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

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

Proposed Indications

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

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

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

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

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

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

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

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

Executive Summary:

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

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

Introduction:

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

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

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

Table 1. Overview of ABP 501 Clinical Program

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

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Extrapolation of Existing Data to Support Biosimilarity to IBD Indications:

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

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

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

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

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

Each of the issues outlined will be briefly discussed.

Mechanism of Action

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

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

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

[4] Id.

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

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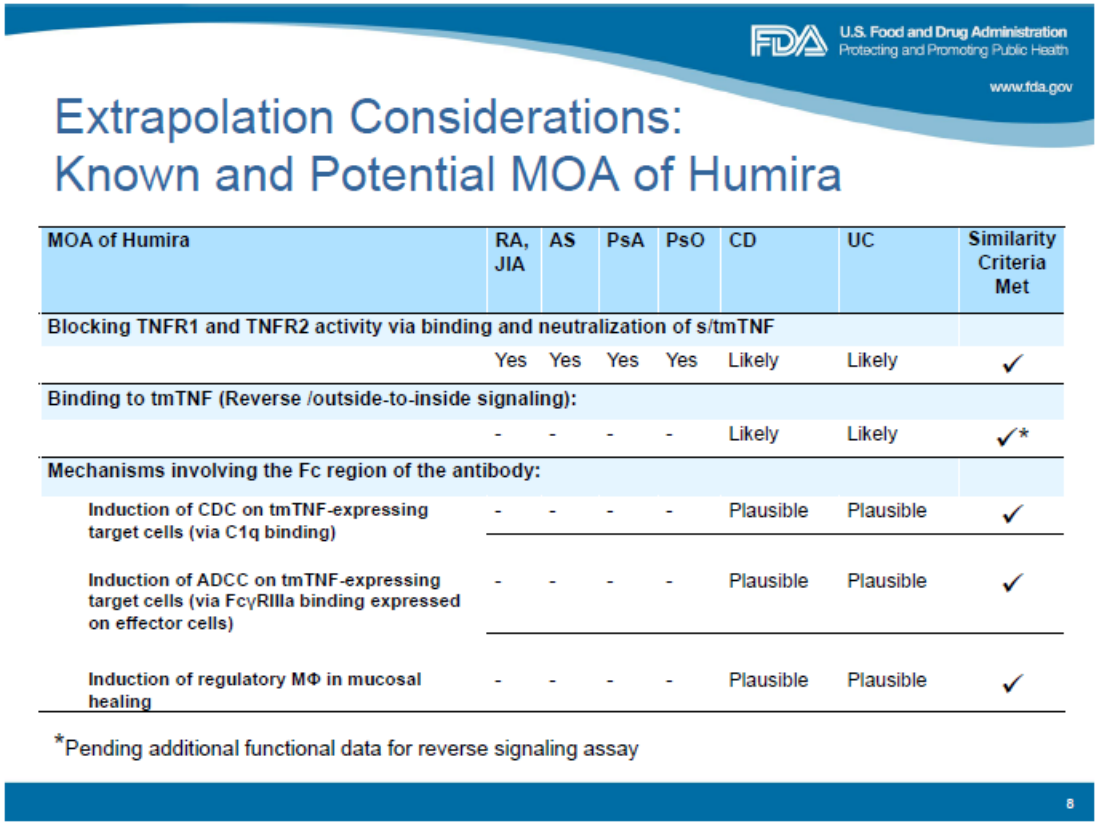
Table 2. Mechanisms of Action, US-Licensed Humira



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Extrapolation Considerations: Known and Potential MOA of Humira

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

*Pending additional functional data for reverse signaling assay

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Pharmacokinetics (PK)

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

Safety and Immunogenicity

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

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

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

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

Conclusion:

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

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

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/s/

AISHA P JOHNSON
09/14/2016

ANIL K RAJPAL
09/14/2016

DONNA J GRIEBEL
09/15/2016