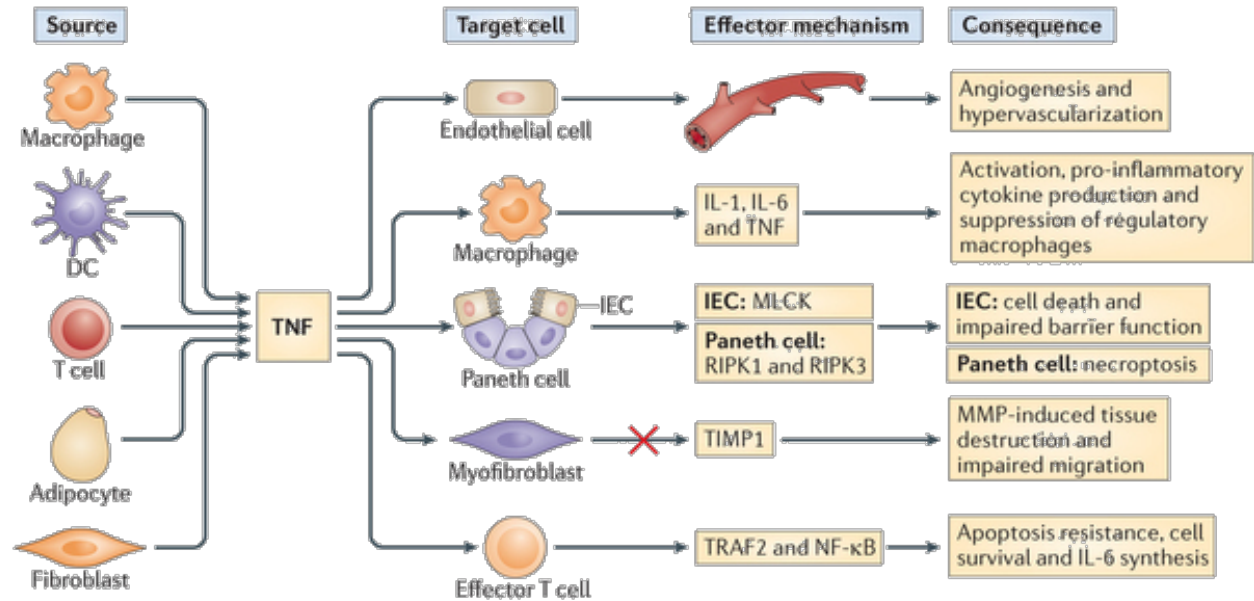
ABP 501 is a proposed biosimilar to US-licensed Humira. An analytical similarity program was designed utilizing the proposed biosimilar, ABP 501, US-licensed Humira and EU-approved Humira. The program had two objectives. First, an analytical similarity assessment of the proposed biosimilar to US-licensed Humira was needed to support a demonstration that it is “highly similar” to US-licensed Humira notwithstanding minor differences in clinically inactive components. Secondly, a comparison of US-licensed Humira, EU-approved Humira and ABP 501 was needed to establish the analytical component of the scientific bridge to justify the relevance of data generated using EU-approved Humira as the comparator in some clinical and nonclinical studies. The results of these comparisons show that the three products met the pre-specified criteria for analytical similarity, including statistical equivalency criteria for the potency bioassay (apoptosis inhibition) and TNF- α binding affinity. Thus, a pair-wise analytical comparison of ABP 501 to US-licensed Humira supports a demonstration that ABP 501

is highly similar to the US-licensed Humira. Further, an adequate analytical bridge between EU-approved Humira, US-licensed Humira, and ABP 501 was established as part of the scientific bridge to justify 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.

Pathophysiologic Role of TNF- α and Mechanisms of Action of Humira

Tumor Necrosis Factor (TNF)- α is considered to be a master cytokine critical for the function of the immune system as well as inflammatory responses. It exists as both soluble and membrane-bound forms that are produced by a range of immune-related or other cell types. The consequences of the effector function of TNF- α are also varied and include tissue destruction, activation of pro-inflammatory cytokines, and cell death. Thus, dysregulation of this master pro-inflammatory cytokine can have multiple clinical consequences in diseases like RA or inflammatory bowel disease (IBD).

Figure 1. TNF- α : A “Master Cytokine”



Source: Neurath, 2014⁴

TNF- α exists in both in a 26 kDa membrane bound (mTNF- α or aka tmTNF- α) form and a 17 kDa soluble form (sTNF- α), both of which form non-covalently linked homo-trimers. Because both forms are active, signals may be passed locally from cell-to-cell via mTNF:TNF-R interactions, or more distally through release of sTNF. sTNF- α is

⁴ Neurath, M. Nature Reviews Immunology, 2014, 14(5), 329-342.

generated following cleavage by members of a class of metalloproteinases called “sheddases”, which include TNF-converting enzyme (TACE, ADAM17) and ADAM 10. While under normal physiological conditions, the concentration of TNF- α found in bodily fluids is almost undetectable, stimulation by external sources can increase concentrations to measurable and sometimes very high levels. Biological responses to TNF- α are mediated through two structurally distinct, cognate TNF receptors, TNF-R1 (p55) and TNF-R2 (p75). These high affinity receptors are present as preassembled trimers on the cell surface. Most cells constitutively express TNF-R1 on their surface; in contrast, TNF-R2 is inducible and expressed preferentially on hematopoietic and endothelial cells.

Adalimumab is an IgG1 kappa monoclonal antibody, with a high affinity and avidity for TNF- α , including both the soluble and membrane-bound forms. It functions primarily via the variable region’s complementary determining region (CDR) surface by binding, neutralizing and sequestering excess sTNF- α produced in local inflammatory disease tissue sites. Another potential variable region-mediated mechanism of action is the mediating of reverse signaling via binding and cross-linking mTNF on inflammatory cells or induction of regulatory macrophages. Finally, there are some potential functions dependent on the Fragment crystallizable region (Fc) part of the antibody that may be important. These include antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) of lysis of mTNF+ inflammatory T-cells or other cells associated with particular disease states. The relative importance of merely sequestering sTNF vs. eliciting other effector functions on mTNF+ cells may vary between disease states. A summary of known and potential (likely or plausible), mechanisms of action of US-licensed Humira are listed in Table 1.

Table 1. Known and Potential (Likely or Plausible) Mechanisms of Action 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: ant body-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 literature on the topic of mechanisms of action of TNF inhibitors^{5,6,7}

ABP 501 Manufacturing

ABP 501 is produced using a mammalian cell line in large scale bioreactor culture followed by a drug substance purification process that includes various steps designed to isolate and purify the protein product. Residual levels of process-related impurities such as host cell proteins (HCP), host cell DNA, and other process-related impurities specific to the ABP 501 manufacturing process were evaluated in the testing of ABP 501 drug substance. Data were provided that demonstrate that the manufacturing process for ABP 501 drug substance is sufficient to reduce the levels of these impurities to very low levels, (e.g., ppm for HCP and pg/mg for DNA).

The ABP 501 drug product was developed as a single-use pre-filled syringe or a single-use autoinjector in some of the same strengths approved for US-licensed Humira (i.e. 40 mg/0.8 mL); and it also has the same dosage form and route of administration as those approved for US-licensed Humira . The ABP 501 drug product formulation has different inactive ingredients than US-licensed Humira. (b) (4)

⁵ Oikonomopoulos A et al., Current Drug Targets, 2013, 14, 1421-1432.

⁶ Tracey D et al., Pharmacology & Therapeutics 117 (2008) 244–279.

⁷ Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.



(b) (4)

The manufacturing process for ABP 501 drug substance remained unchanged throughout development with the exception of small enhancements in the manufacturing process to improve robustness. A new commercial filling site is introduced for the manufacture of commercial drug product. The drug product manufactured for commercial launch was demonstrated to be comparable to the drug product manufactured by the clinical process and used in the analytical similarity assessment.

The ABP 501 final drug substance and drug product processes are considered fully validated, and the manufactured product is of a consistent quality. The controls that have been established for the routine manufacture of ABP 501 drug substance and ABP 501 drug product meet regulatory requirements. An assessment of the manufacturing facilities took place from May 31, 2016 to June 6, 2016, by a group of Agency inspectors. The team verified that the drug substance and drug product sites are acceptable from a current good manufacturing practices (cGMP) perspective.

Analytical Similarity Assessment

Determining high analytical similarity of ABP 501 to US-licensed Humira, and establishing the adequacy of the analytical portion of the scientific bridge between ABP 501, US-licensed Humira, and EU-approved Humira was accomplished by Amgen’s evaluation and comparison of analytical data (generated by Amgen) using multiple lots from each of the three products. The FDA performed confirmatory statistical analysis of the submitted data. As many as 10 lots of ABP 501, 18 lots of the EU-approved Humira, and 24 lots of US-licensed Humira were used for analysis, although not all lots were assessed using each test. For the most critical assays, those that directly measured the primary mechanism of action of the product, TNF- α binding and neutralization, at least 10 lots of each product were included in the analysis. The number of lots that were analyzed using each assay was chosen by the Applicant, Amgen, based on their assessment of the variability of the analytical method and availability of material.

The expiration dates of the US-licensed Humira lots and EU-approved Humira lots that were analyzed spanned approximately 5 years and 4 years, respectively. The ABP 501 lots that were used for analysis were manufactured between 2011 and 2015.

The analytical similarity assessment of ABP 501 with US-licensed Humira supports a demonstration that ABP 501 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components. Pairwise comparisons of ABP 501, US-licensed Humira, and EU-approved Humira were used to support the analytical portion of the scientific bridge between the three products to justify the relevance of the comparative data generated using EU-approved Humira from some clinical and non-clinical studies.

The analytical similarity exercise used a comprehensive range of methods listed in Table 3, which included orthogonal methods that measured the same critical quality attribute (CQA) from different perspectives. Many assays were designed to specifically address and measure potential mechanisms of action of adalimumab, including those Fc-mediated functions. All methods were validated or qualified prior to the time of testing and demonstrated to be suitable for intended use.



Table 3. Quality Attributes and Methods Used to Evaluate Analytical Similarity of ABP 501, US-licensed Humira, and EU-approved Humira

Quality Attribute	Methods
Primary structure	<ul style="list-style-type: none"> • Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection (reduced and non-reduced) • Amino Acid Analysis • Intact Molecular Mass (LC-MS) • Reduced and Deglycosylated Molecular Mass (LC-MS)
Protein content	<ul style="list-style-type: none"> • Concentration (UV280)
Higher order structure	<ul style="list-style-type: none"> • Near UV circular dichroism • FTIR • Liquid Chromatography Coupled with Mass Spectrometry (LC-MS)(disulfide bond characterization) • Differential Scanning Calorimetry
Size Variants/Aggregates	<ul style="list-style-type: none"> • Size Exclusion Chromatography (UV Detection) • Size Exclusion Chromatography with Light Scattering Detection (SEC-LSD) • Field Flow Fractionation • Analytical Ultracentrifugation Sedimentation Velocity • CE-SDS (Reduced and Non-Reduced)
Charge	<ul style="list-style-type: none"> • cIEF • CEX-HPLC
Glycosylation	<ul style="list-style-type: none"> • Glycan Mapping
Potency	<ul style="list-style-type: none"> • Apoptosis inhibition bioassay
Binding assay – sTNF	<ul style="list-style-type: none"> • ELISA
Binding assay – mTNF	<ul style="list-style-type: none"> • Cell-based
Binding assay – Fc	<ul style="list-style-type: none"> • FcγRIIIa V type binding affinity (AlphaLISA) • FcγRIIIa F type binding affinity (AlphaLISA) • FcγRIIa binding affinity (AlphaLISA) • FcγRIa binding affinity (AlphaLISA) • FcRn binding affinity (cell-based) • C1q binding assay (ELISA)
Bioassay/ mechanism of action exploration	<ul style="list-style-type: none"> • ADCC (NK cells as effectors) • CDC • Inhibition of sTNFα-induced IL-8 in HUVEC • Specificity against LTα in HUVEC assay • Inhibition of sTNFα- induced cell death in L929 cells • Inhibition of sTNFα-induced chemokines in whole blood • Inhibition of T-Cell proliferation (MLR) • Induction of regulatory macrophages
Sub-visible Particles	<ul style="list-style-type: none"> • Micro Fluid Imaging • Light Obscuration
General Properties	<ul style="list-style-type: none"> • Deliverable Volume • Osmolality • pH • Appearance • Polysorbate (b) (4)

Primary Structure

To support a demonstration that the proposed biosimilar ABP 501 product is highly similar to US-licensed Humira, it is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as US-licensed Humira. To achieve this goal, expression constructs were designed to encode a protein sequence that matches US-licensed Humira by the ABP 501 production cells. This can be confirmed at the protein level by methods including a variety of mass spectrometry approaches and tryptic peptide mapping.

Peptide mapping

The primary structure of ABP 501, EU-approved Humira and US-licensed Humira, was assessed by peptide map data. This data demonstrated that ABP 501 has a matching chromatographic profile (i.e., map) to that of US-licensed Humira and EU-approved Humira. No additional peptides or missing peptides were detected in the comparison between the three products.

Further primary structure analysis

Additional measures for the assessment of primary structure were also performed. Specifically, the molecular mass was determined under a series of additional conditions. These included the determination of the molecular mass for the intact antibody, the determination of the molecular mass under reducing conditions (where the heavy and light chains of each molecule were evaluated individually), and upon enzymatic removal of the glycan from the single glycosylation site, Asn301. The molecular mass measured in each experiment matched the expected molecular mass. The results were similar, within the expected variability of the method, for ABP 501, EU-approved Humira and US-licensed Humira.

Additionally, analysis by mass spectrometry confirmed the expected presence of eight disulfide bonds in each of the three products.

Protein Content

US-licensed Humira is filled into a single-use, pre-filled syringe or a single-use autoinjector with either a deliverable volume of 0.4 mL or 0.8 mL. The drug product manufacturing process of ABP 501 was designed to match the protein content of US-licensed Humira, within reasonable manufacturing tolerances. A demonstration that protein content matched between pre-filled syringes of US-licensed Humira and ABP 501 was performed by expulsion of the drug product solution, followed by protein concentration measurement by UV-spectroscopy. The data confirm that total protein amounts in the ABP 501 drug product and US-licensed Humira met pre-specified acceptance criteria.

Higher Order Structure (HOS)

Proper folding is critical for the effective function and serum life of antibodies. The secondary and tertiary structures of the adalimumab products were evaluated by Fourier Transform Infrared (FTIR) spectroscopy, near UV circular dichroism (CD), and Differential Scanning Calorimetry (DSC). FTIR and near UV CD spectroscopy provides information regarding secondary structure (α -helix, β -sheet and random coil structures) and DSC provides information on tertiary structure. For each product, similar results were observed.

Aggregates

Biopharmaceuticals typically contain very low levels of protein aggregates (<1%) which are measured and controlled at lot release. Small amounts of aggregation are present in both ABP 501 and US-licensed Humira. Aggregation is typically detected and quantified by the size-exclusion chromatography assay (SEC-HPLC). The average level of aggregates in US-licensed Humira quantified by Amgen's SEC-HPLC assay was 0.3%, while ABP 501 was 0.2%. These levels of aggregation are consistent with levels seen in other biopharmaceutical products.

Additional measures which evaluated aggregates were also performed, including Size Exclusion Chromatography with Light Scattering Detection (SEC-LSD), Field Flow Fractionation and Analytical Ultracentrifugation Sedimentation Velocity. Each confirmed similar aggregate levels between ABP 501 and US-licensed Humira.

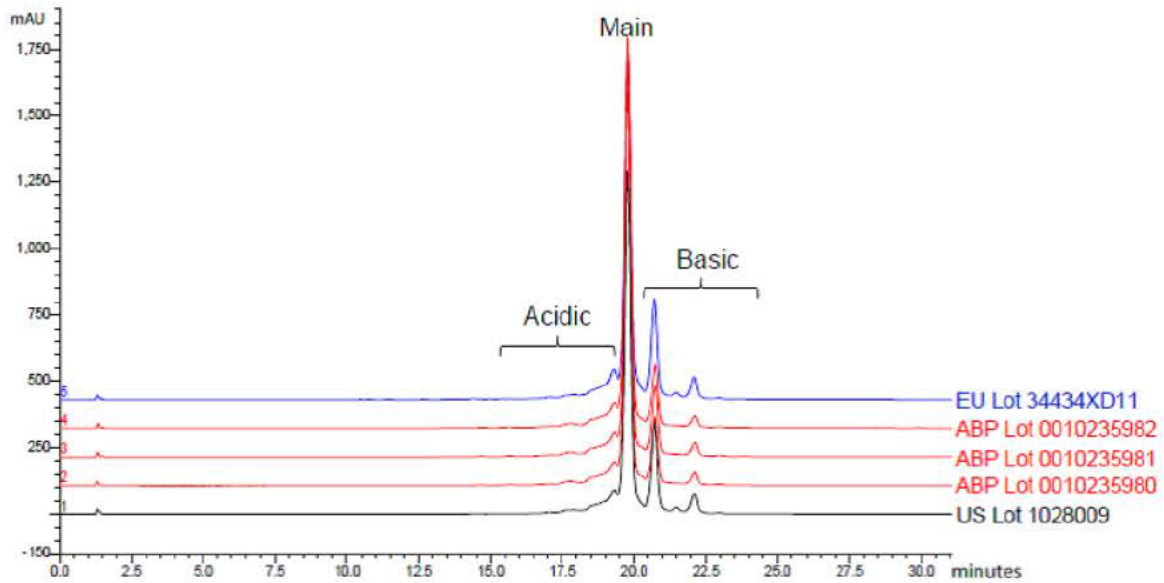
From a quality standpoint, high levels of aggregation may impact product immunogenicity when injected into patients, but levels below 1% are frequently observed in this class of products.

Charge

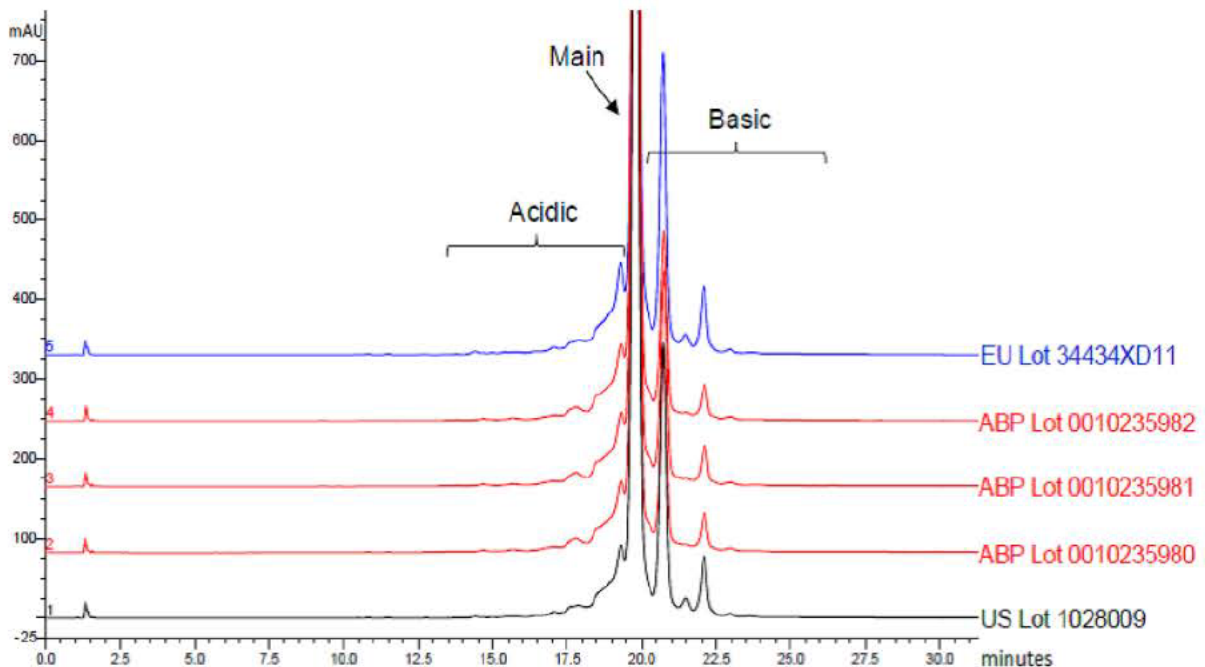
Charge heterogeneity is commonly observed for all monoclonal antibodies. The heterogeneity derives from post-translational modifications that typically include: deamidation, glycation, oxidation, and heterogeneity of the cleavage of the C-terminal chain. These changes result in a complex charge profile for all monoclonal antibodies. In addition to the separation based on surface charge, surface heterogeneity and even glycosylation may also influence the profile observed. The charge profile for both ABP 501 and US-licensed Humira are resolved into three distinct regions that are commonly observed in monoclonal antibody products: acidic peaks, basic peaks, and the main peak. A sample chromatographic overlay of ABP 501, US-licensed Humira, and EU-approved Humira is presented in Figure 2.

Figure 2. Chromatographic Comparison of Charge Variant Profile for ABP 501, US-licensed Humira and EU-approved Humira”

Full View



Expanded View

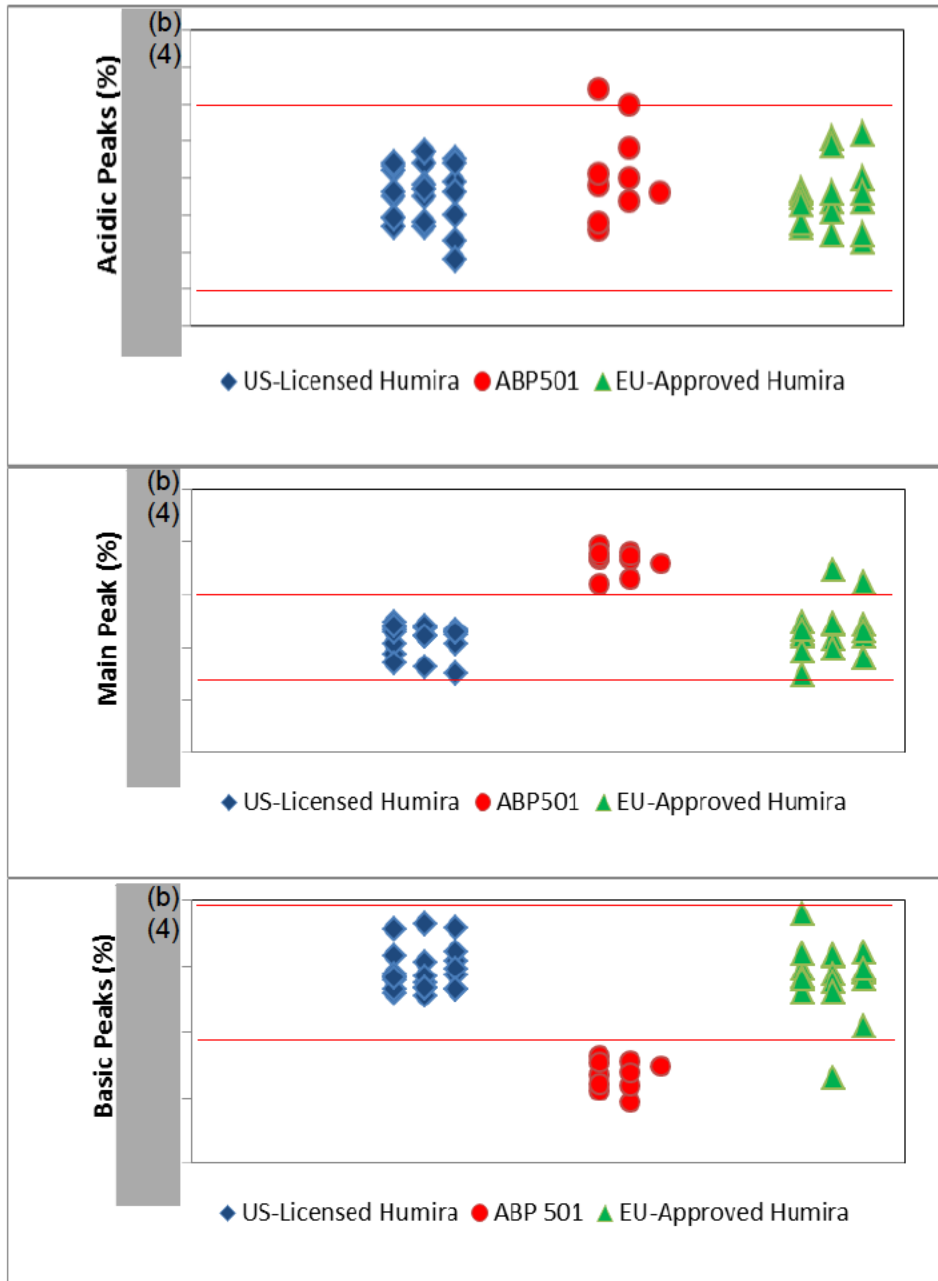


Source: Figure excerpted from the Amgen 351(k) BLA submission

As observed in Figure 2, the profiles are visually quite similar. However, some differences are observed in the levels or proportion of % acidic peaks, % main peak,

and % basic peaks. Specifically, ABP 501 displays lower levels of basic peaks, and consequently, a trend to slightly higher percentage of acidic peaks and main peaks. (b) (4)

Figure 3. Comparison of Charge Variant Profile Peak Levels for ABP 501, US-licensed Humira and EU-approved Humira”



Source: FDA analysis of the Amgen 351(k) BLA submission

To evaluate the nature of the observed differences, the Applicant performed extensive characterization. These studies demonstrated that the difference in the levels of the % basic peak is predominately due to the presence of C-terminal lysine that is not present in the main peak. Both US-licensed Humira and ABP 501 show clipping of the lysine residue at the C-terminus, however levels of clipping are higher for ABP 501, and thus, the value for % basic peak is lower. This clipping is common for monoclonal antibodies products⁸, and does not affect the potency of the product.

With respect to the acidic peaks, characterization revealed that deamidation, glycation, fragmentation, and sialylation form the species that elute in the acidic peaks. Fractions were collected for the acidic peaks, and even dramatically enhanced acidic peak levels were shown to have minimal effect on the potency of the product. We note that these differences are not considered to have clinically significant consequences.

Glycosylation

Glycosylation of antibodies is typically heterogeneous; up to twenty different detectable N-linked glycan forms can exist in an antibody sample. Antibodies produced in mammalian cell culture systems will vary in glycan pattern somewhat from product-to-product, and to a lesser degree, from lot-to-lot. There are typically predominant species like G0F (no terminal galactoses, with a fucose at the base) or G1F (one terminal galactose, with a fucose).

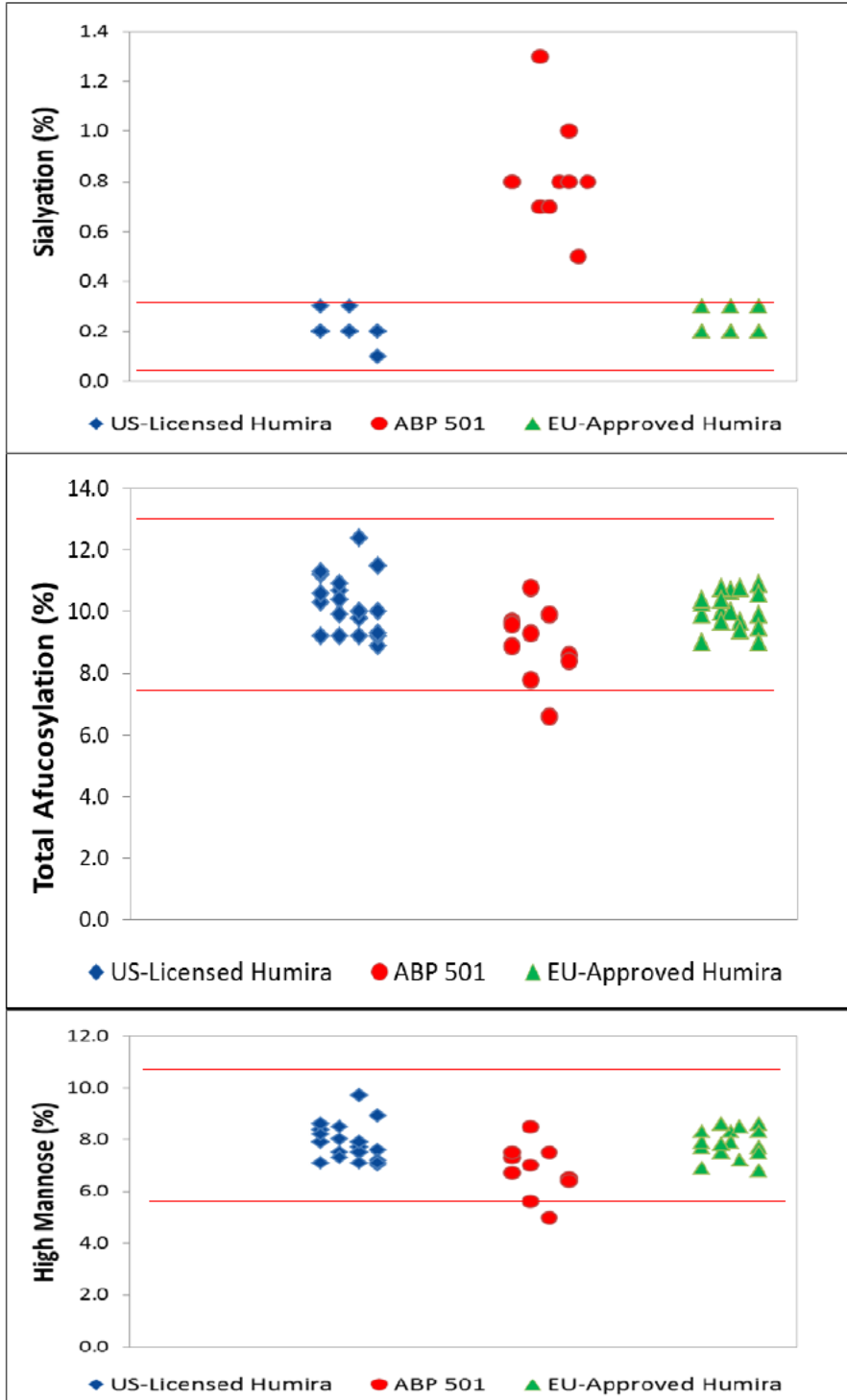
Some types, such as forms with fucose at the base of the biantennary structure, can influence the Fc three-dimensional structure to lower the binding affinity to receptors like FcγRIII. These changes can have an impact on binding to FcγRIII and are important to measure and control in antibody-based biopharmaceuticals. Additional changes in glycosylation, specifically, levels of % high mannose and % sialylation, can influence PK profile.⁹

Slight differences in several of the key glycans are presented below in Figure 4. For the purposes of calculation, the % total afucosylation was calculated as the sum of all glycan structures lacking core fucose, which includes complex, hybrid, and terminal mannose glycans. The % high mannose was calculated as the sum of all high mannose glycans, M5 to M8. The % sialylation was calculated as the sum of all complex and hybrid glycan structures which contain at least 1 terminal sialic acid. The % galactosylation content was calculated as the sum of all complex and hybrid glycan structures which contain at least 1 terminal galactose.

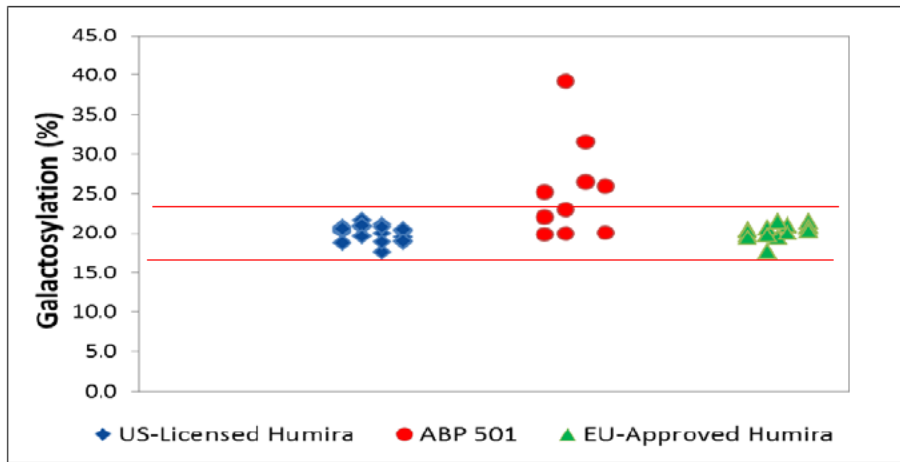
⁸ Yi, D. et. al, MAbs. 2012 Sep 1; 4(5): 578–585.

⁹ Liu, L. J Pharm Sci. 2015 Jun;104(6):1866-84.

Figure 4. Comparison of Glycan Profile for ABP 501, US-licensed Humira, and EU-approved Humira



Source: FDA analysis of the Amgen 351(k) BLA submission



Source: FDA analysis of the Amgen 351(k) BLA submission

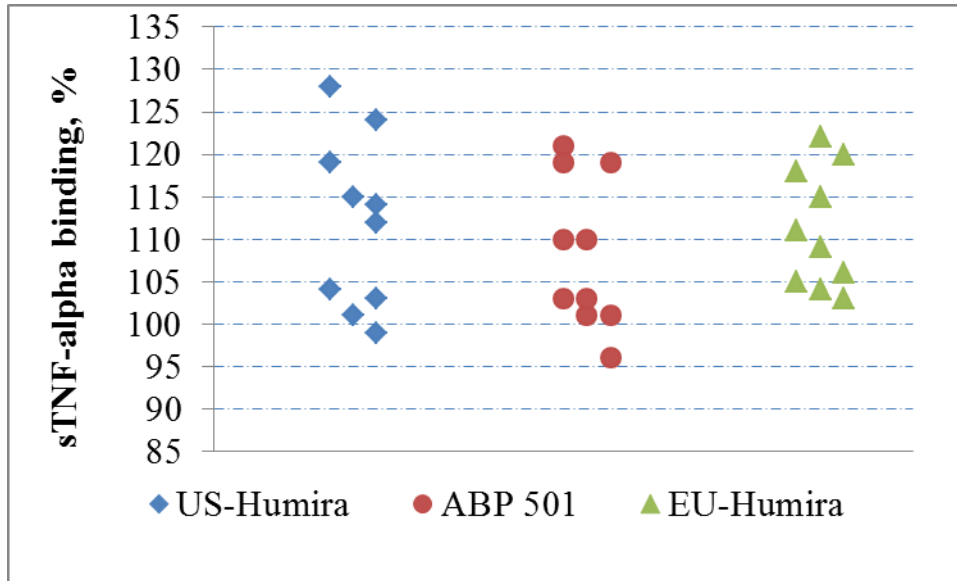
As observed in Figure 4, differences are observed in the % high mannose (trend toward lower for ABP 501), % total afucosylation (trend toward lower for ABP 501), % sialylation (higher for ABP 501), and % galactosylation (higher for ABP 501). The red bars depict the quality range analysis provided by the Applicant. However, given the similar PK profiles for ABP 501 and US-licensed Humira (see the section on Clinical Pharmacology below below), similar ADCC activity and binding to FcγRIIIa (see discussion in the subsection on Fc Function below) between ABP 501 and US-licensed Humira, and similar CDC activity for ABP 501 and US-licensed Humira (see discussion in the subsection on Fc Function below), these slight differences do not preclude a finding that the products are highly similar notwithstanding minor differences in clinically inactive components. We also note that these slight differences are not expected to have clinically meaningful consequences.

Biological Activity

A number of bioassays were designed and qualified to evaluate potential adalimumab functions, including binding and neutralization of TNF-α as well as Fc effector functions. The data are reported as a percentage relative to the Applicant’s in-house ABP 501 reference standard.

TNF-α binding was also assessed using an enzyme linked immunosorbent assay (ELISA). A comparison of the relative binding affinity of ABP 501, EU-approved Humira and US-licensed Humira for TNF-α was performed with 10 lots of each product. Because of the criticality of this function, these data (see Figure 5) were subjected to a statistical analysis using equivalence testing. The TNF-α binding affinity of ABP 501 was considered statistically equivalent to the TNF-α binding affinity (by ELISA) of US-licensed Humira if the 90% confidence interval (CI) of the mean difference in TNF-α binding affinity (by ELISA) between ABP 501 and US-licensed Humira is entirely within an equivalence acceptance criterion calculated from Amgen’s data on US-licensed Humira. Descriptive statistics for the TNF-α binding Affinity data of ABP 501, US-licensed Humira, and EU-approved Humira are listed in Table 4.

Figure 5. Comparative Binding Affinity (ELISA) of ABP 501, US-licensed Humira, and EU-approved Humira to Human TNF- α



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

The statistical equivalence analyses shown in Table 5 regarding the TNF- α binding affinity (by ELISA) of ABP 501 support a demonstration that ABP 501 is highly similar to that of US-licensed Humira. Further, these analyses support the analytical component of the scientific bridge between US-licensed Humira, EU-approved Humira and ABP 501 to justify the relevance of comparative data generated from clinical and non-clinical studies that used EU-approved Humira.

Table 4. Descriptive Statistics for the TNF α Binding Affinity (ELISA) of ABP 501, US-licensed Humira, and EU-approved Humira

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
ABP 501	10	108	8.9	96	121
US-licensed Humira	10	112	10.0	99	128
EU-approved Humira	10	111	7.0	103	122

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

Table 5. Equivalence Testing Results for the TNF α Binding Affinity (ELISA) of ABP 501, US-licensed Humira, and EU-approved Humira

Product	Number of batches	Comparator Product	Number of batches	Equivalent
ABP 501	10	US-licensed Humira	10	Yes ^a
ABP 501	10	EU-approved Humira	10	Yes ^b
EU-approved Humira	10	US-licensed Humira	10	Yes ^c

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

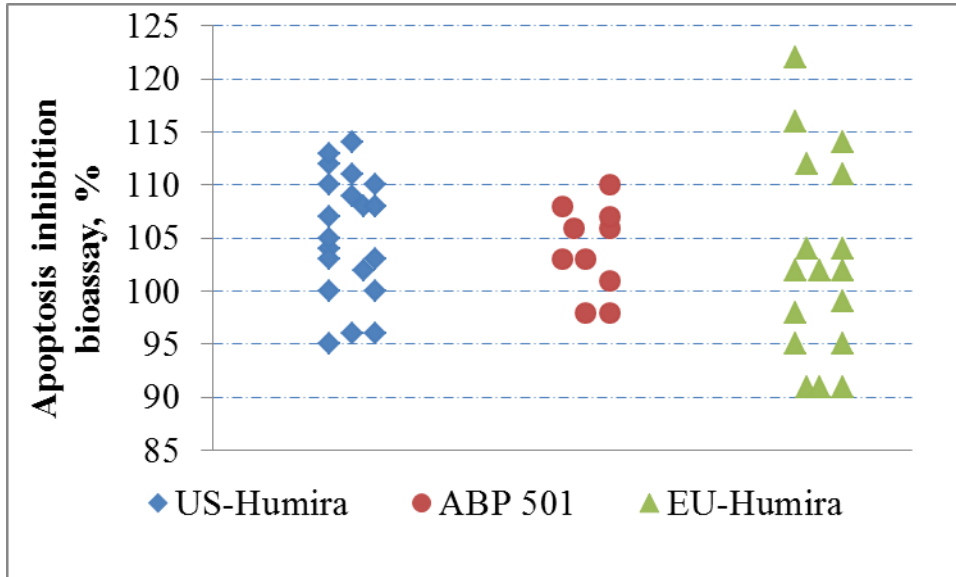
^a The 90% confidence interval for the mean difference in TNF α binding affinity (ELISA) between ABP 501 and US-licensed Humira, (-10.93, 3.73)%, falls entirely within the equivalence margin, (-14.97, 14.97)%.

^b The 90% confidence interval for the mean difference in TNF α binding affinity (ELISA) between ABP 501 and EU-approved Humira, (-9.23, 3.23)%, falls entirely within the equivalence margin, (-10.54, 10.54)%.

^c The 90% confidence interval for the mean difference in TNF α binding affinity (ELISA) between EU-approved Humira and US-licensed Humira, (-7.34, 6.14)%, falls entirely within the equivalence margin, (-14.97, 14.97)%.

The primary mechanism of action of the three products was also measured using an apoptosis inhibition bioassay. This assay measures the ability to inhibit TNF- α -induced cell death in human histiocytic lymphoma cell line U-937. These data (see Figure 6) were also subjected to a statistical analysis using equivalence testing with a 90% confidence interval (CI). The apoptosis inhibition activity of ABP 501 was considered statistically equivalent to the apoptosis inhibition activity of US-licensed Humira if the 90% confidence interval (CI) of the mean difference in the apoptosis inhibition activity between ABP 501 and US-licensed Humira is entirely within an equivalence acceptance criterion calculated from the Applicant’s data on US-licensed Humira. Descriptive statistics for the apoptosis inhibition activity data are listed in Table 6.

Figure 6. Biological Activity of ABP 501, US-licensed Humira, and EU-approved Humira



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

The summary presented in Table 7 regarding the apoptosis inhibition activity of ABP 501 supports a demonstration that ABP 501 is highly similar to that of US-licensed Humira. Further, these analyses support the analytical component of the scientific bridge between US-licensed Humira, EU-approved Humira and ABP 501 to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-approved Humira.

Table 6. Descriptive Statistics for the Apoptosis Inhibition Bioassay Data of ABP 501, US-licensed Humira, and EU-approved Humira

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
ABP 501	10	104	4.1	98	110
US-licensed Humira	21	105	5.7	95	114
EU-approved Humira	17	103	9.4	91	122

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

Table 7. Equivalence Testing Results for the Apoptosis Inhibition Bioassay of ABP 501, US-licensed Humira, and EU-approved Humira

Product	Number of batches	Comparator Product	Number of batches	Equivalent
ABP 501	10	US-licensed Humira	21	Yes ^{a*}
ABP 501	10	EU-approved Humira	17	Yes ^{b*}
EU-approved Humira	17	US-licensed Humira	21	Yes ^c

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

^a The 90% confidence interval for the mean difference in the Apoptosis Inhibition activity between ABP 501 and US-licensed Humira, (-4.50, 1.93)%, falls entirely within the equivalence margin, (-8.18, 8.18)%.

^b The 90% confidence interval for the mean difference in the Apoptosis Inhibition activity between ABP 501 and EU-approved Humira, (-3.37, 5.82)%, falls entirely within the equivalence margin, (-14.04, 14.04)%.

^c The 90% confidence interval for the mean difference in the Apoptosis Inhibition activity between EU-approved Humira and US-licensed Humira, (-6.97, 1.88)%, falls entirely within the equivalence margin, (-8.57, 8.57)%.

* The 90% confidence interval is adjusted for the sample size imbalance.

Fc function

Antibodies can also activate immune effector functions via molecular bridging between the Fc part of the antibody and soluble (e.g., C1q) or cell membrane-bound (e.g., FcγR proteins) molecules. Functions activated in this manner include antibody-dependent cellular cytotoxicity (ADCC), initiated by bridging effector and target cells via Fc-binding receptors on the effector cell surface and complement-dependent cytotoxicity (CDC). In CDC, the complement system is activated by targeting C1q binding to a cell surface, which initiates a biological cascade that ultimately results in pore formation in the target cell membrane.

The Fc- receptors, FcγRI, FcγRII, FcγRIII, FcRn, are diverse in structure and location of cell expression. The predominant Fc receptor type on natural killer (NK) cells is FcγRIII (a or b forms), while other leukocytes express a more broad range. NK cells are highly potent immune cells believed to play a predominant role in the host rejection of both tumor and virally infected cells. Thus, different ADCC effector cells can be recruited based on which Fc receptor is bound.

The binding strength of ABP 501, EU-approved Humira, and US-licensed Humira to various Fc receptors was measured. The binding activity was measured using AlphaLISA assays (FcγRI and FcγRIIIa) or a cell-based assay (FcRn). Overall, the binding affinities of the three products were similar for FcRn, FcγRI and FcγRIIIa (data not shown).

Particular consideration was given to the evaluation of binding to FcγRIIIa and ADCC activity given the precedent that glycosylation pattern, in particular levels of afucosylation can affect ADCC activity.¹⁰

To evaluate binding to FcγRIIIa (158V), the high affinity FcγRIIIa receptor, 10 lots of ABP 501, 10 lots of US-Approved Humira, and 10 lots of EU-licensed Humira were used. As noted in Table 8, similar binding affinity was observed for all three products and fell within the quality range of US-licensed Humira proposed by the Applicant (quality range not shown).

Table 8. FcγRIIIa Binding of ABP 501, US-licensed Humira and EU-approved Humira

Binding (SPR)^a	ABP 501	EU-Humira	US-Humira
FcγRIIIa V type%	90%	95%	93%

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

^a-All data are expressed at % activity relative to a ABP 501 reference standard included in the same assay.

Antibodies function not only by binding and neutralizing antigens via their antigen binding complementary determining region (CDR) surface, but also by activating or down-modulating other parts of the immune system. An example of down modulation would be antibody-mediated reverse signaling, where antibody cross-linked cells may undergo apoptosis or be inhibited from secreting pro-inflammatory cytokines.

Biological Assays that Address Potential Mechanisms of Action

The main activity of adalimumab is believed to be TNF-α binding and sequestration, mediated via the variable region CDR surface. However, other potential mechanisms involving mTNF-α binding exist, such as reverse signaling (discussed below and summarized in Peake et al., 2013.¹¹ Also, antibodies can mediate effector functions via their Fc portion like ADCC or CDC. In theory, the Fc portion of adalimumab could play a role in adalimumab function in some indications, as summarized in Table 1.

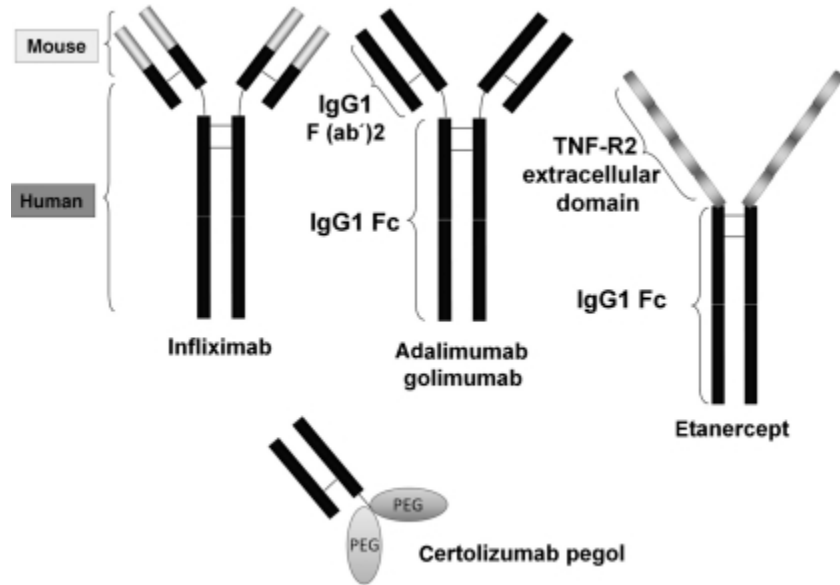
Antibody-Dependent Cellular Cytotoxicity (ADCC)

¹⁰ Liu, L. J Pharm Sci. 2015 Jun;104(6):1866-84

¹¹ Peake, S. T. C., et al. Inflammatory bowel diseases, 2013, 19(7), 1546-1555.

When features of the broad class of TNF- α antagonists are examined (Humira, Enbrel, Remicade, Simponi, Cimzia), there is a suggestion that Fc-related mechanisms might be involved. This is summarized in Figure 7 below.

Figure 7. The Role of Fc in the Anti-TNF- α Class Mechanism(s) of Action



	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab (pegol)
Fc-mediated MOA					
ADCC	Moderate	Low	Moderate	Moderate	None
CDC	Moderate	Low	Moderate	Moderate	None
FDA-approved Conditions of Use					
RA	Yes	Yes	Yes	Yes	Yes
CD/UC	Yes/Yes	No/NS	Yes/Yes	NS/Yes	Yes/NS

Source: Figure from Horiuchi, T., et al. *Rheumatology (Oxford)*. 2010 Jul; 49(7): 1215–1228. FDA summary of existing literature on the topic of Fc functions of TNF-blockers.^{12,13,14,15}

As shown in the third row, all listed TNF- α antagonists have demonstrated efficacy and are approved for the treatment of RA. However, this is not true for all indications as shown in the bottom row, where the efficacy in Crohn’s Disease (CD) and ulcerative colitis (UC) has not been demonstrated for all listed TNF- α antagonists. Enbrel (etanercept), which has low ADCC activity, is not approved for treatment of CD or UC.

¹² Arora, T., et al. *Cytokine*, 2009 45(2), 124-131.
¹³ Kaymakcalan, Z. et al. *Clinical immunology*, 2009, 131(2), 308-316.
¹⁴ Mitoma, H. et al. *Gastroenterology*, 2005, 128(2), 376-392.
¹⁵ Olesen, C.M, et.al., *Pharmacology & Therapeutics* 159 (2016), 110-119.

Published literature supports a lack of efficacy of etanercept in CD based on a small study (N=49) using a dose approved in RA¹⁶.

In addition, Cimzia (which has no ADCC activity), reduces signs and symptoms and maintain clinical response, but does not achieve and maintain/sustain clinical remission, as summarized in Figure 7. Although it is possible that other factors contributed to this outcome, such as inadequate dosing, it also raises a question as to whether absence of ADCC activity could have played a role.

In theory, ADCC could be involved with the mechanism of action of adalimumab by eliminating mTNF+ inflammatory cells like macrophage or T-cells and thereby down modulating disease activity in inflamed sites. ADCC is an immune function where effector cells such as NK cells lyse target cells via antibody bound to the surface of the targets. The antibody Fc portion is able to recruit the effector cells via FcγR: Fc bridging. FcγRIIIa or CD16 is the main form of FcγR on NK cells, a highly potent type of immune cells that target antibody bound tumor or virally infected cells. While there is no direct *in vivo* or clinical evidence that ADCC plays a role in adalimumab efficacy, it is discussed in the literature¹⁷ and was adequately addressed by Amgen, as discussed below.

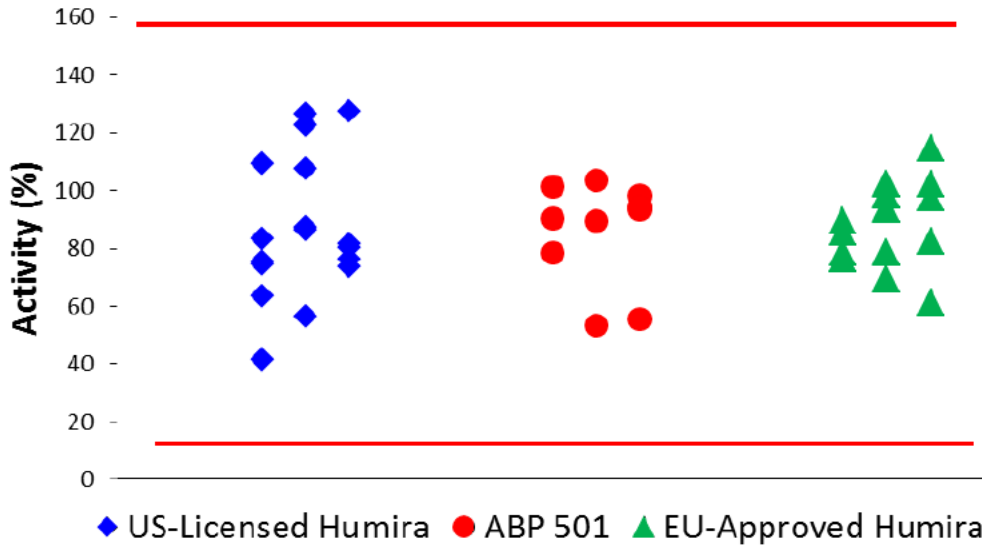
ADCC activity may vary with the strength of the FcγR: Fc bridging, which in turn may be dependent on the glycan composition on the antibody (see discussion above). To fully evaluate the role that ADCC may play in ABP 501 and US-licensed Humira function and evaluate the impact of slight differences in glycosylation, Amgen designed an ADCC assay to compare the activity of ABP 501 with US- licensed Humira. The assay used CHO M7 cells that stably express a TNFα converting enzyme (TACE)-resistant form of mTNFα on their cell surfaces, as target cells. NK92-M1 cells, stably transfected with human FcγRIIIa (also known as CD16), are used as effector cells. Data are presented in Figure 8.

Unlike TNF-α binding, there is uncertainty regarding the criticality of Fc effector function for the adalimumab mechanism of action. Thus, tests for Fc functions were not examined for statistical equivalence, rather they were examined with respect to quality range testing defined by Amgen's data on US-licensed Humira.

¹⁶ Sandborn WJ, Hanauer SB, Katz S, et al. Gastroenterology 2001;121:1088–94.

¹⁷ Peake, S. T. C., et al. Inflammatory bowel diseases, 2013, 19(7), 1546-1555.

Figure 8. ADCC of ABP 501, US-licensed Humira, and EU-approved Humira Using NK92-M1 Cells as Effector Cells



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

The data support a demonstration that ABP 501 is highly similar to US-licensed Humira because the ADCC activity of ABP 501 is within the quality range set by Amgen’s data on US-licensed Humira.

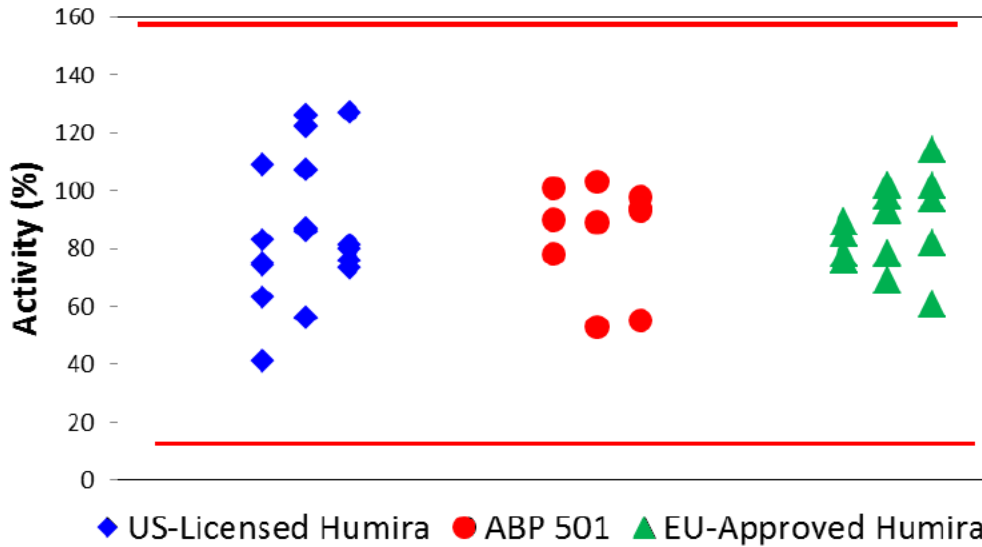
C1q Binding and Complement Dependent Cytotoxicity (CDC)

C1q binding is the first step in the initiation of the complement cascade. To assess the ability of ABP 501 to initiate this signaling cascade, both binding to C1q (data not presented) and CDC activity were assessed. The CDC activity of ABP 501 was evaluated in a functional cell-based assay in which CHO M7 cells have been transfected to stably express a TACE-resistant form of transmembrane TNF α on their cell surface. The CHO M7 cells are loaded with calcein-AM and complement is added.

There is no direct evidence addressing whether CDC is involved with adalimumab function, nor is there direct evidence that it is irrelevant. There is some precedent¹⁸ that changes in galactosylation (see glycan profiling discussion) can influence CDC activity. As demonstrated in Figure 9, similar CDC activity is observed between ABP 501, US-licensed Humira, and EU-approved Humira based on a quality range analysis relative to US-licensed Humira.

¹⁸ Liu, L. J Pharm Sci. 2015 Jun;104(6):1866-84.

Figure 9. CDC Activity of ABP 501, US-licensed Humira, and EU-approved Humira Using NK92-M1 Cells as Effector Cells



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

Reverse Signaling and Apoptosis

Reverse signaling is a cellular feedback that occurs when a molecule that is normally a signaling molecule, like mTNF- α on immune cells (e.g., NK cells and monocytes), is instead bound and/or cross-linked by an antibody transducing a signal back to that cell instead of forward to another cell. In theory, reverse signaling by adalimumab can transduce a signal to mTNF⁺ cells inducing a response like suppression of cytokine release and even apoptosis. Published literature suggests that adalimumab is likely to function this way in IBD patients (Table 1). For example, this contention is supported by studies using *in vivo* immunofluorescent staining of patient colon and/or TUNEL assays of IBD patient biopsies as well as *in vitro* studies using cultured clinical isolates.¹⁹

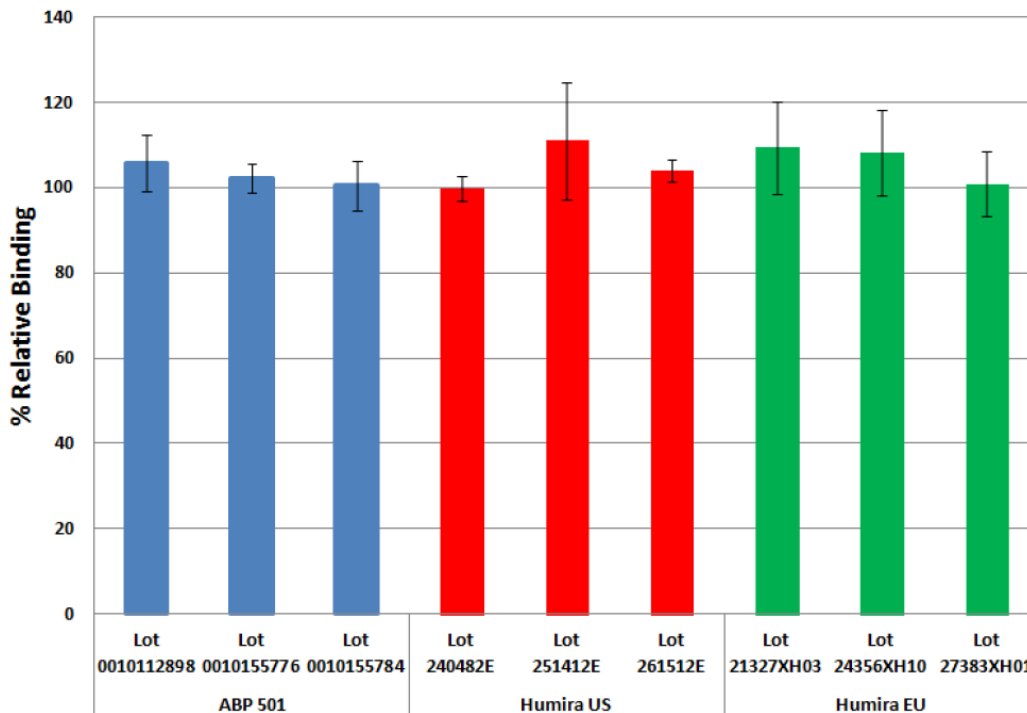
To address the potential for ABP 501 to mediate reverse signaling, Amgen evaluated the binding of ABP 501 and US-licensed Humira to the trans-membrane form of TNF- α in a cell-based competition assay using CHO cells expressing non-cleavable TNF- α . Binding to mTNF- α is the first step within the reverse signaling pathway and provides an indirect measure of this activity. Similar binding affinity was observed for ABP 501, US-licensed Humira, and EU-approved Humira. Data showing this comparison are presented in Figure 10. Of note, Amgen did not provide data from a confirmatory functional assay that directly measures the downstream effects of reverse signaling. Thus, FDA has requested additional data in support of the assessment of reverse

¹⁹ Atreya, R., et. al. Nature Medicine, 2014 20(3), 313-318.

signaling activity, though this request was not submitted soon enough for these supportive data to be available in the briefing book and is still pending.

Importantly, based on the submitted robust analytical data (i.e., the extensive structural characterization, other functional assays, binding to mTNF- α , and evaluation of a related IBD mechanism, *Activation of Regulatory Macrophages*, discussed in the next subsection) that evaluate attributes of ABP 501 that may potentially influence its performance in IBD, the Agency does not expect differences in reverse signaling activity that would preclude the demonstration that ABP 501 is highly similar to US-licensed Humira.

Figure 10. Comparison of Binding Affinity to mTNF- α for ABP 501, US-licensed Humira, and EU-approved Humira



Source: Adapted from figure in Amgen 351(k) BLA submission

Activation of Regulatory Macrophages

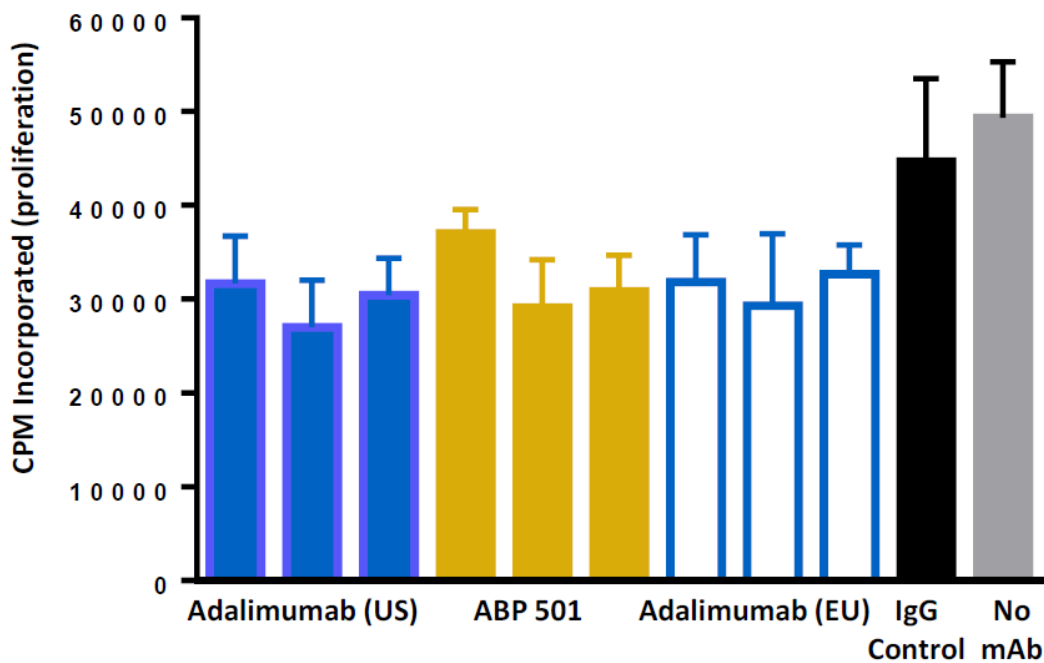
Amgen also developed assays to measure and compare the induction of regulatory macrophages based on the research on this topic and the possible role this mechanism may play in IBD indications.²⁰ As noted in Table 1, though distinct from *Reverse*

²⁰ Vos, A. C. W., et al. *Gastroenterology*, 2011, 140(1), 221-230.

Signaling and Apoptosis, this mechanism is considered plausible to explain the efficacy in these indications. The study used a mixed lymphocyte reaction (MLR) which evaluated both the ability to induce regulatory macrophages and consequently, their ability to inhibit T-cell proliferation. Primary PBMCs were incubated with the three products, and evaluated for activity. Data that demonstrates similar activity for ABP 501, US-licensed Humira, and EU-approved Humira with respect to T cell proliferation are presented in

Figure 11. Additionally, Amgen thermally degraded samples of ABP 501 (60°C for 14 days) prior to a second evaluation in this MLR study and demonstrated the MLR assay to be sufficiently sensitive to observe diminished activity for degraded samples (data not shown).

Figure 11. Comparison of Binding Affinity to mTNF-α for ABP 501, US-licensed Humira, and EU-approved Humira



Source: Adapted from figure in Amgen 351(k) BLA submission

Sub-Visible Particles

There is a consensus among immunologists that the immune system may be sensitive to particles in the 1 to 25 μm size range. Additionally, product-related particles of this size may increase the development of anti-product antibodies. Product-specific immune responses (i.e., anti-Humira or anti-ABP 501 antibodies) could potentially impact

product safety and efficacy²¹ and were assessed as part of the ABP 501 development program. This comparison included both clinical data (discussed in greater detail in the section on Immunogenicity below) as well as quality attributes, such as sub-visible particles, that may impact product immunogenicity.

Subvisible particles in the 10 to 25 μM range are typically controlled in injectable pharmaceutical products at lot release using compendial light obscuration techniques, which will be used by Amgen as a control strategy. Amgen also performed analytical similarity of ABP 501, US-licensed Humira and EU-approved Humira for proteinaceous particles in the 2-10 μM range. Two techniques, microflow imaging (MFI) and light obscuration (HAIC), were used. The Applicant used a pooling approach to create additional lots of drug product in order to generate additional lots of material. The analytical similarity assessment included 7 lots of both US-licensed Humira and EU-approved Humira, and 15 lots of ABP 501. Similar results were observed for all products based on a quality range analysis.

Comparative Stability Studies

Amgen has evaluated comparative stability of ABP 501, US-licensed Humira and EU-approved Humira in an accelerated stability trend study. Separate studies were performed at three different temperatures for differing durations: at 50°C for 14 days, at 40°C for 3 months, and at 25°C for 6 months. Analyses performed revealed the accumulation of aberrant charge isoforms (CEX-HPLC), fragmentation (rCE-SDS), and loss of potency (*in vitro* bioactivity) to be stability-indicating parameters. The stability patterns of the three products were equivalent.

Process-related Substances and Impurities

The types and levels of process-related substances and impurities in the three products were assessed quantitatively by the methods typically used by the biotechnology industry. Such substances originate from the complex biological culture system (e.g., HCPs, DNA and media components, etc.) or the purification process (e.g., leachates from chromatography resins). The goal in bioprocessing is to remove these inevitable undesirable components of bioreactor cell culture to levels as low as achievable by the downstream purification. The three products all achieved acceptably low levels of residual impurities (data not shown).

General Properties

The Applicant included additional measures in their analytical similarity assessment that considered general characteristics. These studies included the deliverable volume of the prefilled syringe, the osmolality (the amount of solute per quantity of solvent), the pH

²¹ Rosenberg AS, Verthelyi D, Cherney BW. J Pharm Sci. 2012 Oct;101(10):3560-7.

of the drug product solutions, visual appearance, and polysorbate (b) (4) content (b) (4) (b) (4)). Similar results for ABP 501, US-licensed Humira, and EU-approved Humira were observed.

Summary of Analytical Similarity Assessment

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. As noted in the *Reverse Signaling and Apoptosis* section, additional data in support of evaluation of reverse signaling as one of the potential mechanisms of action in IBD is pending at the time of this document. These data, if determined to be adequate, would further support a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. 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 mTNF- α , and evaluation of a mechanism unique to IBD indications, *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.

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 and nonclinical studies that used EU-approved Humira, to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira.

7 Pharmacology/Toxicology

Executive Summary

The nonclinical development program for ABP 501 was considered adequate to support clinical development. Two nonclinical studies were submitted in support of the BLA: (1) a toxicokinetic (TK) study in cynomolgus monkeys comparing ABP 501 vs. US-licensed Humira and (2) a toxicity/TK study in cynomolgus monkeys comparing ABP 501 vs. US-licensed Humira.

Collectively, there was no evidence in the aforementioned nonclinical studies conducted in cynomolgus monkeys to indicate potential clinical safety concerns associated with ABP 501 administration. The TK and repeat-dose toxicity profiles of ABP 501 were considered comparable to that of US-licensed Humira in cynomolgus monkeys.

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 are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective.

Conclusion

In summary, the animal studies submitted, demonstrate the similarity of ABP 501 to US-licensed Humira in terms of the nonclinical pharmacokinetic and repeat-dose toxicity profiles. From the Pharmacology and Toxicology perspective, 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.

8 Clinical Pharmacology

Executive Summary

The objectives of clinical pharmacology program are 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 pharmacokinetic (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.

Description of Relevant Clinical Pharmacology Studies

The PK of ABP 501 following SC administration has been characterized in studies using US-licensed Humira and/or EU-approved Humira as the comparator product. The summary of each relevant study design is described below.

- Study 217 was a randomized, double-blind, three-arm, parallel-group study following a single 40-mg/0.8 mL SC injection via 1-mL PFS to compare the PK, safety, tolerability, and immunogenicity of ABP 501, EU-approved Humira, and US-licensed Humira in healthy subjects (N=67-69/arm). The PK endpoints evaluated in this study were AUC_{inf} , AUC_{0-last} , and C_{max} .

As described in the draft guidance for Industry entitled, “Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product,”²² a single-dose, randomized study is generally the preferred design for PK similarity assessments. A parallel group design is appropriate for adalimumab because it has a long half-life and high immune response rate that may affect the PK similarity assessments upon repeated dosing. Additionally, conducting the study in healthy subjects is reasonable as it is more sensitive in evaluating the product similarity due to lack of potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. The 40 mg SC dose tested is relevant as it is within the approved adult dose range of 40 to 160 mg of US-licensed Humira.

- Study 262 was a randomized, double-blind, active comparator-controlled, 26-week study in subjects with moderate to severe RA who had an inadequate response to methotrexate (MTX). (N=262-264/group). Subjects received ABP 501 or US-licensed Humira (1:1 ratio) at 40 mg SC every 2 weeks (Q2W), and the last dose is at week 22. Trough serum concentrations were assessed for comparison between ABP 501 and US-licensed Humira in RA patients.
- Study 263 was a randomized, double-blind, active comparator-controlled study in adult subjects with at least 6 months duration of moderate to severe Ps. Subjects received ABP 501 or EU-approved Humira (1:1 ratio, N=173-174/group) at an initial loading dose of 80 mg SC on week 1/day 1 followed by 40 mg SC starting 1 week after the loading dose, then Q2W thereafter. At week 16, eligible subjects who continued treatment beyond week 16 were re-randomized in a blinded fashion 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 in a 1:1 ratio to either continue treatment with EU-approved Humira or to transition to and continue treatment with ABP 501. Trough serum concentrations were assessed for comparison between ABP 501 and EU-approved Humira in PS patients.

Results of Clinical Pharmacology Studies

Study 217: Pharmacokinetics Results

In the dedicated PK study 217, 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%) as summarized in Table 9 and depicted in Figure 12.

²² Guidance for Industry “Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product.” May 2014.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf>

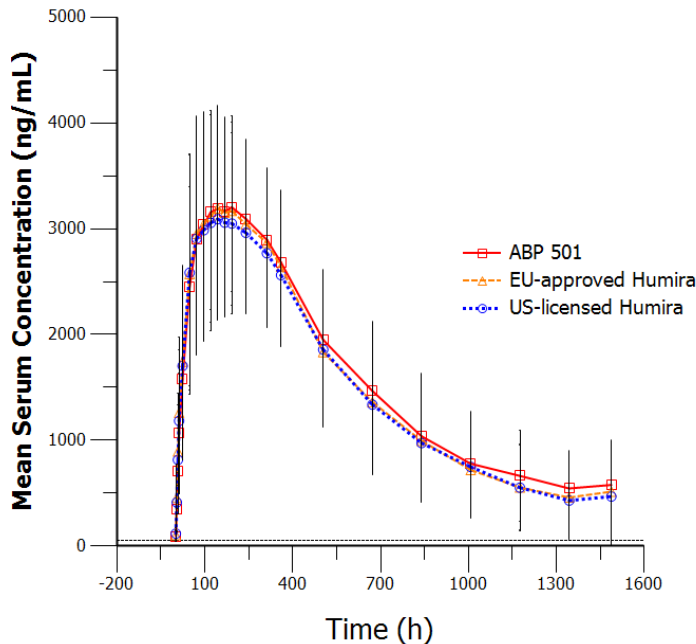
These data establish the PK similarity between ABP 501 and US-licensed Humira. Further, they establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP 501 to US-licensed Humira.

Table 9. PK Analysis of the 3-Way PK Bridging/PK Similarity Study 217

Comparison	Parameter	Adjusted GMR%	90% CI (%)
ABP 501 vs US-licensed Humira	Cmax	103.23	(94.37, 112.93)
	AUC0-t	102.83	(90.48, 116.87)
	AUC0-inf	107.52	(94.19, 122.74)
ABP 501 vs EU-approved Humira	Cmax	96.22	(87.80, 105.45)
	AUC0-t	101.60	(89.14, 115.80)
	AUC0-inf	104.95	(91.82, 119.95)
EU-approved Humira vs US-licensed Humira	Cmax	107.29	(94.36, 121.98)
	AUC0-t	101.21	(84.28, 121.55)
	AUC0-inf	102.45	(84.89, 123.64)

Source: FDA analysis of data from Amgen 351(k) BLA submission
 CI: confidence interval; GMR: geometric mean ratio

Figure 12. PK Profiles Following a Single SC Dose 40mg of ABP 501, EU-approved Humira, or US-licensed Humira in Healthy Subjects (Study 217)

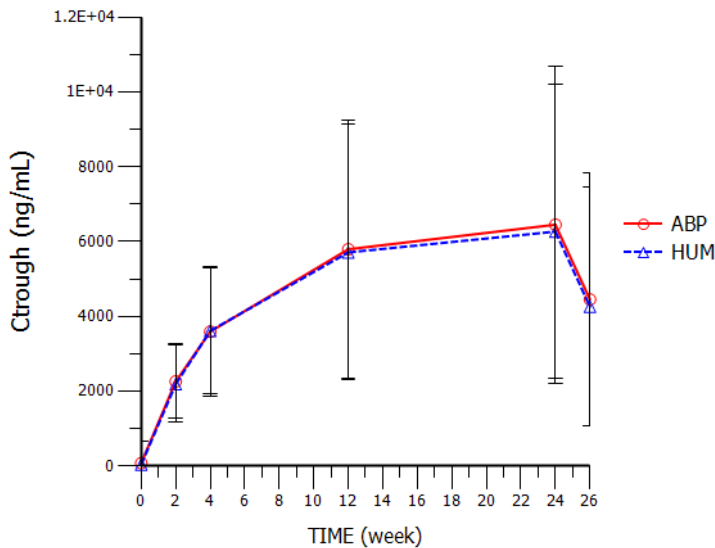


Source: FDA analysis of data from Amgen 351(k) BLA submission

Study 262 Pharmacokinetics Results

In study 262, trough serum concentrations for ABP 501 and US-licensed Humira were compared. PK samples were collected pre-dose on day 1 and at weeks 2, 4, 12, 24, and at the end of study visit (week 26) in RA patients. As shown in Figure 13, the trough concentrations are comparable at each time point between ABP 501 and US-licensed Humira.

Figure 13. Trough Concentration at Weeks 4 and 12 Following Multiple SC Dosing (40 mg) of ABP 501 or US-Licensed Humira in RA Patients (Study 262)

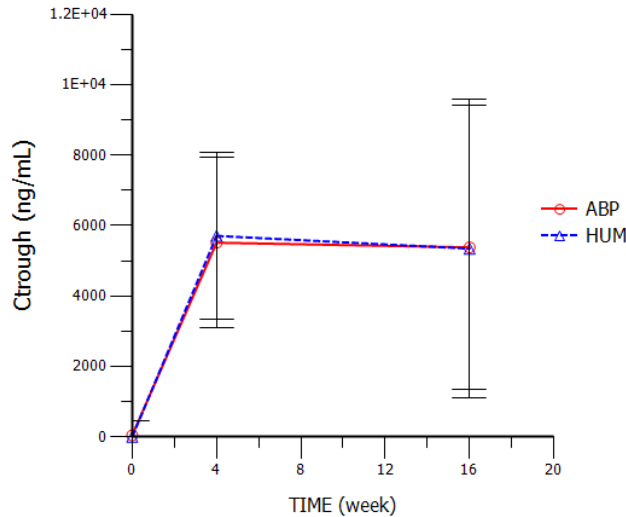


Source: FDA analysis of data from Amgen 351(k) BLA submission

Study 263 Pharmacokinetics Results

In study 263, sparse PK samples were collected at pre-dose on day 1 and at weeks 4, 16, 20, 32, and at the end of study visit. Figure 13 showed the trough concentrations for ABP 501 and EU-approved Humira at week 4 and 16 before the re-randomization. The trough concentrations are comparable at each time point between ABP 501 and EU-approved Humira.

Figure 14. Ctrough at Weeks 4 and 16 Following Multiple SC Doses of ABP 501 or EU-approved Humira in PsO Patients (Study 263)



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

Extrapolation of the PK Data for ABP 501

The PK of ABP 501 is comparable across the various studied populations including healthy subjects and patients with RA and PsO. 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.²³ The pharmacokinetics of US-licensed Humira in patients with AS were similar to those in patients with RA. 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. Since similar PK was demonstrated between ABP 501 and US-licensed Humira as discussed above, a similar PK profile would be expected for ABP 501 in patients across the indications being sought for licensure.

Clinical Pharmacology Summary

Overall, the submitted clinical pharmacology studies are adequate to:

- 1) Demonstrate similarity of exposure between ABP 501 and US-licensed Humira. The PK study 217, conducted in healthy subjects, is considered sufficiently sensitive to detect clinically significant differences in exposure among the

²³ FDA-approved Humira labeling

products. Single-dose PK similarity pre-specified margins were met. The demonstration of similar exposure supports a finding of biosimilarity between the ABP 501 and US-licensed Humira.

- 2) Establish the PK component of the scientific bridge to justify 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.
- 3) Justify the relevance of the PK findings from the ABP 501 clinical program to the indications that were not directly studied in the ABP 501 clinical program, for which US-licensed Humira is licensed and for which the Applicant is seeking licensure.

9 Clinical Outcomes

Executive Summary

To support the demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira, in addition to the PK similarity study in healthy volunteers (Study 217) discussed above, Amgen submitted clinical safety, immunogenicity, and efficacy data from two contemporaneous comparative clinical studies. The key design features of these studies are summarized in Table 10:

Table 10. Key Design Features of ABP 501 Clinical Studies

Study <i>(Dates conducted)</i>	Objective	Design	Subjects	Treatments
PK Similarity Study				
20110217 <i>07/12-10/12</i>	3-way PK similarity, safety, immunogenicity	R, PG, SD, 3-way PK bridging	203 Healthy Subjects	40 mg SC: <ul style="list-style-type: none"> • ABP 501 • US-Humira • EU-Humira
Comparative Clinical Studies				
20120262 <i>10/13-11/14</i>	Efficacy, safety, immunogenicity in RA	26 Weeks, R, DB, PG	526 Patients with RA	40 mg SC Q2W+MTX: <ul style="list-style-type: none"> • ABP 501 • US-Humira
20120263 <i>10/13-03/15</i>	Efficacy, safety, immunogenicity in PsO	R, DB, PG Re-randomized at Week 16 to either continue EU-Humira or transition to ABP 501	350 Patients with PsO	80 mg SC Day 1, then 40 mg SC Q2W from Wk2: <ul style="list-style-type: none"> • ABP 501 • EU-Humira
<small>R: randomized; PG: parallel group; SD: single dose; DB: double-blind; RA: rheumatoid arthritis; PsO: plaque psoriasis; SC: subcutaneous; Q2W: every 2 weeks; MTX: methotrexate</small>				

- Study 20120262 (Study 262) was a randomized, double-blind comparative clinical study of ABP 501 and US-licensed Humira in subjects age 18 to 80 with moderate to severe rheumatoid arthritis (RA) who had an inadequate response to methotrexate (MTX). The study enrolled 526 subjects, 264 randomized to the ABP 501 arm and 262 randomized to the US-licensed Humira arm and all randomized patients received at least one 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 71.2% of patients randomized to ABP 501 and 72.1% 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 $\pm 12\%$ 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. There was about 6% dropout in the study, leading to some missing data in important analyses. However, tipping point sensitivity analyses demonstrated that the conclusion of similarity was credible despite the missing data. The totality of available information also largely supports the assay sensitivity of Study 262. Therefore, the collective evidence from Study 262 supports similar efficacy between ABP 501 and US-licensed Humira in patients with RA.
- Study 20120263 (Study 263) was a randomized, double-blind comparative clinical study of ABP 501 and EU-approved Humira in subjects age 18 to 75 years old with moderate to severe plaque psoriasis. The study included data on subjects who underwent a single transition from EU-approved Humira to ABP 501 after Week 16. The study enrolled 350 subjects, 175 randomized to the ABP 501 arm and 175 randomized to the EU-approved Humira arm, of which 347 received at least one dose of study product. Subjects were enrolled in Europe, Canada, and Australia. The primary endpoint was the percent improvement in PASI (Psoriasis Area Severity Index) from Week 1 to Week 16. The pre-specified similarity margin for the confidence interval for the difference in means was $\pm 15\%$. The mean percent improvement in PASI score was similar on the ABP 501 and EU-approved Humira arms (80.9% vs. 83.1%) and the corresponding 90% confidence interval for the difference of (-6.6, 2.2) was within the pre-specified margin of $\pm 15\%$. The results on the secondary endpoints of PASI 75, static Physician's Global Assessment (sPGA) response, and reduction in body surface area (BSA) were consistent with the results of the primary endpoint. The enrolled population in Study 263 was similar to the populations enrolled in two historical placebo-controlled trials of Humira (Saurat (2008)²⁴ and Menter

²⁴ Saurat JH et al, Br J Dermatol. 2008; 158: 558-66

(2008)²⁵). The point estimate for percent improvement in PASI for EU-approved Humira from Study 263 was similar to the estimates observed for this endpoint in the two historical studies (83% in Study 263 vs. 76-81% in the historical studies). At Week 16, subjects who achieved at least PASI 50 response (at least 50% improvement from baseline) continued into the second treatment period. All subjects originally randomized to ABP 501 continued treatment with ABP 501 through Week 48. Subjects originally randomized to EU-approved Humira were re-randomized 1:1 to either continue treatment with EU-approved Humira or switch to ABP 501 through Week 48 to provide a descriptive comparative assessment of safety and immunogenicity between these re-randomized cohorts.

The safety analysis of the ABP 501 clinical program in the two studied conditions of use, RA and PsO, and in healthy subjects in the PK single dose Study 217, has not identified notable difference in the safety profile between ABP 501, US-licensed Humira, and EU-approved Humira. Further, the single transition from EU-approved Humira to ABP 501 after Week 16 in Study 263 did not result in increase in adverse events, supporting the safety of the clinical scenario where non-treatment naïve patients transition to ABP 501. The clinical safety and immunogenicity data using two labeled doses (40 mg Q2W SC on the background, and a loading dose of 80 mg on Day 1, followed by 40 mg Q2W SC starting one week later) for US-licensed Humira either as a monotherapy or in combination with methotrexate, in two distinct patient populations, showed similar safety profile between ABP 501 and US-licensed Humira (Study 262) and EU-approved Humira (Study 263).

The FDA review of the clinical data from the comparative clinical studies in patients with RA and PsO supports a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the studied indications.

Analysis of Clinical Efficacy Data from ABP 501 Clinical Program

Comparative Clinical Study 262 in RA

Study Design

Study 262 was a randomized, double-blind comparative clinical study of ABP 501 and US-licensed Humira in subjects with moderate to severe rheumatoid arthritis despite treatment with methotrexate. The study consisted of patients of ages 18 to 80 years who had been diagnosed with RA, as determined by meeting 2010 American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) classification criteria for at least 3 months prior to screening. Active disease was defined by the presence of six or more swollen joints, six or more tender joints, and at least one of the

²⁵ Menter A et al, J Am Acad Dermatol. 2008; 58(1): 106-15

following: an erythrocyte sedimentation rate (ESR) greater than 28 mm/h, and a serum C-reactive protein (CRP) concentration greater than 1.0 mg/dL. Patients had been on methotrexate for at least 12 consecutive weeks, with a stable dose (7.5 to 25 mg/week) for at least 8 weeks, and they also received folic acid during the study. Patients previously treated with two or more biological therapies for RA or who had received disease-modifying antirheumatic drugs (DMARDs) other than methotrexate (e.g., leflunomide, cyclosporine, azathioprine, or cyclophosphamide) in the past 4 weeks were excluded. Subjects were randomized 1:1 to ABP 501 or US-licensed Humira administered via subcutaneous (SC) injection at a dose of 40 mg every 2 weeks until week 22. No dose reductions or changes were allowed. Randomization was stratified by region (Eastern Europe versus Western Europe versus North & Latin America) and prior biologic use for RA (with prior biologic use capped at 40% of the study population). The primary timepoint for efficacy assessment was Week 24.

Brief Description of Efficacy Endpoints

The primary endpoint 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 (CRP) 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 $\pm 12\%$, 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.

Discussion on the Similarity Margin

The Applicant pre-specified a similarity margin of (0.748, 1/0.748) with respect to the risk ratio and provided a justification for the margin based on historical data from one randomized clinical trial of adalimumab (Keystone 2004)²⁶ and the goal of preserving at least 50% of the effect size of US-licensed Humira. The Agency does not agree with the Applicant’s selection of historical studies, as three important studies were not included in the meta-analysis. The Agency also does not agree with the proposed (0.748, 1/0.748) margin. Instead, FDA recommends the use of the absolute difference scale, as this scale is considered important from a clinical perspective for an evaluation of benefit-risk in clinical trials in RA. The Agency also recommends a margin of ±12%.

The ±12% similarity margin was based on considerations aimed at weighing the clinical importance of different losses in effect against the feasibility of different study sizes. In a comparative clinical study designed with 90% power to reject absolute differences greater than 12% in magnitude, observed differences larger than approximately 6% will result in a failure to establish similarity. Therefore, the comparative clinical study will be able to rule out losses in ACR20 response greater than 12% with high (at least 95%) statistical confidence, and will be able to rule out losses greater than around 6% with moderate (at least 50%) statistical confidence. The lower bound of the proposed similarity margin (-12%) also corresponds to the retention of roughly 50% of conservative estimates of treatment effect sizes relative to placebo for adalimumab (e.g. see Table 1).

Table 11. Historical Effect of Humira on ACR20 Response in Placebo-Controlled Trials

Study	Week	MTX + Placebo		MTX + Adalimumab		Difference in % Response
		N	ACR Response	N	ACR Response	
Keystone (2004) ²⁷	24	200	30%	207	63%	34%
Weinblatt (2003) ²⁸	24	62	15%	67	67%	53%
Kim (2007) ²⁹	24	63	37%	65	62%	25%
Chen (2009) ³⁰	12	12	33%	35	54%	21%
Meta-Analysis (fixed effects ¹): Difference (95% CI)						35.0% (28.2%, 41.9%)
Meta-Analysis (random effects ²): Difference (95% CI)						35.4% (22.5%, 48.2%)
Heterogeneity p-value						0.04

¹ Based on Mantel-Haenszel weights

² Based on DerSimonian-Laird weights

²⁶ Keystone EC et al, Arthritis & Rheumatism. 2004; 50: 1400-1411

²⁷ Keystone EC et al, Arthritis & Rheumatism. 2004; 50: 1400-1411

²⁸ Weinblatt ME et al, Arthritis & Rheumatism. 2003; 48: 35-45

²⁹ Kim HY et al, J Rheumatology 2007; 10: 9-16

³⁰ Chen DY et al, J Formosan Medical Association. 2009; 108: 310-319

Study Conduct

The treatment groups in Study 262 were generally 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 target population of moderate-to-severe rheumatoid arthritis 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.

Study 262 randomized 526 subjects; 264 to ABP 501 and 262 to US-licensed Humira. Approximately 6% of subjects discontinued treatment during the double-blind treatment period (Table 12). The most common reasons for treatment discontinuation were adverse events and consent withdrawn.

Table 12. Disposition of Subjects in Study 262

	ABP 501	US-licensed Humira	Overall
N	264	262	526
Completed	243 (92%)	251 (96%)	494 (94%)
Withdrew from Study	21 (8%)	11 (4%)	32 (6%)
Adverse Event	6 (2%)	2 (1%)	8 (2%)
Patient consent withdrawn	11 (4%)	6 (2%)	17 (3%)
Patient lost to follow-up	2 (1%)	2 (1%)	4 (1%)
Significant protocol violation	1 (1%)	0 (0%)	1 (0%)
Other	1 (1%)	1 (1%)	2 (1%)

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

Efficacy Findings

Study 262 met the pre-specified similarity criterion for the primary endpoint of ACR20 response at Week 24. 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 13).

Table 13. 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 $\pm 12\%$. Patients who discontinued treatment were considered non-responders (NRI) in this analysis (Table 14).

Table 14. 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 $\pm 12\%$ (Table 15).

Table 15. 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

Missing Data

As described in the section on study conduct above, there was some early patient withdrawal in Study 262, leading to missing data in important analyses. Therefore, we requested from the Applicant and evaluated tipping point analyses to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing-not-at-random assumptions).

Table 16 displays estimated differences between ABP 501 and US-licensed Humira in the ACR20 response at Week 24, with varying assumptions about the differences on each treatment arm between outcomes in patients who withdrew from the study early and outcomes in patients who completed the study. As a point of reference, the response probabilities among completers on ABP 501 and US-licensed Humira were

77% and 75%, respectively. As seen in the table, there were no scenarios in which the 90% CI fails to rule out a 12% loss in the ACR20 response. Therefore, these tipping point sensitivity analyses support the findings of the key efficacy analyses in Study 262.

Table 16. Tipping Point Sensitivity Analysis for the ACR20 Response at Week 24

Shift for ABP 501 ¹	Shift for US-licensed Humira ¹				
	-0.700	-0.525	-0.350	-0.175	0.000
-0.700	0.002 (-0.063, 0.067)	-0.005 (-0.072, 0.061)	-0.014 (-0.080, 0.052)	-0.019 (-0.085, 0.047)	-0.023 (-0.088, 0.042)
-0.525	0.013 (-0.052, 0.078)	0.005 (-0.060, 0.071)	-0.003 (-0.068, 0.063)	-0.008 (-0.073, 0.057)	-0.012 (-0.077, 0.053)
-0.350	0.024 (-0.041, 0.088)	0.016 (-0.049, 0.081)	0.008 (-0.057, 0.072)	0.003 (-0.062, 0.067)	-0.001 (-0.066, 0.063)
-0.175	0.035 (-0.030, 0.100)	0.027 (-0.038, 0.93)	0.019 (-0.046, 0.084)	0.014 (-0.051, 0.079)	0.010 (-0.055, 0.075)
0.000	0.048 (-0.016, 0.111)	0.040 (-0.025, 0.105)	0.032 (-0.033, 0.096)	0.026 (-0.038, 0.090)	0.023 (-0.041, 0.086)

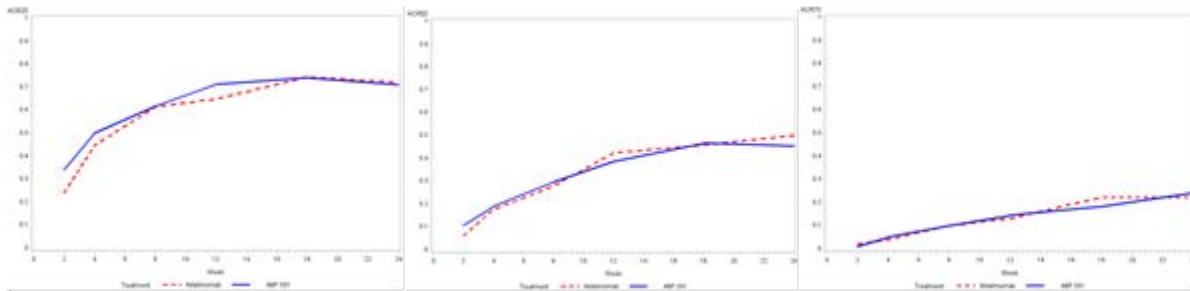
¹ Assumed difference in Week 24 ACR20 response between completers and dropouts. Responses in ABP 501/US-licensed Humira completers were 0.77/0.75

Source: Applicant's analysis of data from Amgen 351(k) BLA submission

Secondary Endpoints

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 (Figure 15). 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 17). In particular, the 90% CI (-0.20, 0.21) 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.

Figure 15. ACR20/50/70 Response¹ Probabilities over Time, Study 262



¹ Defined by remaining in the study and meeting ACR20 response criteria at Weeks 2, 4, 8, 12, 18, and 24

Table 17. 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

Assay Sensitivity and the Constancy Assumption

To reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must have assay sensitivity, or the ability to detect meaningful differences between the products, if such differences exist. In addition, to reliably evaluate whether the experimental treatment retains a certain proportion of the effect of the comparator versus placebo, the constancy assumption must be reasonable. The constancy assumption assumes that estimates of the effect of the comparator from historical, placebo-controlled trials are unbiased for the setting of the comparative clinical study. Table 8 describes key characteristics of four historical randomized, double-blind, parallel-group, placebo-controlled clinical trials of adalimumab in patients with active RA despite treatment with methotrexate, alongside key characteristics of Study 262. Important aspects of the design of the historical studies, including key inclusion/exclusion criteria, permitted concomitant medications, and baseline disease severity, were largely similar if not identical across the five

studies. One notable difference was the allowance of anti-TNF experience. The historical placebo-controlled trials did not allow anti-TNF experience while the comparative clinical study allowed it (although the proportion was relatively small at 28%). Estimated treatment effects with respect to ACR20 for the four historical trials were displayed earlier in Table 1. The estimated effects ranged from 21% to 53% on the absolute difference scale, with an overall estimated effect size of 35%. Thus, the information in Tables 1 and 8 indicates that (1) the designs of the four historical placebo-controlled clinical trials were largely similar to that of comparative clinical Study 262; and (2) there were relatively large and consistent treatment effects across the four historical studies.

This evidence of historical sensitivity to effects of adalimumab in similarly designed clinical trials provides some support for a conclusion that Study 262 had assay sensitivity. It is also important that a study designed to evaluate similarity has quality conduct, because conduct issues such as violations in eligibility criteria, poor adherence, cross-over between arms, or missing data tend to bias results toward the alternative hypothesis of equivalence. In Study 262, there were only 10 (1.9%) patients with failed eligibility criteria and only 2 patients received the wrong treatment prior to Week 24. Also, approximately 6% of patients discontinued treatment prior to Week 24 - this proportion is lower than the historical discontinuation rates, which ranged from 7% to 22%. With this high level of adherence, any potential concern about bias toward equivalence due to low adherence is mitigated. Since the discontinuation rate on the active control was only 4%, potential concerns about decreased efficacy relative to historical studies and violations in the constancy assumption are also mitigated. We also examined whether the within-group responses in the comparative clinical study were similar to those observed in previous placebo-controlled trials. The 72% ACR20 response rate on US-licensed Humira in Study 262 is slightly higher than historical rates, which ranged from 54% to 67%.

In summary, the design, conduct, and within-group response rates of Study 262 were largely similar to those characteristics in four historical clinical trials that demonstrated relatively large and consistent treatment effects of adalimumab over placebo. Therefore, the totality of available information supports the assay sensitivity of Study 262, in addition to the constancy assumption.

Table 8. Comparison of Key Characteristics of Historical Randomized, Placebo-Controlled Clinical Trials¹ of Adalimumab in RA and Comparative Clinical Study 262

	Study				
	Keystone	Weinblatt	Kim	Chen	Study 262
Selected inc/exc criteria	≥9 TJC; ≥6 SJC; CRP >1 mg/dL; RF+ or ≥1 joint erosion	≥9 TJC; ≥6 SJC	≥9 TJC; ≥6 SJC	≥9 TJC; ≥6 SJC	≥6 TJC; ≥6 SJC; ESR >28 mm/hr or CRP >1 mg/dL; RF+ or ACCP+
Anti-TNF experience allowed?	No	No	No	No	Yes (28%)
Concomitant DMARDS	Stable MTX, corticosteroids, NSAIDS	Stable MTX, corticosteroids, NSAIDS	Stable MTX	Stable MTX	Stable MTX
Region/Country	US & Canada	US & Canada	Korea	Taiwan	EU, NA, & LA
Baseline Characteristics of Study Population ²	TJC: 27; SJC: 19; Disease Duration: 11 yrs; HAQ-DI: 1.5	TJC: 28; SJC: 17; Disease Duration: 12 yrs; HAQ-DI: 1.6	TJC: 19; SJC: 12; Disease Duration: 6 yrs; KHAQ-DI: 1.4	TJC: 33; SJC: 22; Disease Duration: 6 yrs; HAQ-DI: 1.7	TJC: 24; SJC: 14; Disease Duration: 9 yrs; HAQ-DI: 1.5
Time of ACR20 Evaluation	Week 24	Week 24	Week 24	Week 12	Week 24
ACR20 Response on Humira	63%	67%	62%	54%	72%
Withdrawal on Humira	22% by Week 52	7% by Week 16 (34% escaped to ADA)	9%	N.A.	6%

Abbreviations: SJC=swollen joint count; TJC=tender joint count; DMARD=disease-modifying anti-rheumatic drug; EU=Europe; NA=North America; LA=Latin America; US=United States

¹ Based on best attempts to identify/estimate characteristics from literature review

² Means or medians, depending on what was reported in publication

In summary, the results of Study 262 demonstrated similar efficacy between ABP 501 and US-licensed Humira in patients with moderate-to-severe rheumatoid arthritis despite MTX therapy. The primary analysis of Week 24 ACR20 response ruled out the FDA-suggested margin of ±12%, and these results were supported by the analyses of key secondary endpoints and sensitivity analyses to address the potential effect of missing data.

Comparative Clinical Study 263 in PsO

Study Design

Study 263 was a randomized, double-blind comparative clinical study of ABP 501 and EU-approved Humira in subjects with moderate to severe plaque psoriasis. The study included data (including immunogenicity) on subjects transitioning from EU-approved Humira to ABP 501. Study 263 was conducted without any design input from the FDA. The study enrolled subjects age 18 to 75 with stable moderate to severe plaque psoriasis for at least 6 months involving at least 10% body surface area (BSA), PASI \geq 12, and static Physician's Global Assessment (sPGA) \geq 3 (moderate). Subjects were to be candidates for systemic therapy or phototherapy and were to have previously failed, had inadequate response, intolerance to, or contraindication to at least one conventional anti-psoriatic systemic therapy. The study enrolled 350 subjects, 175 randomized to the ABP 501 arm and 175 randomized to the EU-approved Humira arm, of which 347 received at least one dose of study product. Subjects were enrolled at 49 centers in 6 countries (Australia, Canada, France, Germany, Hungary, and Poland). Randomization was stratified by geographic region (Eastern Europe, Western Europe, Other) and prior biologic use for psoriasis. Subjects received subcutaneous injection of 80 mg at Week 1, 40 mg at Week 2 and 40 mg every 2 weeks thereafter. The primary timepoint for efficacy assessment was Week 16. At Week 16, subjects treated with EU-Humira, who achieved at least PASI 50 response (at least 50% improvement from baseline) continued into the second treatment period. Subjects originally randomized to ABP 501 continued treatment with ABP 501 through Week 48. Subjects originally randomized to EU-approved Humira were re-randomized 1:1 to either continue treatment with EU-approved Humira or undergo a single transition to ABP 501 through Week 48. Subjects were followed through Week 52.

Brief Description of Efficacy Endpoints

The primary endpoint was the percent improvement in PASI from Week 1 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 $\pm 15\%$. As mentioned in the section on Relevant Regulatory History above, 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).

Discussion on the Similarity Margin

Study 263 had a pre-specified similarity margin of $\pm 15\%$ for the primary endpoint of percent improvement in PASI. The Applicant did not provide a rationale in their protocol for the size of the proposed margin, and the margin was not discussed with FDA prior to the study. While ideally the similarity margin would be selected based on a consensus of what magnitude of difference for the endpoint is not clinically meaningful, in practice sample sizes may be constrained by feasibility concerns. Thus, although FDA and the Applicant did not discuss potential margins prior to the study, FDA examined available information from published literature to simulate how the issue of the appropriateness of the proposed similarity margin could have been approached prior to the study.

FDA considered two approaches for evaluating the Applicant’s proposed similarity margin. In the first approach, FDA calculated the percent preservation of the historical treatment effect of Humira relative to placebo. In the second approach, FDA used historical estimates of variability in the percent improvement in PASI endpoint to assess how the range of expected potential outcomes for the endpoint would compare with the proposed similarity margin. FDA evaluated historical published data from trials with Humira and other TNF- α inhibitors for the percent improvement in PASI endpoint. Three publications of historical placebo-controlled trials of Humira presented the mean percent improvement in PASI (Table 18). The average treatment effect across the three studies was approximately 60%.

Table 18. Historical Effect of Humira on Percent Improvement in PASI in Placebo-Controlled Trials

Study	Week	Humira		Placebo		Treatment Difference
		N	Mean	N	Mean	
Gordon (2006) ³¹	12	50	70	52	14	56
Saurat (2008) ³²	16	108	81	53	22	59
Menter (2008) ³³	12	814	76	398	15	61
Weighted Mean			76		16	60

None of the Humira publications presented information on the standard deviations for the percent improvement in PASI endpoint, which are needed to construct confidence

³¹ Gordon KB et al, J Am Acad Dermatol. 2006 Oct; 55(4): 598-606

³² Saurat JH et al, [Br J Dermatol](#). 2008 Mar;158(3):558-66

³³ Menter A, et al, J Am Acad Dermatol. 2008 Jan;58(1):106-15.

intervals. Thus, alternate sources are needed to find reasonable estimates of the standard deviation for this endpoint.

Two publications for studies of other TNF- α inhibitors presented standard deviations for the percent improvement in PASI endpoint (Table 19). A standard deviation (SD) estimate of 25, which is approximately midway between the estimates from these two studies (21.4 and 30.7), may be a reasonable approximation for the purpose of constructing confidence intervals to aid in the evaluation the Applicant’s proposed margin.

Table 19. Historical Estimates of the Standard Deviation for the Percent Improvement in PASI Endpoint in Trials of Other TNF- α Inhibitors

Study	Product	Week	N	Mean	Standard Deviation
Leonardi (2003) ³⁴	Enbrel	12	164	64.2	30.7
Reich (2005) ³⁵	Remicade	10	301	85.5	21.4

FDA calculated the percent preservation of the margin relative to the point estimate and approximate lower 95% confidence bound for the treatment effect using the point estimate and sample sizes from the largest of the three Humira studies (Menter) and SD=25. An approximate 95% confidence interval for the treatment effect for percent improvement in PASI for Humira would be 61 ± 3.0 (58.0, 64.0). Thus a 15% margin maintains at least 75% of the expected treatment effect using the point estimate of 61 and at least 74% of the expected treatment effect using the lower 95% confidence bound of 58. Although a 15% margin maintains a substantial portion of the expected treatment effect, because the estimated treatment effect relative to placebo is large, even retaining a substantial portion of the treatment effect relative to placebo could lead to clinically meaningful differences. Thus, FDA also evaluated the expected range of potential outcomes that still would meet various similarity margin criteria using the design assumptions of Study 263.

Under the sample size proposed by the Applicant for Study 263 at the design stage (340 subjects) and SD = 25, we would expect that approximate normal distribution 90% confidence intervals for the treatment difference would have widths approximately $\pm 4.5\%$. Thus, if a standard deviation estimate of 25 is reasonable, we would expect the point estimates for the treatment difference with magnitude up to approximately 10% to have corresponding 90% confidence intervals contained within a similarity margin of $\pm 15\%$ (Table 20). For narrower margins, we would expect point estimates for the difference with magnitude up to about 5% to have corresponding 90% confidence intervals contained within a similarity margin of $\pm 10\%$ and point estimates for the

³⁴ Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22.

³⁵ Reich K et al, Lancet. 2005; 366:1367-74.

difference with magnitude up to about 3% to have confidence intervals contained within a margin of $\pm 7.5\%$. Therefore, in addition to assessing the primary endpoint results using the Applicant's pre-specified margin of $\pm 15\%$, the FDA also assessed the results within this context about how much variability would be expected for a study with design and sample size like Study 263.

Table 20. Magnitude of the Largest Observed Treatment Effect Point Estimate Leading to a Conclusion of Similarity under Various Potential Margins (90% Confidence Interval with N=340 and SD=25)

Potential Margins	$\pm 7.5\%$	$\pm 10\%$	$\pm 12.5\%$	$\pm 15\%$
Magnitude of Maximum Observed Treatment Effect	2.9	5.4	7.9	10.4

Study Conduct

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 target 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.

Study 263 randomized 350 subjects, 175 each to ABP 501 and EU-approved Humira. Approximately 5% of subjects on each arm discontinued treatment during the initial treatment period (Table 21). The most common reasons for treatment discontinuation were adverse events and consent withdrawn. Most subjects (87% of ABP 501 subjects and 89% of EU-approved Humira) continued into the second treatment period where subjects on the EU-approved Humira arm were randomized to continue EU-approved Humira or undergo a single transition to ABP 501 and subjects on the ABP 501 arm continued ABP 501.

In the protocol, the Applicant defined the full analysis set (FAS) as all randomized subjects. For the analyses the Applicant defined the FAS as subjects who were randomized, dispensed medication, and had at least one post-baseline efficacy assessment. The efficacy analyses excluded 3 subjects who were not dispensed medication (one on the ABP 501 arm and 2 on the EU-approved Humira arm), and 2 subjects who had no post-baseline assessments (both on the ABP 501 arm).

Table 21. Disposition of Subjects in Study 263

	ABP 501	EU-approved Humira
Subjects Randomized	175	175
Subjects Treated	174 (99%)	173 (99%)
Discontinued treatment by Week 16	8 (5%)	10 (6%)
Adverse event	4 (2%)	5 (3%)
Consent withdrawn	3 (2%)	2 (1%)
Lost to follow-up	--	1 (<1%)
Protocol violation	1 (<1%)	2 (1%)
Re-randomized at Week 16	152 (87%)	156 (89%)
Not re-randomized at Week 16	23 (13%)	19 (11%)
Protocol-specified criteria ^a	13 (7%)	8 (5%)
Adverse events	6 (3%)	5 (3%)
Consent withdrawn	3 (2%)	2 (1%)
Lost to follow-up	--	2 (1%)
Protocol violations	1 (<1%)	2 (1%)

^a <PASI 50 or missing Week 16 PASI score

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

Efficacy Findings

Primary Endpoint

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 $\pm 15\%$. Correspondingly, the 90% confidence interval also fell within the $\pm 15\%$ margin. Because the lower 90% confidence bound was -6.6, the study would meet the similarity criteria for margins of $\pm 7\%$ or larger. Missing data was imputed using LOCF (Table 22).

Table 22. 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

Missing Data

The Applicant conducted sensitivity analyses using the per protocol population and observed cases for the primary endpoint. The results of these analyses are similar to the analysis in the FAS population (Table 23). FDA conducted additional sensitivity analyses for the handling of missing data. The Applicant’s FAS population excluded two subjects who were dispensed medication but had no post-baseline efficacy assessments. Both subjects were on the ABP 501 arm. Including these subjects in the primary analysis using baseline observation carried forward leads to similar results with a slightly larger estimated treatment difference of -3.1. FDA also conducted sensitivity analyses using relatively extreme differential imputation for the percent improvement in PASI, where subjects with missing data on one arm are imputed assuming no improvement from baseline (0%) and subjects with missing data on the other arm are imputed assuming full improvement (100%). While these two imputation methods shift the estimated treatment difference to -6.3 and +2.3, the 90% confidence bounds for both sensitivity analyses remain within the bounds of -11% to +7% and thus the confidence bounds remain within the pre-specified margins of ±15% even under relatively differential imputation assumptions. Thus the results of the sensitivity analyses for handling missing data are consistent with the primary analysis.

Table 23. Sensitivity Analyses for the Percent Improvement in PASI at Week 16, Study 263

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

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

Secondary Endpoints

The secondary endpoints were PASI 75, sPGA response (clear or almost clear), and reduction in BSA. The Applicant also assessed PASI 50 and PASI 90, though these analyses were not pre-specified. 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 24). Although the point estimates for these secondary endpoints trended towards a lower response on the ABP 501 arm relative the EU-approved Humira arm, the Agency believes 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 comparator Humira to account for the observed trends in the secondary endpoints in Study 263.

Table 24. 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 25).

Table 25. 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

Assay Sensitivity and the Constancy Assumption

To reliably evaluate whether there are clinically meaningful differences between two products, a comparative clinical study must have assay sensitivity, or the ability to detect meaningful differences between the products, if such differences exist. In addition, to reliably evaluate whether the experimental treatment retains a certain proportion of the effect of the comparator versus placebo, the constancy assumption must be reasonable. The constancy assumption assumes that estimates of the effect of the comparator from historical, placebo-controlled trials are unbiased for the setting of the comparative clinical study. The disease-related inclusion criteria for Study 263 were similar to the inclusion criteria for Saurat (2008) and Menter (2008). Gordon (2006) had less restrictive inclusion criteria (Table 26). The Saurat and Menter studies reported mean percent improvement in PASI values at either Week 12 or Week 16 for Humira ranging from 76-81% with corresponding placebo means ranging from 15-22% (Table 18, above). The point estimate for EU-approved Humira from Study 263 was slightly higher than the estimates observed in the historical studies at 83%. Thus, Study 263

does not represent a loss of efficacy relative to historical studies and the constancy assumption and assay sensitivity assumption appear reasonable.

Table 26. Comparison of Key Baseline Characteristics of Historical Randomized, Placebo-Controlled Clinical Trials of Adalimumab in PsO and Comparative Clinical Study 263

	Gordon (2006)	Saurat (2008)	Menter (2008)	Study 263
Selected inclusion criteria	BSA ≥ 5	BSA ≥ 10 PASI ≥ 10 sPGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 sPGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 sPGA ≥ Mod
Region/Country	US, Canada	Europe, Canada	US, Canada	Europe, Canada

In summary, the Applicant has provided data to support the demonstration of similarity in clinical efficacy between ABP 501 and EU-approved Humira in patients with moderate-to-severe plaque psoriasis. The primary analysis was supported by the analysis of key secondary endpoints and sensitivity analyses accounting for the missing data. Although the point estimates for the secondary endpoints trended towards a lower response on the ABP 501 arm relative the EU-approved Humira arm, FDA believes that these results are confounded by variability in dichotomized outcomes, among other reasons, and do not preclude a finding of no clinically meaningful differences between ABP 501 and US-licensed Humira.

Overall Conclusion on Efficacy

In summary, the Applicant has provided statistically robust comparative clinical data demonstrating similar efficacy between ABP 501 and EU-approved Humira in patients with moderate-to-severe RA despite methotrexate, using 40 mg Q2W SC dosing on background methotrexate, and in patients with moderate-to-severe PsO, using a loading dose of 80 mg on Day 1, followed a week later by 40 mg Q2W SC dosing as a monotherapy. The primary analysis was supported by the analysis of key secondary endpoints and sensitivity analyses accounting for the missing data. The results from the ABP 501 clinical program support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira in the indications studied.

Analysis of Clinical Safety in ABP 501 Clinical Program

Adequacy of the safety database

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 health volunteers 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.

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.

Overview of Safety

No new safety signals were identified in the ABP 501 group compared to the known adverse event profile of US-licensed Humira. Overall, there were no major differences in adverse events (AE), serious adverse events (SAE), or AEs leading to discontinuations between the treatment groups. Infections were the most common AE in all treatment groups (ABP 501, US-licensed Humira and EU-approved Humira). Adverse events leading to discontinuation were infrequent and balanced between treatment arms. Reports of hypersensitivity and injection site reactions were balanced between treatment arms with a single case of anaphylaxis reported in an ABP 501-treated male during Study 263. No deaths were reported in the ABP 501 development program. An overview of AEs across the controlled studies is summarized in Table 27.

Table 27. Overview of Deaths, SAEs, and Events of Interest in Studies 262 in RA, 263 in PsO, and 217 in Healthy Subjects

	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)	US-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

Death

As of the original BLA submission, no deaths were reported in the ABP 501 development program.

Nonfatal Serious Adverse Events (SAE)

The proportion of patients who experienced at least one SAE was similar between the two treatment groups, ABP 501 and the comparator, during the controlled period of clinical studies as detailed in Table 27 above. The most frequently reported SAEs were infections and cardiac disorders and were similar between both treatment groups. SAEs across the system organ classes (SOCs) showed a similar distribution with minor numerical differences between each group. There was no notable difference in the incidence of SAEs following a single transition of PsO patients from EU-approved Humira to ABP 501 in Study 263. The different SOC of SAEs or the pattern of SAEs in the studies comparing ABP 501 and Humira was consistent with the known safety profile of US-licensed Humira.

Discontinuations due to Adverse Events

The proportion of patients discontinuing due to an adverse event was similar between ABP 501 and EU-approved Humira as detailed in Table 27 above. Infections were the most common reason for discontinuation in studies 262 and 263. Injection site reactions and drug hypersensitivity were the reason for discontinuation in single cases. There was no notable difference in the incidence of treatment discontinuation due to adverse

events following a single transition of PsO patients from EU-approved Humira to ABP 501 in Study 263.

Adverse Events of Special Interest (AESI)

The selection of AESI was informed by the known safety profile of US-licensed Humira as presented in the USPI and other published data and included infections, including serious and opportunistic infections, malignancies, hypersensitivity, anaphylaxis defined by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) Criteria,³⁶ demyelinating diseases, hematological reactions, heart failure, lupus-like syndrome, liver enzyme elevations, and injection site reactions. Due to the different study design and patient characteristics, the analysis of AESI is presented descriptively for each of the comparative clinical studies.

- ***Infections***

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 ($\geq 2\%$ 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 ($\geq 2\%$ 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

³⁶ Sampson HA et al., J Allergy Clin Immunol. 2006 Feb;117(2):391-7

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 ($\geq 2\%$ 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***

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 resolved.

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***

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 ($\geq 1\%$ 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, erythematous rash, allergic dermatitis, and urticaria. Three events (ABP 501, n=2; US-licensed 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 ($\geq 1\%$ 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, 3%), 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 NIAID/FAAN criteria³⁷ was identified in a ABP 501-treated subject, a 47-year-old man with an ongoing history of asthma, hypertension, diabetes mellitus, obesity, and elevated liver enzymes.

The analysis of the overall incidence of hypersensitivity, including anaphylaxis, indicate that a single transition of non-treatment naïve patients to ABP 501 is not likely to result in clinically significant reactions. These results are also consistent with the similar incidence of anti-drug antibodies between patients who transitioned from EU-approved Humira to ABP 501 compared to patients who continued on EU-approved Humira in the Study 263 as detailed in the subsection on Immunogenicity below.

- ***Injection Site Reactions***

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 ($\geq 1\%$ of subjects) types of injection site reactions included injection site erythema, injection site reaction, and injection site pruritis (data not shown).

³⁷ Sampson HA et al., J Allergy Clin Immunol. 2006 Feb;117(2):391-7

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. 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 PsO subjects compared to the other treatment arms.

- ***Other AESI***

Liver enzyme elevations were reported in approximately 4 to 5 percent in patients in Study 262 and 1 to 2 percent in study 263 with no notable differences between ABP 501 and comparator arms. Heart failure occurred only in study 262 (ABP 501, n=1; US-licensed Humira, n=2). No cases of drug-induced liver injury meeting Hy's law criteria were reported in ABP 501 clinical program. No lupus-like syndrome or demyelinating AEs were reported for subjects in ABP 501 program.

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 studies in the RA and PsO populations. No increase in AESI was observed following a single transition from EU-approved Humira to ABP 501 in Study 263 in PsO patients.

Common AEs

Nasopharyngitis, headache, and upper respiratory tract infection were the most common adverse events in the ABP 501 development program with event rates similar between ABP 501 and the comparator products. Following the single transition in Study 263, the common adverse event profile remained consistent and similar between

subjects who underwent the single transition from EU-approved Humira to ABP 501 and those who continued on EU-approved Humira. 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, further supporting a demonstration that there are no clinically meaningful differences between APB501 and US-licensed Humira in the indications studied.

Laboratory Abnormalities, 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.

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.”³⁸ 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

³⁸ Section 351(k)(2)(A)(i)(I) of the PHS Act.

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.

Immunogenicity Results

Study 217

No pre-existing ADAs were detected in subject samples at baseline. Table 28 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 28. Summary of Binding Antidrug Antibody Results, Study 217

Timepoint	Study 217 in Healthy Subjects		
	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 29, 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 29. 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)	US-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 30. 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 30. 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%)
<small>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</small>			

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 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 NAb 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 31 for Study 262 and in Table 32 for Study 263. The Agency acknowledges 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 31. 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 32. 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 none of the subjects were NAb positive 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 sample size of the subgroups is small resulting in wide confidence intervals.
- Exploratory post-hoc statistical models including the NAb-by-treatment interaction were analyzed for both Study 262 and Study 263 indicating that NAb do not have a statistically significant differential impact on efficacy between ABP 501 and comparator Humira products.

In light of these additional contextual pieces, the Agency does 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 adds to the totality of the

evidence to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

Overall Summary of Safety and Immunogenicity

The submitted safety and immunogenicity data and analyses using two dosing regimens (40 mg Q2W SC on the background of methotrexate, 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, 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. The FDA safety analyses are in consistent with the Applicant's.

10 Considerations for Extrapolation of Biosimilarity

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.³⁹ 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 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. 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.⁴⁰ The pharmacokinetics of US-licensed Humira in patients with AS were similar to those in patients with RA. Additionally, the steady-state trough concentrations were similar between pediatric patients with JIA or CD compared

³⁹ 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>

⁴⁰ FDA-approved Humira labeling.

to adult patients following the administration of US-licensed Humira. Since similar PK was demonstrated between ABP 501 and US-licensed Humira as discussed above, a similar PK profile would be expected for ABP 501 in patients across the indications being sought for licensure.

- 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. In RA, PsA, and AS, the recommended dose is 40 mg Q2W SC. Adalimumab is used without methotrexate in PsO and may be used with or without concomitant immunosuppression in PsA, CD and UC. 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). As stated previously in this document, the Agency has concluded that there is sufficient data to support similar immunogenicity between ABP 501, EU-approved Humira, and US-licensed Humira, and that there are no notable differences in immunogenicity between these products. Accordingly, similar immunogenicity would be expected for patients with JIA, PsA, AS, adult CD, and UC, receiving ABP 501.
- The mechanism(s) of action (MOA) relevant to the extrapolation of data to support biosimilarity in specific indications are discussed below.

Table 33. (Same as Table 1) Known and Potential (Likely or Plausible) Mechanisms of Action 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 literature on the topic of mechanisms of action of TNF inhibitors^{41,42,43}

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 33 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 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.

⁴¹ Oikonomopoulos A et al., Current Drug Targets, 2013, 14, 1421-1432.
⁴² Tracey D et al., Pharmacology & Therapeutics 117 (2008) 244–279.
⁴³ 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.⁴⁴ 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 33 may play a role.⁴⁵ 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.

As outlined in the CMC section above, 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. Based on the submitted robust analytical data (i.e., the extensive structural characterization, other functional assays, binding to mTNF- α , and evaluation of a related IBD mechanism, *Activation of Regulatory Macrophages*) that evaluate attributes of ABP 501 that may potentially influence its performance in IBD, the Agency does not expect differences in reverse signaling activity that would preclude the demonstration that ABP 501 is highly similar to US-licensed Humira to support extrapolation of biosimilarity to IBD indications.

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 IBD.

In aggregate, the evidence indicates that the extrapolation of biosimilarity to the indications for which Amgen is seeking licensure (JIA, PsA, AS, adult CD, and UC), is scientifically justified.

11 Summary

The comparison of the structural and functional properties of the clinical and commercial product lots of ABP 501 and US-licensed Humira supports a demonstration that they are highly similar, notwithstanding minor differences in clinically inactive components.

⁴⁴ 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

⁴⁵ Tracey D et al., “Tumor necrosis factor antagonist mechanisms of action: A comprehensive review”, *Pharmacology & Therapeutics* 117 (2008) 244–279

Amgen provided extensive analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Humira to a demonstration of biosimilarity of ABP 501 to US-licensed Humira.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between ABP 501 and US-licensed Humira, (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved Humira, (3) justify the relevance of the PK findings from the ABP 501 clinical program to the indications that were not directly studied in the ABP 501 clinical program for which US-licensed Humira is licensed and for which Amgen is seeking licensure.

The results of the clinical development program indicate that Amgen's data support a demonstration of "no clinically meaningful differences" between ABP 501 and US-licensed Humira in terms of safety, purity, and potency in the indications studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included two different chronic dosing regimens of ABP 501 and EU-approved Humira (40 mg Q2W SC on the background of methotrexate, and 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 (RA and PsO), and a single dose of 40 mg SC in healthy subjects of ABP 501, EU-approved Humira, and US-licensed Humira, adequately supports a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in RA and PsO. Further, the single transition from EU-approved Humira to ABP 501, as compared with continued treatment with EU-approved Humira during second period of Study 263 in PsO, did not result in different safety or immunogenicity. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to ABP 501.

In considering the totality of the evidence, the data submitted by the Applicant support a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in terms of the safety, purity, and potency of the product.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use to support their request that ABP 501 should receive licensure for the indications for which US-licensed Humira is currently licensed and for which Amgen is seeking licensure.