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RESEARCH**

APPLICATION NUMBER:

761024Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Badrul Chowdhury, M.D., Ph.D. Director, DPARP
Subject	Division Director Summary Review
NDA/BLA # / Supplement #	BLA 761024/original
Applicant Name	Amgen, Inc.
Date of Submission	November 24, 2015
BsUFA Goal Date	September 24, 2016
Proprietary Name / Established (USAN) Name	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)
Proposed Indication(s)	1. Rheumatoid Arthritis (RA) 2. Polyarticular 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)
Action:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Cross-Discipline Team Leader Rev.	Nikolay Nikolov, MD
Office of Biotechnology Products (OBP)	Jun Park, PhD; Joel Welch, PhD; Juhong Liu, PhD; David Frucht, MD; Steven Kozlowski, MD
CMC statistics	Meiyu Shen, PhD; Yi Tsong PhD
Product Quality Microbiology	Bo Chi, PhD; Lakshmi Narasimhan, PhD; Patricia Hughes PhD
Immunogenicity	Jun Park, PhD; William Hallett, PhD

¹ In this document, we 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."

Facilities Inspections	Steven Fong, PhD; Peter Qiu PhD
OBP labeling	Jibril Abdus-Samad, PharmD
Project Manager, OPRO/OPQ	Keith Olin, PharmD
CDRH	Lana Shiu, Alan Stevens
Medical Officer Review	DPARP: Keith Hull, MD, PhD; DDDP: Denise Cook, MD; Gordana Diglisic, MD
Biostats Review	DPARP: Yongman Kim, PhD; Gregory Levin, PhD; DDDP: Kathleen Fritsch, PhD; Mohamed Alosch, PhD
Pharmacology Toxicology Review	Carol Galvis, PhD; Timothy Robison, PhD
Clinical Pharmacology Review	Jianmeng Chen, MD, PhD; Anshu Marathe, PhD
Clinical study inspections, OSI	Roy Blay, PhD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH; Anthony Orencia, MD; Susan Thompson, MD;
PK study inspections, OSIS	Mohsen Rajabi, PhD; Amanda Lewin, PhD; Arindam Dasgupta, PhD; Xiaohan Cai, PhD; Michael Skelly, PhD; Young Moon Choi, PhD
Division of Medication Error Prevention and Analysis	Carlos Mena-Grillasca, RPh; Lubna Merchant, MS, PharmD; Kellie Taylor, PharmD, MPH
Division of Medical Policy Programs—patient labeling	Nyedra Booker, PharmD, MPH; Marcia Williams, PhD; LaShawn Griffiths, MSHS-PH, BSN, RN
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OND=Office of New Drugs

OPRO=Office of Programs and Regulatory Operations

CDRH=Center for Devices and Radiological Health

OSI=Office of Scientific Investigations

OSIS=Office of Study Integrity and Surveillance

CMC=Chemistry, Manufacturing, Controls

OPQ=Office of Pharmaceutical Quality

DDDP=Division of Dermatology and Dental Products

OPDP=Office of Prescription Drug Promotion

1. Introduction

This is a 351(k) biologics license application (BLA) submitted by Amgen, Inc. for ABP 501, a proposed biosimilar to Humira (adalimumab). Amgen is seeking licensure of ABP 501 (tradename “Amjevita”) on the basis of the following:

- Analytical data intended to support the following purposes:
 - A demonstration that ABP 501 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet required quality standards
 - A demonstration that ABP 501 and US-licensed Humira are highly similar
 - Provide the analytical element of the scientific bridge to justify the relevance of comparative data that were generated using European Union (EU)-approved Humira to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira.
- The clinical pharmacology program for ABP 501 included Study 217, a single-dose, 3-way pharmacokinetic (PK) study evaluating ABP 501, US-licensed Humira, and EU-approved Humira intended to support the following purposes:
 - To support the PK similarity of ABP 501 and US-licensed Humira, and

- To provide the PK element of the scientific bridge to justify the relevance of comparative data generated using EU-approved Humira to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira.
 - To provide information on steady state PK, from two comparative clinical studies, Study 262 and 263 (discussed further below).
- The clinical development program for ABP 501 consisted of two comparative clinical studies:
 - Study 262 is a 26-week randomized, double-blind, parallel group comparative clinical study in 526 patients with moderate to severely active RA on background methotrexate (MTX), randomized 1:1 to ABP 501 or US-licensed Humira at a dose of 40 mg every other week subcutaneously.
 - Study 263, a randomized, double-blind, parallel group comparative clinical study in 350 patients with chronic moderate to severely active plaque psoriasis (PsO) who were treated with ABP 501 or EU-approved Humira. This study was conducted outside the US. Patients were randomized 1:1 to ABP 501 or EU-approved Humira at a dose of 80 mg subcutaneously (SC) on Day 1, then 40 mg every two weeks starting one-week later. At Week 16, patients who achieved at least PASI 50 response continued to the next period, where patients who were treated with EU-approved Humira were then randomized to undergo a single transition to ABP 501 or continue on EU-approved Humira and were followed through Week 52.
- A scientific justification for extrapolation of biosimilarity to other indications which were not directly studied in the ABP 501 development program but for which US-licensed Humira is licensed and for which Amgen is also seeking licensure, i.e., polyarticular juvenile idiopathic arthritis (JIA) in patients 4 years of age and older, psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult Crohn's Disease (CD), and adult ulcerative colitis (UC).

2. Background

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of the Affordable Care Act that was 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 preclinical 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” (see section 351(i)(2) of the PHS Act). 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).

The foundation of an abbreviated development program for biosimilars is extensive structural and functional characterization of the both the proposed biosimilar product and its reference product which demonstrates that the products are highly similar analytically. Residual uncertainties about the clinical relevance of small differences in the comparative analytical characterization may be addressed by comparative human PK and, if applicable, pharmacodynamic data, clinical immunogenicity, safety, and effectiveness data. However, unlike a stand-alone development program (i.e., BLAs submitted under section 351(a) of the Public Health Service Act), a demonstration of efficacy and safety in each clinical indication is not expected. It is under this relatively new paradigm that Amgen seeks licensure of ABP 501.

Regulatory History

Multiple pre-submission meetings occurred between the applicant and FDA, starting with an initial pre-IND meeting in August 2011. FDA recommendations for the analytical similarity assessment were discussed at Biosimilar Biological Product Development (BPD) Type 2 meetings in April and November 2012. The design of Study 262 was discussed in May 2013. Device aspects for the planned modified SureClick autoinjector were discussed at a BPD2 meeting in January 2014. Analytical similarity acceptance criteria were discussed at a BPD2 meeting in July 2014. Pre-BLA submission topics were discussed at a BPD2 in January 2015 and a BPD4 in June 2015. As part of these meetings, FDA provided recommendations on the design, endpoints, and selection of the similarity margin for the comparative clinical study in RA (Study 262). FDA also recommended that Amgen assess safety and immunogenicity in the setting of patients who undergo a single transition from Humira to ABP 501, compared to patients who continue on Humira. Discussion also included PK similarity expectations and expectations regarding scientific justification for extrapolation of biosimilarity. Of note, Amgen conducted a second comparative clinical study ex-US in patients with plaque psoriasis, which was designed and conducted without FDA input, except that the study incorporates FDA's recommended assessment of the safety and immunogenicity of patients who undergo a single transition from Humira to ABP 501.

3. CMC/Device

Manufacturing and Product Quality Evaluation

Drug substance

ABP 501 is a human monoclonal antibody based on a human immunoglobulin G1 (IgG1) framework. It is produced in Chinese Hamster Ovary (CHO) cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each) of the kappa subclass. ABP 501 contains 32 total cysteine residues involved in both intra-chain and inter-chain disulfide bonds. ABP 501 binds specifically to TNF- α and blocks its

interaction with the p55 and p75 cell surface TNF receptors. ABP 501 does not bind or inactivate lymphotoxin (TNF- β). ABP 501 also binds Fc γ Rs and induces both antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in vitro.

The drug substance (DS) manufacturing process, detailed in the product quality reviews, is well-controlled. The DS is manufactured at Amgen, Inc., Thousand Oaks, California.

Submitted data support an expiration dating period of (b) (4) months when stored at (b) (4) C.

Drug product

ABP 501 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 will be supplied as a single-use sterile liquid solution for subcutaneous injection in a 1 mL prefilled syringe (PFS) (40 mg/0.8 mL or 20 mg/0.4 mL, with (b) (4) or 29g needle) or as a single-use prefilled SureClick autoinjector (40 mg/0.8 mL). The PFS contains 50 mg/mL drug product (DP) in 10 mM acetate, 9.0% (w/v) sucrose, 0.10% (w/v) polysorbate 80, pH 5.2, in a deliverable volume of 0.4 mL or 0.8 mL. The autoinjector (AI) contains a 27g PFS with a deliverable volume of 0.8 mL. The DP is manufactured at Amgen Manufacturing Ltd, Juncos, Puerto Rico. Submitted data support an expiration dating period of 30 months when stored at 2°C to 8°C.

Microbiology

The microbiology review team has concluded that the DS and DP are recommended for approval from a product quality microbiology perspective.

Device Evaluation

The Center for Devices and Radiological Health (CDRH) performed an evaluation of the design of the device constituent parts of the prefilled syringe (PFS) with needle safety device and the autoinjector (AI) configurations. The PFS incorporates a rigid needle shield and a flange extender. (b) (4)

The PFS configurations include:

- (b) (4)
- 40 mg (0.8 mL) PFS with a 29g staked-in-place needle
- (b) (4)
- 20 mg (0.4 mL) PFS with a 29g staked-in-place needle.

The AI is based on the SureClick injector platform (developed by (b) (4) for Immunex Corporation, an Amgen Inc. company) which is a currently approved and marketed device used to administer Enbrel (etanercept). The Enbrel SureClick device and the ABP 501 SureClick device will be differentiated by different exterior colors. Otherwise the autoinjector materials, construction, and function remain unchanged. The ABP 501 SureClick AI contains a 27g PFS with a deliverable volume of 0.8 mL of 50 mg/mL ABP 501. The ABP 501

SureClick has a shorter injection time than the Enbrel SureClick (b) (4) Previously reviewed Human Factors Study data for the Enbrel SureClick, submitted by the applicant in support of the BLA for ABP 501 (BLA 761024), were considered adequate to support the ABP 501 SureClick. The CDRH reviewer determined the devices' design verification, controls, and performance met requirements and the PFS and AI are acceptable for approval.

Facilities Inspections

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Amgen Inc., Thousand Oaks (FEI 2026154) and Amgen Manufacturing Ltd., Juncos, Puerto Rico (FEI 1000110364) proposed for ABP 501 DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable on the basis of their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is considered adequate for approval from a facilities assessment perspective.

Summary

In summary, the review team has determined that the DS and DP manufacturing process is well controlled and adequate to support approval. Two postmarketing commitments are recommended, and are described in detail in Section 13 below.

Analytical Similarity Evaluation

The analytical similarity evaluation included comprehensive methods that assessed the primary structure and post-translational modifications, higher order structure, size variants, hydrophobic variants, charge variants and glycoform variants. Comparative analytical data was evaluated from multiple lots of ABP 501, US-licensed Humira, and EU-approved Humira. Comparative data between ABP 501 and US-licensed Humira were used to assess the analytical similarity of ABP 501. TNF- α neutralization (apoptosis inhibition assay) and TNF α binding (enzyme-linked immunosorbent assay [ELISA]) were identified as methods to be evaluated by statistical equivalence testing. Pairwise comparisons of ABP 501, US-licensed Humira, and EU-approved Humira were used to support the analytical element of the scientific bridge between the three products to justify the relevance of the comparative data generated using EU-approved Humira in clinical study 263.

TNF α Binding Assay Results

Data on TNF α binding (ELISA) with ABP 501 and US-licensed Humira met criteria for statistical equivalence, supporting a finding that ABP 501 is highly similar to US-licensed Humira. In addition, 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 element of the scientific bridge for the clinical study conducted with EU-approved Humira.

TNF α Neutralization Assay Results

TNF α neutralization was assessed using an apoptosis inhibition bioassay. This assay measures the ability of the test agent to inhibit TNF α -induced cell death in the human histiocytic lymphoma cell line U-937. These data demonstrated that ABP 501 and US-licensed Humira met criteria for statistical equivalence, supporting a finding that ABP 501 is highly similar to US-licensed Humira. In addition, TNF α neutralization between ABP 501 and EU-approved Humira, and between US-licensed Humira and EU-approved Humira met the criteria for statistical equivalence, which also supports the analytical element of the scientific bridge for the clinical study conducted with EU-approved Humira.

Similarity of Other Quality Attributes

The amino acid sequences of ABP 501 and US-licensed Humira are identical. A multitude of other quality attributes, including secondary and higher order structure, Fc (effector) function, and other structural/functional characteristics were assessed by quality range analysis and by qualitative comparisons. These attributes also support a finding that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. Amgen developed functional assays to assess each potential mechanism of action for ABP 501, including reverse signaling of membrane TNF α (mTNF α) positive cells, ADCC and CDC of mTNF α positive cells, and induction of regulatory macrophages in mucosal healing. In each case, results support a finding that ABP 501 is highly similar to US-licensed Humira. The glycan profile showed small differences between the products: a trend toward lower % high mannose and total afucosylation with ABP 501 and a trend toward higher % sialylation and galatoseylation with ABP 501 compared to US-licensed Humira. However, given that ABP 501 and US-licensed Humira were shown to have highly similar ADCC activity, CDC activity, and binding to Fc γ RIIIa, and PK similarity was also demonstrated, the slight differences in glycan profile were not considered to be clinically meaningful and do not preclude a finding that the products are highly similar.

Summary

In summary, FDA reviewers from the Office of Biotechnology Products (OBP) and Office of Biostatistics (OB) have evaluated the analytical similarity of ABP 501, US-licensed Humira, and EU-approved Humira and have determined that ABP 501 is analytically highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components. Additionally, Amgen provided an adequate analysis for the purposes of establishing the analytical element of the scientific bridge between ABP 501, US-licensed Humira and EU-approved Humira to justify the relevance of comparative data generated with EU-approved Humira to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira. Reviewers from OBP, Office of Compliance, and Center for Devices and Radiological Health have reviewed the product quality, manufacturing, and device aspects and have determined the submitted data are adequate to support approval.

4. Nonclinical Pharmacology/Toxicology

The pharmacology and toxicology studies submitted in support of the BLA included two studies in cynomolgus monkeys comparing ABP 501 and US-licensed Humira. Collectively, there was no evidence in the aforementioned nonclinical studies to indicate potential safety concerns associated with ABP 501 administration. The toxicokinetic and repeat-dose toxicity profile of ABP 501 was considered similar to that of US-licensed Humira in cynomolgus monkeys. The nonclinical pharmacology, pharmacokinetic, and repeat-dose toxicity data showed comparable exposure and safety between ABP 501 and US-licensed Humira. There are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology program in this application served several purposes:

- 1) To evaluate the PK similarity between ABP 501 and US-licensed Humira (Study 217)
- 2) To provide the PK element of the scientific bridge between ABP 501, US-licensed Humira and EU-approved Humira (Study 217)
- 3) To provide information on steady state PK (from Study 262 in patients with RA and from Study 263 in patients with PsO).

Study 217 was a randomized, parallel group, single-dose study in 203 healthy subjects randomized 1:1:1 to ABP 501, US-licensed Humira, and EU-approved Humira. This study was the pivotal clinical pharmacology study evaluating the PK similarity of ABP 501 and US-licensed Humira. The pairwise comparisons of ABP 501, US-licensed Humira, and EU-approved Humira met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUC_{0-inf} , AUC_{0-last} , and C_{max} within the interval of 80% to 125%). Therefore these data 1) establish PK similarity of ABP 501 and US-licensed Humira, and 2) establish the PK component of the scientific bridge to justify the relevance of data generated with EU-approved Humira to support a demonstration of the biosimilarity of ABP 501 to US-licensed Humira.

Similar trough concentrations were demonstrated for ABP 501 and US-licensed Humira in patients with RA on background methotrexate therapy (Study 262) and for ABP 501 and EU-approved Humira administered as monotherapy in patients with PsO (Study 263).

In summary, the Office of Clinical Pharmacology has determined that an adequate PK bridge has been demonstrated between ABP 501, US-licensed Humira, and EU-approved Humira. Importantly, 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.

6. Clinical Microbiology

Not applicable. Refer to Section 3 for Product Quality microbiology information.

7. Clinical/Statistical-Efficacy

Amgen conducted two contemporaneous comparative clinical studies, Study 262 and Study 263:

- 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 enrolled 526 subjects at 92 centers in 12 countries in Europe, North America, and Latin America. 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. 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. 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). 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.

Study 262 Results

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). FDA did not agree with this approach and had recommended a similarity margin of $\pm 12\%$ for the proportion of ACR20 responders. However, in a supportive analysis of ACR20 response in the subset of patients who completed the study and adhered to the protocol (per-protocol population), the 90% confidence interval for the difference in ACR20 response rates was within the FDA-suggested margin of $\pm 12\%$. Results for secondary endpoints, such as ACR50 and ACR70 responses, and change in DAS28-CRP were also similar for the ABP 501 and US-licensed Humira treatment groups. Therefore, the results of

Study 262 support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

Study 263 Results

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 $\pm 15\%$. Correspondingly, the 90% confidence interval also fell within the $\pm 15\%$ margin. Because the lower 90% confidence bound was -6.6, the study would meet the similarity criteria for margins of $\pm 7\%$ or larger.

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. 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. 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. Therefore, the review team has concluded that the results of Study 263 also support a demonstration of no clinically meaningful differences.

8. Safety

The primary safety data were derived from the two comparative clinical studies in RA (Study 262) and in PsO (Study 263). In Study 263, at Week 16, a total of 77 subjects underwent a single transition from EU-approved Humira to ABP 501 to assess additional risks, if any, in safety and immunogenicity resulting from a single transition from EU-approved Humira to ABP 501 to address the safety of the clinical scenario where non-treatment naïve patients transition to ABP 501. Supportive safety and immunogenicity information was also provided from the single-dose PK study in healthy subjects (Study 217). A total of 582 subjects were treated with ABP 501 across the three studies.

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 generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP 501 to US-licensed Humira.

Safety Summary

As shown in Table 1 below, overall, there were no major differences between treatment groups in adverse events (AE), serious adverse events (SAE), or AEs leading to discontinuations. 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. 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 approved labeling for US-licensed Humira.

Table 1: Safety Overview, Studies 262, 263, and 217.

	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 US-Humira: US-licensed Humira; EU-Humira: EU-approved Humira; AE: adverse event; SAE: serious adverse event							

There were no notable differences in AE or SAEs in patients who stayed on EU-approved Humira vs. those who underwent a transition from EU-approved Humira to ABP 501 (data not shown).

Immunogenicity Summary

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 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.

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 and 110/173 (64%) of EU-approved Humira-treated subjects developed binding ADAs. Regarding neutralizing ADAs, 17/174 (10%) treated with ABP 501 were positive and 24/173 (14%) treated with EU-approved Humira were positive. 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. Further, the titers of neutralizing antibodies were similar between the treatment groups.

Summary

In summary, no new safety signals were identified with ABP 501 compared to the known adverse event profile of US-licensed Humira. Immunogenicity data from populations with and without concomitant immunosuppressive therapy suggest there is not an increased risk of development of ADAs with treatment with ABP 501 as compared to US-licensed Humira and EU-approved Humira. Further, ADA formation did not increase following a single transition from EU-approved Humira to ABP 501. Therefore, the safety and immunogenicity data support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira.

9. Advisory Committee Meeting

An Arthritis Advisory Committee (AAC) meeting was held for this application on July 12, 2016. This meeting included experts in product quality assessment, clinical pharmacology, rheumatology, dermatology, and gastroenterology, as well as patient, consumer, and industry representatives. The Committee discussed the analytical data for ABP 501 and generally agreed that ABP 501 was highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components.² The Committee also discussed the clinical data

² The Agency requested functional data on reverse signaling during the review cycle and shortly before the Arthritis Advisory Committee (AAC) on July 12, 2016. (The applicant subsequently submitted the requested data; as discussed above, these data support a finding that ABP 501 is highly similar to US-licensed Humira.) Because this request was outstanding at the time of the AC meeting, 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

with ABP 501 in RA and PsO, and generally agreed there were no clinically meaningful differences between ABP 501 and US-licensed Humira in these indications. The Committee then discussed the scientific justification for supporting a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira for additional indications for which US-licensed Humira is licensed: JIA in patients 4 years of age and older, PsA, AS, adult CD, and adult UC). Panel members generally agreed that this extrapolation was justified. For the voting question, panelists were asked whether, based on the totality of the evidence, ABP 501 should receive licensure as a biosimilar product to US-licensed Humira for each of the indications for which US-licensed Humira is currently licensed and for which Amgen is seeking licensure (i.e., RA, JIA in patients 4 years of age and older, AS, PsA, PsO, adult CD and adult UC). The Committee voted 26 to 0 in favor of licensure of ABP 501 for these indications.

10. Pediatrics

As a proposed biosimilar, ABP 501 triggers the requirements of the Pediatric Research Equity Act (PREA) for every indication for which licensure is sought. The ABP 501 pediatric plan was discussed at the Pediatric Review Committee (PeRC) meeting of July 27, 2016. PeRC agreed with the applicant's current request for waivers and deferrals.

11. Other Relevant Regulatory Issues

- **Inspections:** No issues precluding approval were found on inspection of the manufacturing facilities or of selected clinical sites.
- **Financial Disclosure:** No issues.

12. Labeling

The proprietary name for ABP 501 will be Amjevita. FDA has determined that the use of a distinguishing suffix in the nonproprietary name is necessary to distinguish this product from US-licensed Humira (adalimumab). The nonproprietary name for ABP 501 will be adalimumab-atto. 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. 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

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>

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.

The general approach taken for the Amjevita labeling is to have the labeling incorporate relevant data and information from the current FDA-approved labeling for US-licensed Humira, with appropriate product-specific modifications. This approach is informed by the consideration that biosimilar product labeling that is consistent with the reference product labeling should more clearly convey FDA's conclusion that the two products are highly similar and there are no clinically meaningful differences.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

The action on this biologics license application will be Approval.

- **Assessment of Biosimilarity**

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" (see section 351(i)(2) of the PHS Act).

A multitude of quality attributes, including primary, secondary and higher order structure, Fc (effector) function, and other structural/functional characteristics were assessed by quality range analysis and by qualitative comparisons. Comparative TNF α binding and TNF α neutralization for ABP 501 and US-licensed Humira met statistical equivalence criteria. These attributes support a finding that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components.

Comparative PK data between ABP 501 and US-licensed Humira met the acceptance criteria for PK similarity (90% confidence intervals for the ratios of geometric mean of AUC_{inf}, AUC_{last}, and C_{max} within the interval of 80% to 125%). Comparative analytical characterization data and PK similarity data between ABP 501, US-licensed Humira, and EU-approved Humira provided a scientific justification for the relevance of comparative data generated with EU-approved Humira in Study 263 to support a demonstration of biosimilarity to US-licensed Humira. Therefore clinical efficacy, safety, and immunogenicity data from Study 263 in PsO patients, which evaluated ABP 501 and EU-approved Humira, support the data from Study 262 in RA patients, which evaluated ABP 501 and US-licensed Humira. Both of these studies support a finding 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.

Extrapolation

The applicant sought licensure for all the indications for which US-licensed Humira is licensed, based on a development program that included data from a comparative clinical study in RA and a comparative clinical study in PsO. To support extrapolation of the finding of biosimilarity to other conditions of use (i.e., JIA, AS, PsA, adult CD and adult UC), the applicant provided a scientific justification.

The primary mechanism of action (MOA) of adalimumab is through inhibition of the binding of soluble TNF α (sTNF) to cell-surface receptors and through binding transmembrane TNF α , inhibiting subsequent signal transduction and adhesion molecule expression. The scientific literature indicates that this is the primary MOA for RA, JIA, AS, PsA, and PsO, and is a likely MOA in CD and UC. However, the available scientific evidence suggests that for TNF inhibitors in inflammatory bowel disease (IBD), in addition to binding and neutralization of sTNF, other MOA may play a role.³ Reverse (outside-to-inside) signaling via binding to transmembrane TNF is a likely MOA. Mechanisms involving the Fc (constant) region are plausible as well, including induction of complement dependent cytotoxicity on transmembrane TNF-expressing target cells (via C1q binding), induction of antibody-dependent cellular cytotoxicity on transmembrane TNF-expressing target cells (via Fc γ RIIIa binding), and induction of regulatory macrophages in mucosal healing.

Amgen has provided data supporting a demonstration that ABP 501 and US-licensed Humira are highly similar, based on extensive structural and functional analytical characterization. In addition, Amgen has addressed each of the known and potential MOA and provided data to support the conclusion that ABP 501 and US-licensed Humira would be expected to have similar activity with respect to these MOA.

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.⁴ 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.⁵ 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

³ Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", *Pharmacology & Therapeutics* 117 (2008) 244–279

⁴ FDA-approved Humira labeling

⁵ FDA-approved Humira labeling

population, and the results were influenced by the type of immunoassay used.⁶ 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.⁷ These usage scenarios were assessed in Amgen's RA Study 262 (concomitant use of methotrexate) and Amgen's PsO Study 263 (use with a loading dose of 80 mg SC on Day 1, followed by 40 mg Q2W SC starting one week later, but without concomitant immunosuppressive therapy). There are sufficient data to indicate similar immunogenicity between ABP 501, EU-approved Humira, and US-licensed Humira. Accordingly, similar immunogenicity would be expected between ABP 501 and US-licensed Humira in patients with JIA, PsA, AS, adult CD, and UC.

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.

In aggregate, the evidence supports that extrapolation of biosimilarity to JIA in patients 4 years of age and older, AS, PsA, adult CD and adult UC is scientifically justified.

Conclusion

Therefore, the information submitted by the Applicant demonstrates that ABP 501 is biosimilar to US-licensed Humira and should be licensed.⁸

- **Postmarketing Risk Evaluation and Mitigation Strategies**

None.

- **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. Also, under PREA, Amgen is required to submit a pediatric assessment for the 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.

⁶ FDA-approved Humira labeling

⁷ FDA-approved Humira labeling

⁸ 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."

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

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):

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

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

/s/

SARAH K YIM
09/23/2016

BADRUL A CHOWDHURY
09/23/2016