CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761024Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	*Electronic Stamp Date*
From	Nikolay P. Nikolov, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	351(k) BLA 761024
Applicant	Amgen, Inc.
Date of Submission	November 24, 2015
Scientific BsUFA Goal Date	September 24, 2016
Proprietary Name (Proposed) / Nonproprietary names	Amjevita, (b) (4) / ABP 501[1], adalimumab-atto
Dosage Forms / Strength	• 20 mg/0.4 mL solution in a single-dose prefilled syringe (PFS) • 40 mg/0.8 mL solution in a single-dose PFS • 40 mg/0.8 mL solution in a single-use prefilled autoinjector (AI)
Route of Administration	Subcutaneous
Proposed Indication(s)	1. Rheumatoid arthritis (RA) 2. Juvenile idiopathic arthritis (JIA) in patients 4 years of age and older 3. Psoriatic arthritis (PsA) 4. Ankylosing spondylitis (AS) 5. Adult Crohn's disease (CD) 6. Adult ulcerative colitis (UC) 7. Adult plaque psoriasis (PsO)
Recommended:	*Approval*

1. Introduction

This document is a cross discipline team leader (CDTL) review of the biologics license application (BLA) 761024 submitted by Amgen under section 351(k) of the Public Health Service Act (PHS Act) for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab). Amgen is seeking licensure of ABP 501 for the following indications for which US-licensed Humira is licensed:[2]

[1] In this document, I generally refer to Amgen's proposed product by the Amgen descriptor "ABP 501" which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product was determined to be "adalimumab-atto."
[2] FDA-approved Humira labeling

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

- 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 a 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 demonstrates 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 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-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 a spectrum of chronic dosing regimens of ABP 501 and US-licensed Humira (40 mg Q2W SC on the background of methotrexate, for Study 262, and EU-approved Humira with a loading dose of 80 mg on Day 1, followed by 40 mg Q2W SC starting one week later as monotherapy for Study 263) 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.

2. Background

The BPCI Act

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of the Affordable Care Act, which 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(i) 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 can be assessed 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.

Reference Product

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with a reference product. 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 should 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.

Relevant Regulatory History

The first interaction between Amgen and 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 US-licensed Humira to ABP 501 to provide a descriptive comparison with patients who continue on Us-licensed 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.

3. CMC/Product Quality

CMC Reviewer: Jun Park, Ph.D.; Acting Review Chief: Joel Welch, Ph.D.
CMC Statistical Reviewer: Meiyu Shen, Ph.D.; CMC Statistical Supervisor: Yi Tsong, Ph.D.
OBP Director: Steven Kozlowski, M.D.
Microbiology Reviewers: Bo Chi, Ph.D. (for Drug Substance) and Lakshmi Narasimhan, Ph.D. (for Drug Product); Acting Branch Chief: Patricia Hughes, Ph.D.
Facilities Reviewer: Steven Fong, Ph.D.; Branch Chief: Peter Qiu, Ph.D.
CDRH Review Team: Lana Shiu, Alan Stevens

- **General product quality considerations**

ABP 501 is a human monoclonal antibody based on a human immunoglobulin G1 (IgG1) framework produced in Chinese hamster ovary (CHO) cells. It consists of two heavy chains (451 amino acid residues each with N-linked glycan at the consensus glycosylation site on Asn301) and two light chains (214 amino acid residues each). The ABP 501 drug substance (DS) is subject to (b) (4) The manufacturing process for ABP 501 DS remained unchanged throughout development with the exception of small enhancements in the

manufacturing process to improve robustness. All drug substance lots were manufactured at One Amgen Center Drive, Thousand Oaks, CA 91320 (designated as ATO in this document). The DS is stored at (b) (4)ºC (described as (b) (4)ºC). The stability data support an ABP 501 DS expiration d d of (b) (4)months when stored between (b) (4)ºC.

The ABP 501 drug product (DP) was developed as a single-use pre-filled syringe and a single-use autoinjector in strengths approved for US-licensed Humira; it also has the same dosage form and route of administration as those approved for US-licensed Humira. ABP 501 is proposed to be supplied as a single-use sterile liquid solution for subcutaneous injection in 1 mL pre-filled syringe (PFS 40 mg/ 0.8 mL or 20 mg/0.4 mL) or as a single-use prefilled SureClick autoinjector (40 mg/ 0.8 mL). The ABP 501 DP formulation has different inactive ingredients than US-licensed Humira. The PFS contains 50 mg/mL DP in 10 mM acetate, 9.0% (w/v) sucrose, 0.10% (w/v) polysorbate 80, pH 5.2 in deliverable volume of 0.4 mL or 0.8 mL. The autoinjector is a single-use, disposable, (b) (4) pre-assembled presentation used for the DP. The AI contains a 27-gauge PFS with a deliverable volume of 0.8 mL of 50 mg/mL ABP 501. A new commercial filling site was introduced for the manufacture of commercial drug product. The DP 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. Analytical comparability was also demonstrated between the 0.8 mL PFS and the assembled autoinjector using biochemical, biophysical, and biological analytical methods. The DP is manufactured in Amgen Manufacturing Ltd, Juncos, Puerto Rico 00777 (designated as AML (b) (4) in this document) which has previously been approved for multi-product, (b) (4) manufacture of other sterile injectable products. The stability data support ABP 501 DP expiration dating period of 30 months when stored between 2ºC and 8ºC.

The Division of Microbiology Assessment review teams concluded, and I concur, that the DS and the DP are recommended for approval from a quality microbiology perspective.

The ABP 501 final DS and DP processes are fully validated, and the manufactured product is of a consistent quality. The controls that have been established for the routine manufacture of ABP 501 DS and ABP 501 DP meet regulatory requirements. However, the product quality review team recommends, and I agree with, the following post-marketing commitments (PMCs):

1. Perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.
2. Perform supplemental method validation and introduce a non-reduced CE-SDS test into the integrated control strategy for drug substance manufacture. Submit the analytical procedure, validation report, the proposed acceptance criterion, and the data used to set the acceptance criterion that will be provided in a CBE-0 supplement.

- **Analytical Similarity Assessment**

To determine whether ABP 501 is highly similar to US-licensed Humira, and to establish the adequacy of the analytical portion of the scientific bridge between ABP 501, US-licensed

Humira, and EU-approved Humira, Amgen evaluated and compared analytical data from multiple lots of 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 exercise used a comprehensive range of methods, 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 Fc-mediated functions. All methods were validated or qualified prior to the time of testing and demonstrated to be suitable for intended use.

- Primary Structure

The primary structure of ABP 501, US-licensed Humira, and EU-approved Humira was assessed by peptide mapping. These 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. The primary structure was also assessed by additional methods. 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 between ABP 501, US-licensed Humira, and EU-approved 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, PFS 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 ABP 501, US-licensed Humira, and EU-approved Humira, 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. Analytical comparability was

demonstrated between the 0.8 mL PFS and the assembled autoinjector, as discussed in the subsection on general product quality considerations above.

- Higher Order Structure

The secondary and tertiary structures of ABP 501, US-licensed Humira, and EU-approved Humira 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.

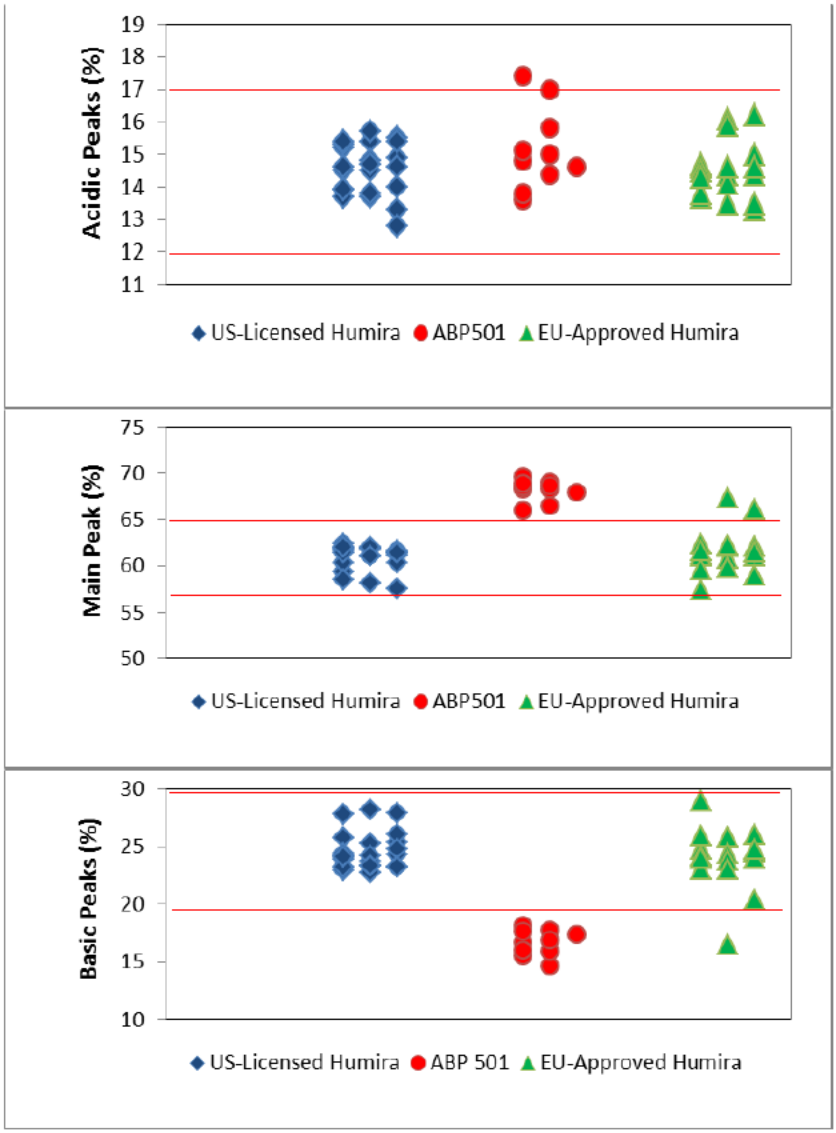
- Aggregates

Biopharmaceuticals typically contain very low levels of protein aggregates (<1%) which are measured and controlled at lot release and throughout shelf-life of the products. Small amounts of aggregation were present in ABP 501, US-licensed Humira, and EU-approved 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 and are below the levels which may potentially impact product immunogenicity. Additional measures, including Size Exclusion Chromatography with Light Scattering Detection (SEC-LSD), Field Flow Fractionation and Analytical Ultracentrifugation Sedimentation Velocity, confirmed similar aggregate levels between ABP 501, US-licensed Humira, and EU-approved Humira.

- Charge

Charge heterogeneity is commonly observed for all monoclonal antibodies and derives from post-translational modifications that typically include: deamidation, glycation, oxidation, and heterogeneity of the cleavage of the C-terminal chain. The charge profile for ABP 501, US-licensed Humira, and EU-approved Humira are resolved into three distinct regions that are commonly observed in monoclonal antibody products: acidic peaks, basic peaks, and the main peak. While the charge profiles are visually similar between the three products, some differences were 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 as depicted in Figure 1. The red bars depict the quality range analysis relative to US-licensed Humira provided by the Applicant.

Figure 1. 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

The Applicant provided data to demonstrate that 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. ABP 501, US-licensed Humira, and EU-approved Humira 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 products[3], and does not affect the potency of the product. 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

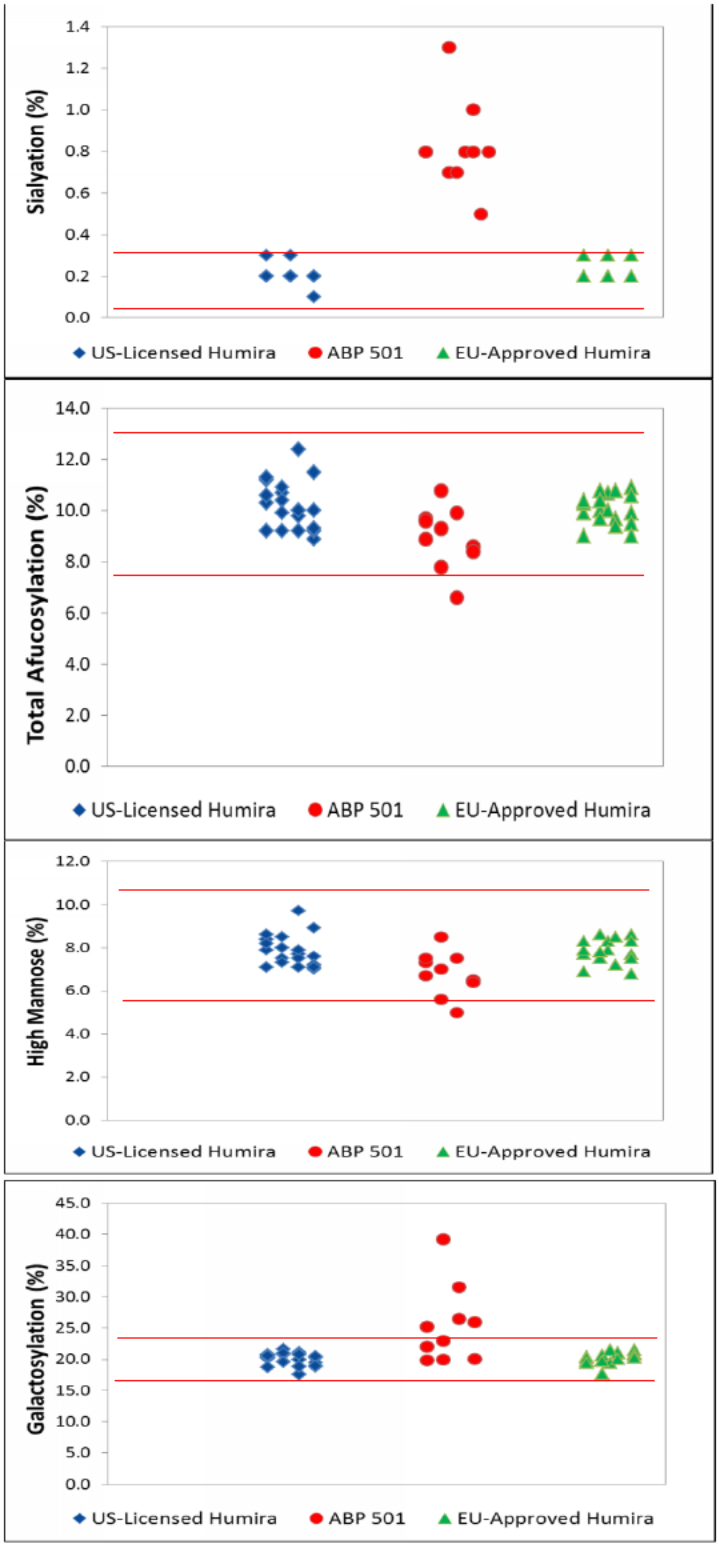
[3] Yi, D. et. al, MAbs. 2012 Sep 1; 4(5): 578–585.

peak levels were shown to have minimal effect on the potency of the product. Respectively, these differences are not considered to have clinically significant consequences.

- Glycan Structures

As shown in Figure 2, sight differences are observed in the % high mannose (trend toward lower for ABP 501), % total afucosylation (trend toward lower for ABP 501), % sialyation (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, US-licensed Humira, and EU-approved Humira (see the section on Clinical Pharmacology below below), similar ADCC activity, binding to FcγRIIIa (see discussion in the subsection on Fc Function below) and CDC activity for the three products (see discussion in the subsection on Fc Function below), these slight differences do not preclude a finding that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. We also note that these slight differences are not expected to have clinically meaningful consequences.

Figure 2. Comparison of Glycan Profile for ABP 501, US-licensed Humira, and EU-approved Humira



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

- Biological Activity and Mechanisms of Action

A number of bioassays were designed and qualified to evaluate potential functions of ABP 501, US-licensed Humira, and EU-approved Humira, including critical quality attributes such as binding and neutralization of TNF-α, as well as Fc effector functions.

TNF-α binding

The product quality team concluded, and I agree, that the data on TNF-α binding, assessed using an enzyme linked immunosorbent assay (ELISA), met the criteria for statistical equivalence between ABP 501 and US-licensed Humira (Table 1) and support a demonstration that ABP 501 is highly similar to US-licensed Humira. In addition, the product quality team concluded, and I agree, that TNF-α binding between ABP 501 and EU-approved Humira, and between US-licensed Humira and EU-approved Humira, met the criteria for statistical equivalence, which supports the analytical portion of the scientific bridge for clinical studies conducted with EU-approved Humira.

Table 1. Statistical Equivalence Testing Results for the TNFα 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 TNFα 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 TNFα 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 TNFα 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)%.

Inhibition of TNF-α-mediated Apoptosis

An apoptosis inhibition bioassay was used to measure neutralization of TNF-α. The product quality team concluded, and I agree, that the apoptosis inhibition activity data met the criteria for statistical equivalence between ABP 501 and US-licensed Humira (Table 2) and support a demonstration that ABP 501 is highly similar to US-licensed Humira. In addition, the product quality team concluded, and I agree, that apoptosis inhibition activity between ABP 501 and EU-approved Humira, and between US-licensed Humira and EU-approved Humira, met the criteria for statistical equivalence, which supports the analytical portion of the scientific bridge for clinical studies conducted with EU-approved Humira.

Table 2. Statistical 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 Receptor Binding

The binding affinity and activity of ABP 501, US-licensed Humira, and EU-approved Humira to various Fc receptors was measured. The binding activity was measured using AlphaLISA assays (FcγRI and FcγRIIa) or a cell-based assay (FcRn). Overall, the binding affinities of the three products were similar for FcRn, FcγRI and FcγRIIa (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.[4] Similar binding affinity to FcyRIIIa (158V), the high affinity FcyRIIIa receptor, was observed for all three products (10 lots each) and fell within the quality range of US-licensed Humira proposed by the Applicant (data not shown).

Fc Function: Antibody-Dependent Cellular Cytotoxicity (ADCC)

Unlike TNF-α binding, there is uncertainty regarding the criticality of Fc effector functions for the mechanism of action of US-licensed Humira (see Table 17 below). Thus, tests for Fc functions were examined for ABP 501, US-licensed Humira, and EU-approved Humira, using quality range testing defined by Amgen's data on US-licensed Humira rather than for statistical equivalence. These 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 (data not shown).

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

Fc Function: C1q Binding and Complement Dependent Cytotoxicity (CDC)

Despite the small differences observed in glycosylation patterns, similar CDC activity in validated assays was observed between ABP 501, US-licensed Humira, and EU-approved Humira based on a quality range analysis relative to US-licensed Humira (data not shown).

Fc Function: Reverse Signaling

The reverse signaling assay assesses the Fab and Fc-mediated functions of adalimumab and ABP 501 through engagement of transmembrane TNF-α (tmTNF) on the target cells and transmission of a signal into the cells which can cause apoptosis.

The Agency requested functional data on reverse signaling during the review cycle.[5] Amgen subsequently developed and validated an assay and provided results demonstrating similar apoptosis mediated by reverse signaling between ABP 501, US-licensed Humira, and EU-approved Humira based on a quality range analysis relative to US-licensed Humira (data not shown). The product quality review team determined, and I agree, that the results from the reverse signaling assay provided by the Applicant were acceptable and support a conclusion that ABP 501 is highly similar the US-licensed Humira.

Fc Function: Activation of Regulatory Macrophages

Amgen also developed and validated 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 inflammatory bowel disease (IBD) indications.[6] The data demonstrated similar activity for ABP 501, US-licensed Humira, and EU-approved Humira with respect to T cell proliferation in a mixed lymphocyte reaction (data not shown).

- Sub-Visible Particles

Subvisible particles in the 10 μM 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 analytical similarity assessment included 7 lots of both US-licensed Humira and

[5]These data were requested shortly before the Arthritis Advisory Committee (AAC) on July 12, 2016. In the materials provided to the AAC, FDA requested that the AAC evaluate the discussion and voting questions based on the premise that the additional data provided by the sponsor would not preclude a demonstration that ABP 501 is biosimilar to US-licensed Humira. See *Final Questions for the July 12, 2016 Meeting of the Arthritis Advisory Committee (AAC)* available at http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975.htm

[6] Vos, A. C. W., et al. Gastroenterology, 2011, 140(1), 221-230.

EU-approved Humira, and 15 lots of ABP 501. Similar results were observed for all products based on a quality range analysis.

- 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 Applicant provided data to demonstrate that the three products achieved acceptably low levels of residual impurities (data not shown).

- Comparative Stability Studies

Amgen 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 similar.

Conclusions on Analytical Similarity Assessment

In summary, 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. The product quality team concluded, and I agree, that the evidence submitted supports a demonstration that ABP 501 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components. 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, as well as Fc-mediated functions as potential mechanisms of action in IBD indications support a demonstration that ABP 501 has the same mechanisms of action as US-licensed Humira, to the extent that the mechanisms of action are known for US-licensed Humira. In aggregate, the analytical data (i.e., the extensive structural and functional characterization) 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 team also noted that the impurity profile of ABP 501 is acceptable and supports approval, and I agree.

Some tests indicate that slight differences in quality attributes are observed, including glycosylation pattern and charge variant profile. However, the product quality team concluded, and I agree, that these slight differences do not preclude a demonstration that ABP 501 is highly similar to US-licensed Humira. When ABP 501 is compared to US-licensed Humira, the biological functions that these subtle differences might impact are nevertheless

within the quality range of US-licensed Humira and do not preclude a demonstration that ABP 501 is highly similar to US-licensed Humira.

The product quality team also concluded, and I agree, that Amgen provided a sufficiently robust analysis, that includes three pairwise comparisons of ABP 501, US-licensed Humira, and EU-approved Humira that met the pre-specified criteria for analytical similarity, for the purposes of establishing the analytical component of the scientific bridge among the three products to justify the relevance of comparative data generated from clinical studies that used EU-approved Humira, to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira.

- **Devices**

The proposed presentations for ABP 501 include a subset of those currently approved for US-licensed Humira. ABP 501 is supplied as a single-use sterile liquid solution for subcutaneous injection in 1 mL pre-filled syringe (PFS 40 mg/ 0.8 mL or 20 mg/0.4 mL) and as a single-use prefilled SureClick autoinjector (40 mg/ 0.8 mL). The device constituent parts, the PFS and the autoinjector configurations, of the proposed ABP 501 presentations were reviewed by the Center for Devices and Radiological Health (CDRH).

The ABP 501 PFS is a single-use, disposable, handheld drug delivery device. The PFS incorporates a rigid needle shield (RNS), which is a non-rigid rubber needle shield with a rigid plastic cover, and a flange extender. (b) (4) ABP 501 is developed in the following PFS presentations:

- (b) (4) (not proposed for marketing at this time)
- 40 mg (0.8 mL) PFS with a 29-gauge (29G) staked-in-place needle
- (b) (4) (not proposed for marketing at this time)
- 20 mg (0.4 mL) PFS with a 29G staked-in-place needle

After assembly the different PFS presentations can be differentiated by the label, the color of the device constituent parts and the secondary packaging.

The autoinjector is based off of the SureClick platform (developed by (b) (4) on behalf of Immunex Corporation, an Amgen Inc. company) used for the administration of Enbrel (BLA 103795). The difference between the Enbrel SureClick device and the ABP 501 SureClick device is the exterior color to help patients differentiate between the two products. The proposed autoinjector materials of construction and device function specifications remain unchanged from Enbrel SureClick with the exception of color changes instituted in order for the patient to differentiate the 2 drugs. The ABP 501 SureClick autoinjector is a single-use, disposable, (b) (4) pre-assembled presentation used for the DP. The autoinjector contains a 27-gauge PFS with a deliverable volume of 0.8 mL of 50 mg/mL ABP 501. ABP 501 SureClick has shorter injection time than the Enbrel SureClick (b) (4)

The Applicant provided comprehensive device functional testing for both the PFS and the autoinjector presentations and the CDRH review team concluded that the PFS and the ABP 501 SureClick autoinjector configurations meet essential performance requirements. Based on the design verification/validation data in the application, and the amended additional in-process controls and release specification information, the CDRH review team's conclusion supports approval of ABP 501. I concur with the CDRH recommendation.

To support the proposed ABP 501 SureClick autoinjector, the Applicant submitted human factors study data. These data were derived from the studies conducted by Amgen for the Enbrel SureClick platform and that were previously reviewed by the Agency under BLA 103795. Because the Enbrel SureClick human factor study included representative RA, PsA, AS, and PsO users (populations with impaired dexterity similar to the intended users of ABP 501), DMEPA concluded that the Enbrel SureClick autoinjector human factors validation data submitted by Amgen support the approval of the ABP 501 SureClick autoinjector for all the conditions of use sought for licensure of ABP 501. I agree with DMEPA's conclusions.

The product quality team concluded, and I agree, that analytical comparability was also demonstrated between the 0.8 mL PFS and the assembled autoinjector, as discussed in the subsection on general product quality considerations above.

Given the above considerations, the data submitted by the applicant regarding the SureClick autoinjector were deemed sufficient and support approval of ABP 501 SureClick autoinjector.

- **Facilities review/inspection**

FDA's Office of Process and Facilities (OPF) conducted an assessment of the manufacturing facilities for this BLA. The OPF team concluded that adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the ATO (FEI 2026154) and AML (b) (4)(FEI 1000110364) facilities proposed for ABP 501 DS and DP manufacture. The descriptions were verified by inspection. These manufacturing sites, the proposed testing facilities, (b) (4) (FEI (b) (4)), (b) (4) (FEI (b) (4)), and (b) (4) (FEI (b) (4)), and the proposed cell bank preparation/storage facility, (b) (4) (FEI (b) (4)), are currently in a state of current good manufacturing practice (cGMP) compliance. The OPF team recommended that BLA 761024 be approved from the standpoint of facilities assessment. I concur with this recommendation.

4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology Reviewer: Carol M. Galvis, Ph.D.; Pharmacology/Toxicology Team Leader: Timothy W. Robison, Ph.D.

The ABP 501 nonclinical development program was considered adequate to support clinical development. Two nonclinical studies were submitted in 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.

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. The Pharmacology and Toxicology team concluded, and I agree, that 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.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Reviewer: Jianmeng Chen, M.D., Ph.D.
Clinical Pharmacology Team Leader: Anshu Marathe, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations**

Description of Relevant Clinical Pharmacology Studies

The objectives of the ABP 501 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 key design features of the three studies are summarized in Table 3. The pivotal PK similarity study (Study 217) was conducted in healthy subjects and compared ABP 501, US-licensed Humira, and EU-approved Humira. In addition, PK and immunogenicity were assessed in the two comparative clinical 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).

Table 3. Key Design Features of ABP 501 Clinical Studies

Study *(Dates conducted)*	**Objective**	**Design**	**Subjects**	**Treatments**
PK Similarity Study				
20110**217** *07/12-10/12*	3-way PK similarity, safety, immunogenicity	R, PG, SD, 3-way PK bridging	203 Healthy Subjects	40 mg SC: • ABP 501 • US-Humira • EU-Humira
Comparative Clinical Studies				
20120**262** *10/13-11/14*	Efficacy, safety, immunogenicity in RA	26 Weeks, R, DB, PG	526 Patients with RA	40 mg SC Q2W+MTX: • ABP 501 • US-Humira
20120**263** *10/13-03/15*	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: • ABP 501 • EU-Humira

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

Results of Clinical Pharmacology Studies

Study 217: Pharmacokinetics Results

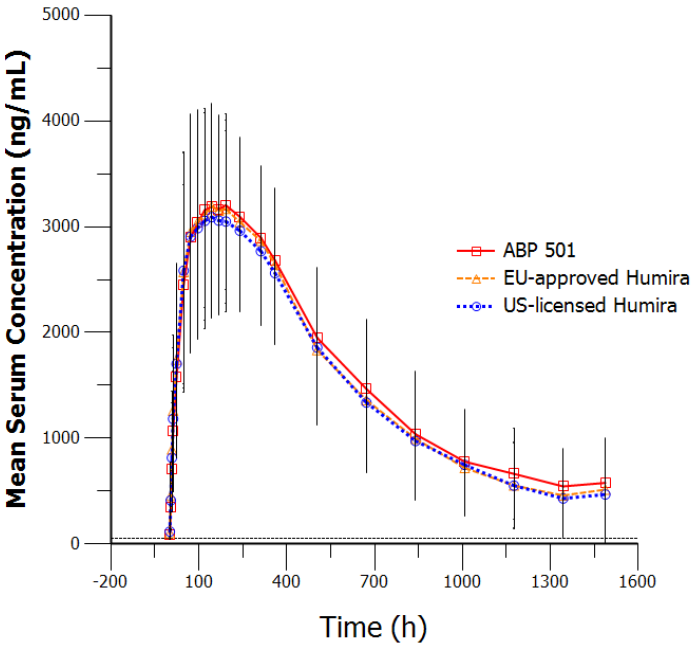
In the dedicated PK study 217, the three pairwise comparisons of ABP 501, US-licensed Humira and EU-approved Humira met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%) as summarized in Table 4 and depicted in Figure 3. These data establish the PK similarity between ABP 501 and US-licensed Humira. Further, they establish the PK component of the scientific bridge that justifies 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 4. PK Analysis of the 3-Way PK Bridging/PK Similarity Study 217

Comparison	Parameter	Adjusted GMR%	90% CI (%)
ABP501 vs US-licensed Humira	**Cmax**	103.73	(96.40, 111.62)
	AUC0-t	105.75	(95.26, 117.41)
	AUC0-inf	110.76	(99.47, 123.32)
ABP501 vs EU-approved Humira	**Cmax**	95.74	(88.89, 103.12)
	AUC0-t	98.70	(88.75, 109.76)
	AUC0-inf	101.87	(91.37, 113.56)
EU-approved Humira vs US-licensed Humira	**Cmax**	108.34	(100.65, 116.62)
	AUC0-t	107.15	(96.43, 119.06)
	AUC0-inf	108.73	(97.68, 121.03)
CI: confidence interval; GMR: geometric mean ratio ANCOVA Analysis with weight as a Covariate			

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

Figure 3. 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

Studies 262 and 263: Pharmacokinetics Results

In study 262, trough serum concentrations for ABP 501 and US-licensed Humira were assessed at multiple time points. The trough concentrations were comparable between ABP 501 and US-licensed Humira at each time point assessed (data not shown). The trough concentrations from sparse PK sampling were comparable at Weeks 4 and Week 16 (the time point before re-randomization) between ABP 501 and EU-approved Humira (data not shown).

Thus, the clinical pharmacology results from Study 262 (comparing ABP 501 and US-licensed Humira in RA patients with concomitant use of methotrexate), and Study 263 (comparing ABP 501 and EU-approved Humira administered as monotherapy in plaque psoriasis patients) support the PK similarity findings from Study 217.

Clinical Pharmacology Conclusions

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 sensitive to detect clinically meaningful differences in exposure among the products. The pre-specified margins were met in the single-dose PK similarity study. The evidence of similar exposure supports a demonstration 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.

The Office of Clinical Pharmacology has determined that PK similarity has been demonstrated between ABP 501 and US-licensed Humira, and the results from the PK studies add to the totality of evidence to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira. I concur with this assessment. The PK studies have not raised any new uncertainties and the clinical pharmacology data support a demonstration of biosimilarity between ABP 501 to US-licensed Humira.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary Statistical Reviewer for DPARP: Yongman Kim, Ph.D.
Statistical Team Leader for DPARP: Gregory Levin, Ph.D.
Primary Statistical Reviewer for DDDP: Kathleen Fritsch, Ph.D.
Statistical Team Leader for DDDP: Mohamed Alosh, Ph.D.
Primary Clinical Reviewer for DDDP: Denise Cook, M.D.; Clinical Team Leader DDDP: Gordana Diglisic, M.D.
Primary Clinical Reviewer for DPARP: Keith M. Hull, M.D., Ph.D.; Clinical Team Leader for DPARP: Nikolay Nikolov, M.D.

Overview of the Clinical Program

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, Study 262 and 263, described in detail in this section below. The key design features of these studies are summarized in Table 3 above. Of note, the comparative clinical efficacy data in Study 263 were derived using EU-approved Humira as the comparator. However, Amgen provided sufficient analytical and clinical PK bridging data (Study 217) between ABP 501, US-licensed Humira, and EU-approved Humira to justify the relevance of the comparative data generated using EU-approved Humira in Study 263 to support a demonstration of no clinically meaningful differences between ABP 501 to US-licensed Humira.

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 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 folinic 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.

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 ages 18 to 75 years 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 a 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-approved 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

Study 262

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 ±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.

Study 263

The primary endpoint in Study 263 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 ±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 Similarity Margin

The determination of a similarity margin is a critical aspect of the design of the comparative clinical study because it determines the null hypothesis being tested in the primary analysis, i.e., the differences in efficacy that the study will need to rule out at an acceptable significance level.

Study 262

The Applicant pre-specified a similarity margin of (0.738, 1/0.738) 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)[7] and the goal of preserving at least 50% of the effect size of US-licensed Humira. The Agency however, recommended that the margin selection be based on data from three additional published studies (Table 5). FDA further recommended 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 recommended 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% would result in a failure

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

to establish similarity. Therefore, the comparative clinical study would be able to rule out losses in ACR20 response greater than 12% with high (at least 95%) statistical confidence, and would 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, as derived from the published literature (e.g. see Table 5).

Table 5. Historical Effect of Humira on ACR20 Response in Placebo-Controlled Trials

Study	Week	MTX + Placebo N	MTX + Placebo ACR Response	MTX + Adalimumab N	MTX + Adalimumab ACR Response	Difference in % Response
Keystone (2004)[8]	24	200	30%	207	63%	34%
Weinblatt (2003)[9]	24	62	15%	67	67%	53%
Kim (2007)[10]	24	63	37%	65	62%	25%
Chen (2009)[11]	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

To address the Agency's recommendations on the similarity margin, the Applicant carried out supportive analyses, in which the difference in ACR20 response proportions was the main metric with a similarity margin of ±12%, and patients who withdrew early were treated as non-responders.

Study 263

In Study 263, the Applicant has pre-specified a similarity margin of ±15% for the primary endpoint of percent improvement in PASI. The Applicant did not provide a rationale in their protocol for the size of the proposed margin, and the margin was not discussed with FDA prior to 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, as reflected in published studies of adalimumab[12] relative to placebo. In the second approach, FDA used published, historical estimates of variability in the percent improvement in PASI

[8] Keystone EC et al, Arthritis & Rheumatism. 2004; 50: 1400-1411
[9] Weinblatt ME et al, Arthritis & Rheumatism. 2003; 48: 35-45
[10] Kim HY et al, J Rheumatology 2007; 10: 9-16
[11] Chen DY et al, J Formosan Medical Association. 2009; 108: 310-319
[12] The particular source of adalimumab used in these studies is not relevant for the purpose of informing an appropriate similarity margin.

endpoint to assess what margins would lead to an adequately powered study for a given sample size. FDA evaluated historical published data from trials with adalimumab and other TNF-α inhibitors for the percent improvement in PASI endpoint. Three publications of historical placebo-controlled trials of adalimumab presented the mean percent improvement in PASI (Table 6). The average treatment effect across the three studies was approximately 60%.

Table 6. Historical Effect of Adalimumab on Percent Improvement in PASI in Placebo-Controlled Trials

		Adalimumab		Placebo		
Study	Week	N	Mean	N	Mean	Treatment Difference
Gordon (2006)[13]	12	50	70	52	14	56
Saurat (2008)[14]	16	108	81	53	22	59
Menter (2008)[15]	12	814	76	398	15	61
Weighted Mean			76		16	60

None of these publications presented information on the standard deviations for the percent improvement in PASI endpoint, which are needed to construct confidence intervals. Thus, alternate sources are needed to find reasonable estimates of the standard deviation for this endpoint.

Two publications for studies of other TNF-α inhibitors presented standard deviations for the percent improvement in PASI endpoint (Table 7). Standard deviation (SD) estimates in the range of 20 to 30, may be reasonable approximations for the purpose of constructing confidence intervals to aid in the evaluation the Applicant's proposed margin.

Table 7. 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)[16]	Enbrel	12	164	64.2	30.7
Reich (2005)[17]	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 adalimumab studies (Menter) and a standard deviation estimate in the upper end of the range observed in the Leonardi and Reich studies (SD=30). An approximate 95% confidence interval for the treatment effect for percent improvement in PASI for Humira would be 61 ± 3.6 = (57.4, 64.6). Thus, a lower bound margin of -15 maintains at least 75% of the expected treatment effect using the point estimate of 61 and at least 74% of the expected treatment effect using the lower 95% confidence bound

[13] Gordon KB et al, J Am Acad Dermatol. 2006 Oct; 55(4): 598-606
[14] Saurat JH et al, Br J Dermatol. 2008 Mar;158(3):558-66
[15] Menter A, et al, J Am Acad Dermatol. 2008 Jan;58(1):106-15.
[16] Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22.
[17] Reich K et al, Lancet. 2005; 366:1367-74.

of 57.4. 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 relationship between the study power and various margins for a given sample size using the design assumptions of Study 263.

Using the sample size originally proposed in the protocol of 340 subjects and the assumption that the two treatments have the same effect, we can calculate what margins would lead to a design with adequate power. Using the more conservative standard deviation estimate of 30, a study of the proposed design and sample size would be powered at 90% for margins with magnitude of about ±11 or greater, and this may be a reasonable benchmark margin for interpreting the study results.

Study Conduct

Study 262

The treatment groups in Study 262 were balanced with respect to demographics and baseline characteristics. The study was conducted in Europe, North America, and Latin America. The population enrolled was consistent with the 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 8). The most common reasons for treatment discontinuation were adverse events and consent withdrawn.

Table 8. 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

Study 263

Treatment groups in Study 263 were 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 9). 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.

Table 9. 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

Study Results

Study 262

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 10). In a supportive analysis of ACR20 response in the subset of patients who completed the study and adhered to the protocol (per-protocol population), the 90% confidence interval for the difference in ACR20 response rates was within the FDA-suggested margin of ±12% (data not shown). Further, tipping point sensitivity analyses supported the findings of the key efficacy analyses in Study 262 (data not shown).

Table 10. 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

The secondary endpoints were ACR50/70 responses and DAS28-CRP. The proportions of patients remaining in the study and achieving ACR20 responses at Weeks 2, 4, 8, 12, 18, and 24, in addition to ACR50 and ACR70 response probabilities over time, were similar between the treatment arms (data not shown). Mean changes from baseline in the components of the ACR composite endpoint and the disease activity score (DAS28-CRP) were also similar between the arms in all randomized patients who completed the study (data not shown). In particular, the 95% 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. Overall, the results for the secondary endpoints support the demonstration of similarity.

Study 263

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 Full Analysis Set (FAS) population, the 95% confidence interval for the difference in mean percent improvement in PASI was within the pre-specified margin of ±15%. Correspondingly, the 90% confidence interval also fell within the ±15% margin (Table 11). Because the lower 90% confidence bound was -6.6, the study would meet the similarity criteria for margins of ±7% or larger. The results of the sensitivity analyses for handling missing data are consistent with the primary analysis (data not shown).

Table 11. 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
Missing data was imputed using LOCF
Source: FDA analysis of data from Amgen 351(k) BLA submission

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 12). 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 EU-approved Humira to account for the observed trends in the secondary endpoints in Study 263.

Table 12. 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

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL's conclusions**

In summary, the Applicant has provided statistically robust comparative clinical data demonstrating similar efficacy between ABP 501 and US-licensed Humira in patients with moderate-to-severe RA despite methotrexate, using 40 mg Q2W SC dosing on background methotrexate (Study 262), and between ABP 501 and EU-approved Humira 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 (Study 263). The primary analyses were supported by the analyses of key secondary endpoints and sensitivity analyses accounting for the missing data. The FDA statistical and clinical teams concluded, and I agree, that the results from Studies 262 and 263 support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

None.

8. Safety

Primary Clinical Reviewer for DDDP: Denise Cook, M.D.;
Clinical Team Leader DDDP: Gordana Diglisic, M.D.
Primary Clinical Reviewer for DPARP: Keith M. Hull, M.D., Ph.D.;
Clinical Team Leader for DPARP: Nikolay P. Nikolov, M.D.
OBP Immunogenicity Reviewers: Jun Park, Ph.D., and William Hallett, Ph.D.

- **Studies contributing to safety analyses**

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) 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. A total of 582 subjects were treated with ABP 501 across all three studies. The safety and immunogenicity data 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.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

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 13. No new safety signals were identified in the ABP 501 group compared to the known adverse event profile of US-licensed Humira, as described in the FDA-approved labeling for Humira.

Table 13. 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-Humira 40 mg (n=262)	ABP 501 40 mg (n=174)	EU-Humira 40 mg (n=173)	ABP 501 40 mg (n=67)	US-Humira 40 mg (n=69)	EU-Humira 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 AE: adverse event; SAE: serious adverse event							

Death

There were no deaths in the ABP 501 clinical 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 13 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 SOCs of SAEs or the pattern of SAEs in the ABP 501 clinical program were consistent with the known safety profile of US-licensed Humira[18].

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 13 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 FDA-approved Humira labeling 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,[19] demyelinating diseases, hematological reactions, heart failure, lupus-like syndrome, liver enzyme elevations, and injection site reactions. 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.

[18] FDA-approved Humira labeling
[19] Sampson HA et al., J Allergy Clin Immunol. 2006 Feb;117(2):391-7

Common AE

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 APB 501 and US-licensed Humira in the indications studied.

Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)

No unexpected laboratory findings were reported in ABP 501 clinical program.

- **Immunogenicity**

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

In Study 217, no pre-existing ADAs were detected at baseline. Following a single dose of 40 mg SC of study drug the incidence of ADAs throughout the study was comparable between ABP 501 (43%), US-licensed Humira (50%), and EU-approved Humira (51%). The rate of neutralizing ADA (NAb) was similar between all three treatment arms at 18%, 22%, and 21%, respectively.

In 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 (Table 14).

In 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 (Table

14). 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 14. Summary of Binding and Neutralizing ADAs Following Repeat Dosing in Study 262 (RA) and Study 263 (PsO)

	Rheumatoid Arthritis Study 262		**Plaque Psoriasis Study 263**				
			Through Week 16		Week 16 to EOS		
	ABP 501 40 mg (n=264)	US-Humira 40 mg (n=262)	ABP 501 40 mg (n=174)	EU-Humira 40 mg (n=173)	ABP 501/ ABP 501 40 mg (n=152)	EU-Humira/ EU-Humira 40 mg (n=79)	EU-Humira/ 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 EOS: end of study							

While the development of ADAs appears to increase clearance of the products (overall exposure by AUC was approximately 20% to 30% lower in ADA positive subjects), the impact of ADAs appeared to influence PK similarly following treatment with ABP 501, US-licensed Humira, and EU-approved Humira in Studies 217, 262, and 263 (data not shown).

To investigate the potential impact of the ADA and the NAbs on comparative clinical outcomes, the FDA review team examined the relationship between ADA and NAb, primary efficacy endpoints, and select relevant safety outcomes such as hypersensitivity reactions and injections site reactions as summarized in Table 15 for Study 262 and in Table 16 for Study 263. We acknowledge that such analyses are exploratory in nature and limited by the small sample sizes within subgroups and the non-randomized nature of comparisons, as ADA status is a post-randomization variable and observed differences (or lack thereof) could be attributable to ADA formation or to other confounding variables.

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

Table 15. 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 16. Incidence of Clinical Responses and Safety Outcomes of Interest by ADA and Neutralizing ADA Status in Study 263 in PsO at Week 16

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

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

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

In light of these additional contextual pieces, I 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) or ABP 501 and EU-approved Humira (Study 263). Therefore, there are sufficient data supporting similar immunogenicity between ABP 501, EU-approved Humira, and US-licensed Humira and that immunogenicity data adds to the totality of the evidence to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira. The immunogenicity review team recommends approval of the BLA from immunogenicity perspective and I agree with this recommendation.

- **Discussion of primary reviewer's comments and conclusions**

The safety database submitted for ABP 501 is adequate to provide a reasonable descriptive comparison between the two products. The safety and immunogenicity 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. No new safety signals have been identified compared to the known adverse event profile of US-licensed 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 FDA safety analysis is consistent with the Applicant's.

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 between ABP 501 and EU-approved Humira (Study 263). The DPARP and DDDP clinical review teams and I are in agreement that the submitted safety and immunogenicity data and analyses are adequate to support the conclusion

of no clinically meaningful differences between ABP 501 and US-approved Humira in the indications studied.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion**

None.

- **Discussion of notable safety issues (resolved or outstanding)**

None.

9. Extrapolation of Data to Support Biosimilarity in Other Conditions of Use

Amgen is seeking 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.[20] 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,

[20] Guidance for Industry on 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

- 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's extensive analytical characterization data support a demonstration that ABP 501 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components, and that the data support a demonstration there are no clinically meaningful differences between ABP 501 and US-licensed Humira in terms of safety, purity and potency 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:

- Similar PK was demonstrated between ABP 501 and US-licensed Humira, as discussed in the section on Clinical Pharmacology above. Further, the pharmacokinetics of US-licensed Humira in patients with AS were similar to those in patients with RA.[21] 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.[22] Importantly, ABP 501 was demonstrated to be highly similar to US-licensed Humira, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between ABP 501 and US-licensed Humira in the indications sought for licensure. Thus, a similar PK profile would be expected between ABP 501 and US-licensed Humira in patients across all 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.[23] In RA, PsA, and AS, the recommended dose is 40 mg Q2W SC. Adalimumab is used without MTX in PsO and may be used with or without concomitant immunosuppression in PsA, CD and UC.[24] These usage scenarios were assessed in

[21] FDA-approved Humira labeling
[22] FDA-approved Humira labeling
[23] FDA-approved Humira labeling
[24] FDA-approved Humira labeling

Amgen's RA Study 262 (concomitant use of methotrexate) and Amgen's PsO Study 263 (use with a loading dose of 80 mg SC on Day 1, followed by 40 mg Q2W SC starting one week later, but without concomitant immunosuppressive therapy). There are sufficient data to indicate similar immunogenicity between ABP 501, EU-approved Humira, and US-licensed Humira. Accordingly, similar immunogenicity would be expected between ABP 501 and US-licensed Humira in patients with JIA, PsA, AS, adult CD, and UC.

- Similar clinical safety profile with chronic dosing was demonstrated between ABP 501 and US-licensed Humira in patients with RA and between ABP 501 and EU-approved Humira in patients with plaque psoriasis, and between the three products following single doses in healthy subjects. As analytical and PK similarity was demonstrated between ABP 501 and US-licensed Humira, a similar safety profile would be expected between ABP 501 and US-licensed Humira in patients with JIA, PsA, AS, adult CD, and UC.

- The mechanism(s) of action (MOA) relevant to the extrapolation of data to support biosimilarity in specific indications are summarized in Table 17 and discussed below.

Table 17. 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 published literature on the topic of mechanisms of action of TNF inhibitors[25,2627]

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

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

The primary MOA of adalimumab is direct binding and blocking of TNF receptor-mediated biological activities (see Table 17 above). Adalimumab binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The published scientific literature indicates that this MOA is the primary MOA in RA, JIA, PsA, AS, and PsO. The data provided by Amgen showed similar TNF binding and potency to neutralize TNF-α, supporting the demonstration of analytical similarity pertinent to this MOA. Therefore, based on the above considerations, it is reasonable to extrapolate conclusions regarding similar efficacy and safety of ABP 501 and US-licensed Humira in RA and PsO to JIA, PsA and AS.

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.[28] 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 17 may play a role.[29] 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 section on CMC/Product Quality 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. Further, Amgen addressed each of the known and potential mechanisms of action of US-licensed Humira listed in Table 17 and submitted data to support the conclusion that ABP 501 and US-licensed Humira have the same mechanisms of action for each of the requested indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Thus, the DGIEP review team concluded, and I agree, that based on the totality of the data demonstrating analytical high similarity, PK similarity, and no clinically meaningful differences in RA and PsO between ABP 501 and Humira comparator products, the extrapolation of data to support a finding of biosimilarity for ABP 501 and US-licensed Humira to IBD conditions of use is scientifically justified.

In aggregate, based on the above considerations, extrapolation of data to support a demonstration that there are no clinically meaningful differences between ABP 501 and US-

[28] 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
[29] Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", Pharmacology & Therapeutics 117 (2008) 244–279

licensed Humira for JIA, PsA, AS, adult CD, and UC to support licensure of ABP 501 for the indications being sought is scientifically justified.

10. Advisory Committee Meeting

An Advisory Committee (AC) meeting was determined to be necessary to obtain independent expert advice on issues related to analytical similarity assessment and extrapolation to non-studied indications. The AC meeting was convened on July 12, 2016.[30] The following is a brief summary of the questions to the committee and surrounding discussions.

1. **DISCUSSION:** Please discuss whether the evidence from analytical studies supports a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components.

   Committee Discussion: *Most committee members agreed that the evidence from analytical studies supports a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. One committee member noted that they accepted the similarity of the in vitro Fc binding and Fc-mediated assays to reflect functional in vivo similarity to support the extrapolation to inflammatory bowel disease indications. One committee member noted that differences in post-translational modifications, such as glycosylation, could result in differences in immunogenicity. However, another member noted that in the clinical program similar immunogenicity was observed between ABP 501 and Humira. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Please discuss whether 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 (rheumatoid arthritis (RA) and plaque psoriasis (PsO)).

   Committee Discussion: *Most committee members agreed 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 (rheumatoid arthritis (RA) and plaque psoriasis (PsO)). One committee member stated that the comparative clinical studies in RA and PsO have statistically demonstrated a high degree of similarity in efficacy between ABP 501 and the comparator products. One committee member noted that the study sample was small to detect differences in safety. Some committee members recommended the need for post marketing surveillance to assess long-term safety. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Please discuss whether the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between ABP 501 and

[30] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975 htm

US-licensed Humira for the following additional indications for which US-licensed Humira is licensed:

- Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Adult Crohn's Disease (CD)
- Adult Ulcerative Colitis (UC)

If not, please state the specific concerns and what additional information would be needed to support such a demonstration. Please discuss by indication if relevant.

Committee Discussion: *The committee members did not come to a consensus on whether the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira for the following additional indications for which US-licensed Humira is licensed (JIA in patients 4 years of age and older, PsA, AS, CD and UC). One committee member noted that one can extrapolate by mechanism of action to the rheumatology indications. However, because the mechanism of action in inflammatory bowel disease indications was unclear, this leaves residual uncertainty for the extrapolation to those indications. The committee members who agreed that the data provided adequate justification, added that they were comfortable with the extrapolation to the pediatric population as well. Please see the transcript for details of the committee discussion.*

4. **VOTE:** Does the totality of the evidence support licensure of ABP 501 as a biosimilar product to US-licensed Humira for 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, adult UC, and PsO)?

   Please explain the reason for your vote.

   Vote Result: YES: 26 NO: 0 ABSTAIN: 0

   Committee Discussion: *The committee members unanimously agreed that the evidence support licensure of ABP 501 as a biosimilar product to US-licensed Humira for 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, adult UC, and PsO). Some committee members expressed concerns with the potential for market-place non-medical "switching" of biosimilars. Some committee members recommended mandatory postmarketing surveillance to assess long-term safety, in addition to the data presented. Some committee members also stressed the importance of patient education on biosimilars and interchangeability. Please see the transcript for details of the committee discussion.*

The reader is also referred to the full transcript of the meeting.[31]

11. Pediatrics

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, pediatric assessment**

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(m) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred. Thus, if ABP 501 is licensed only as a biosimilar product, it triggers PREA and Amgen would be expected to address PREA for every indication for which they are seeking licensure.

Following revisions to the initial pediatric study plan (iPSP), based on Agency's feedback, Amgen submitted an agreed iPSP to address the PREA requirements for the following indications as detailed below:

- Rheumatoid Arthritis (RA), Polyarticular juvenile idiopathic arthritis (JIA): Polyarticular JIA has been considered the condition of use to address PREA for products approved for RA. With this BLA, Amgen proposed that the pediatric assessment is complete, for JIA patients between 4 and 17 years old, in part by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to ABP 501. Amgen requested a deferral of the requirements to submit a pediatric assessment for JIA patients 2 to < 4 years of age (b) (4) (b) (4) (b) (4) The Applicant has also submitted requests for waiver of the requirement to submit a pediatric assessment for patients < 2 years old because condition is rare in this age group and such studies would be impossible or highly impracticable.

- Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA): The Applicant has submitted requests for full waiver of the requirement to submit a pediatric assessment for juvenile AS and juvenile PsA because the studies would be impossible or highly impracticable due to the difficulty of making specific diagnoses of juvenile PsA or juvenile AS in the pediatric age range.

[31] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975 htm

- Plaque Psoriasis: Consistent with the agreed iPSP, with this submission, the Applicant submitted a request for a waiver of the requirements to submit a pediatric assessment for patients with pediatric chronic severe plaque psoriasis ages 0 to 17 years old due to safety concerns (b) (4) .

- Crohn's Disease: The Applicant requested a deferral of the requirements to submit a pediatric assessment for patients with Crohn's disease 6 to 17 years of age (b) (4) As a scientific matter, based on emerging epidemiologic data, the Agency has determined that under PREA, pediatric studies would be required for patients with CD down to 2 years of age. However, the Agency has also determined that dedicated studies for patients with CD limited to ages 2 to <6 years old would be impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age. Thus, the Applicant requested a waiver of the requirement to submit a pediatric assessment for patients <6 years old.

- Ulcerative Colitis: The Applicant requested a deferral of the requirements to submit a pediatric assessment for patients with ulcerative colitis 5 to 17 years of age (b) (4) As a scientific matter, based on emerging epidemiologic data, the Agency has determined that under PREA, pediatric studies would be required for patients with UC down to 2 years of age. However, the Agency has also determined that dedicated studies for patients with UC limited to ages 2 to <5 years old would be impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age. Thus, the Applicant requested a waiver of the requirement to submit a pediatric assessment for patients < 5 years old.

The ABP 501 pediatric study plan was discussed at the Pediatric Review Committee (PeRC) meeting on July 27, 2016. The PeRC agreed with the requested waivers and deferrals for RA, JIA, AS, PsA, CD, and UC. (b) (4), (b) (5) Therefore, PeRC agreed with the requested full waiver of the requirement to submit a pediatric assessment for PsO for ABP 501.

PeRC also recommended that PREA post-marketing requirements (PMR) be issued for Amgen to submit a pediatric assessment for patients with JIA 2 to <4 years of age, patients with CD 6 to 17 years of age, patients with UC 5 to 17 years of age, and for Amgen to develop an age appropriate presentation so that this product may be accurately administered to pediatric patients down to 2 years of age with pJIA. I agree with PeRC's recommendations.

12. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not warranted, no issues.
- **Exclusivity**—There is no unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Humira (adalimumab) (BLA 125057; AbbVie Inc.) that would prohibit the approval of ABP 501.
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **OSI audits—**Four clinical sites that enrolled patients in the comparative clinical study 262 in RA and two sites clinical sites that enrolled patients in the comparative clinical study 263 in PsO were selected for inspection. The inspections showed the clinical sites to be in compliance with Good Clinical Practices and were without deficiencies. The sponsor, Amgen, Inc., was also inspected. The OSI investigators concluded that the data submitted were acceptable to support the current BLA.
- **Other discipline consults**—Not applicable
- **Any other outstanding regulatory issues**—Not applicable

13. Labeling

- **Proprietary name**

The Applicant submitted the name Amjevita for review on July 14, 2016. The proposed proprietary name for ABP 501 was Amjevita. The name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be conditionally acceptable and the Applicant was informed on August 19, 2016. The proprietary name of the autoinjector, SureClick, has previously been approved by the Agency.

- **Non-proprietary/Proper name**

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Amgen's ABP 501 is necessary to distinguish this proposed product from Humira (adalimumab). As explained in FDA's draft Guidance for Industry, Nonproprietary Naming of Biological Products,[32] FDA expects that a nonproprietary name that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance of biological products. FDA advised Amgen to provide proposed suffixes in accordance with the draft guidance. FDA has not finalized a policy on the nonproprietary naming of biological products. Accordingly,

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

DMEPA reviewed Amgen's proposed suffixes against the criteria described in the draft guidance.

On August 12, 2016 and September 13, 2016, Amgen submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of ABP 501 along with supporting analyses to demonstrate that the proposed suffixes satisfy the factors described in section V of the draft guidance. The DMEPA review concluded, and I agree, that Amgen's proposed suffix "atto" (adalimumab-atto) is acceptable and should be reflected in the product label and labeling accordingly.

Of note, FDA's determination does not constitute or reflect a decision on a general naming policy for biological products, including biosimilars. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance.[33] As a result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biological products established by FDA. Were the name to change, FDA intends to work with Amgen to minimize the impact this would have to its manufacture and distribution of this product.

- **Important issues raised by brief discussion of OPDP and OSE Division comments**

None

- **Physician labeling**

The applicant proposed a labeling closely mirroring the labeling of US-licensed Humira. In addition, the applicant proposed:

1) Section 6.1, Adverse Reactions: (b) (4)
2) Section 8, Use in Specific Populations: Changes that conform to PLLR formatting.
3) Section 12.3, Pharmacokinetics: (b) (4) .

[33] FDA has received several citizen petitions directed to the nonproprietary naming of biosimilar products. The citizen petition submitted by Johnson & Johnson requests that FDA require biosimilar products to bear nonproprietary names that are similar to, but not the same as, those of their reference products or of other biosimilars (see Docket No. FDA-2014-P-0077). The citizen petitions submitted by the Generic Pharmaceutical Association and Novartis request that FDA require biosimilar products to be identified by the same nonproprietary name as their reference products (see Docket Nos. FDA-2013-P-1153 and FDA-2013-P-1398). Although FDA is designating a proper name that contains a distinguishing suffix for Amjevita, FDA is continuing to consider the issues raised by these citizen petitions, the comments submitted to the corresponding public dockets, and comments submitted to the dockets for the Draft Guidance for Industry on Nonproprietary Naming of Biological Products (August 2015) and the proposed rule, Designation of Official Names and Proper Names for Certain Biological Products (80 FR 52224), with respect to establishing a general naming convention for biological products.

4) Section 14, Clinical Studies: Study description and efficacy results from Studies 262 and 263.

Thus, during the BLA review labeling, revisions were made for consistency with the Draft Guidance for Industry on Labeling for Biosimilar Products (March 2016). (b) (4) [redacted] Data for ABP 501 development program were presented at the Arthritis Advisory Committee on July 12, 2016.[34]

The proprietary name "Amjevita", and the non-proprietary name "adalimumab-atto", should be reflected in the product labeling as appropriate.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

As discussed above.

- **Carton and immediate container labels**

As discussed above in the DMEPA review and recommendations, the proprietary name "Amjevita" and the non-proprietary name "adalimumab-atto", should be reflected in the product Patient labeling/Medication guide as appropriate.

- **Patient labeling/Medication guide**

The applicant proposed a Patient labeling/Medication guide closely tracking that of US-licensed Humira. The proprietary name "Amjevita" and the non-proprietary name "adalimumab-atto", should be reflected in the product Patient labeling/Medication guide as appropriate.

[34] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm481975 htm

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of the 351(k) BLA 761,024 for ABP 501 to 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 Amgen is seeking licensure of ABP 501: RA, JIA in patients 4 years and older, PsA, AS, PsO, Adult CD, and UC.

- **Totality of the Evidence**

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

Amgen provided extensive analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Humira to support 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, and (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved Humira.

The results of the clinical development program indicate that Amgen's data meet the requirement for 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 a spectrum of chronic dosing regimens of ABP 501, US-licensed Humira, and EU-approved Humira (either 40 mg Q2W SC on the background of methotrexate in Study 262, or a loading dose of 80 mg on Day 1, followed by 40 mg Q2W SC starting one week later as monotherapy in Study 263) 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. 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.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to conditions of use not directly studied to support their request that ABP 501 should receive licensure for each of the indications for which US-licensed Humira is currently licensed and for which Amgen is seeking licensure of ABP 501.

In considering the totality of the evidence submitted, the data submitted by the Applicant show that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in terms of the safety, purity, and potency of the product. The information submitted by the Applicant demonstrates that ABP 501 is biosimilar to US-licensed Humira and should be licensed. [35]

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

None.

- **Recommendation for other Postmarketing Requirements and Commitments**

Postmarketing Requirement (PMR):

(b) (4)

For accurate weight-based dosing of patients 2 years of age or older that are less than 15 kg, an age-appropriate presentation is required under PREA. Therefore, I recommend a PREA PMR for the development of a presentation that can be used to accurately administer ABP 501 to pediatric patients who weigh less than 15 kg. Also, under PREA, Amgen is required to submit a pediatric assessment for patients with JIA 2 to <4 years of age, patients with CD 6 to 17 years of age, patients with UC 5 to 17 years of age. Thus, to address the PREA requirements, I recommend the following PREA PMRs:

1. Assessment of Amjevita (adalimumab-atto) for the treatment of pediatric ulcerative colitis in patients 5 to 17 years of age.

   Final Report Submission Date: December 2020

2. Assessment of Amjevita (adalimumab-atto) for the treatment of pediatric Crohn's disease in patients 6 years to 17 years of age.

   Final Report Submission Date: September 2021

3. Assessment of Amjevita (adalimumab-atto) for the treatment of juvenile idiopathic arthritis (JIA) in patients ages 2 to <4 years of age.

   Final Report Submission Date: September 2021

[35] The proposed ABP 501 labeling states: "Biosimilarity of AMJEVITA has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

4. Develop a presentation that can be used to accurately administer Amjevita (adalimumab-atto) to pediatric patients who weigh less than 15 kg.

Final Report Submission Date: September 2021

Postmarketing Commitments (PMC):

I concur with the post-marketing commitments recommended by the product quality review team as listed below:

1. Perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.

Final Report Submission Date: July 2017

2. Perform supplemental method validation and introduce a non-reduced CE-SDS test into the integrated control strategy for drug substance manufacture. Submit the analytical procedure, validation report, the proposed acceptance criterion, and the data used to set the acceptance criterion that will be provided in a CBE-0 supplement.

Final Report Submission Date: December 2016

- **Recommended Comments to Applicant**

None.

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

/s/

NIKOLAY P NIKOLOV
09/23/2016