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APPLICATION NUMBER:

761024Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: BLA 761024

Supporting document/s: SD#27

Applicant's letter date: July 26, 2016

CDER stamp date: July 26, 2016

Product: ABP-501, a proposed biosimilar to US-licensed Humira®

Proposed Indications: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)

Applicant: Amgen, Inc.

Review Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Reviewer: Carol M. Galvis, PhD

Supervisor/Team Leader: Timothy Robison, PhD, DABT

Division Director: Badrul A. Chowdhury, MD, PhD

Project Manager: Sadaf Nabavian

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1 Executive Summary

1.1 Introduction

This review evaluates the nonclinical sections of the proposed labeling for ABP 501, a proposed biosimilar to US-licensed Humira® (adalimumab). BLA 761024 was submitted by Amgen, Inc. on November 25, 2015 under section 351(k) of the Public Health Service Act (PHS Act) to support licensing of ABP 501 as a biosimilar product to US-licensed Humira®. ABP 501 is a monoclonal antibody that targets tumor necrosis factor (TNF)-alpha and blocks TNF-alpha interaction with its receptors.

An integrated review of the nonclinical development program to support approval of this BLA was completed on August 22, 2016. The nonclinical program was judged to be adequate for approval. No new nonclinical information has been submitted by Amgen. This review includes only recommendations for the nonclinical sections of the labeling. The following sections of the prescribing information were reviewed: sections 8.1 “Pregnancy” (only the “Risk Summary” and “Animal Data”), 8.2 “Lactation”, 12.1 “Mechanism of action”, and 13 “Nonclinical Toxicology”.

The original draft labeling was submitted by Amgen with the original BLA on November 25, 2015. However, revised draft labeling was submitted on July 26, 2016, based on the version of the US-licensed Humira’s label from June 30, 2016 and conforms to the FDA requirements under the Pregnancy and Lactation Labeling Rule (PLLR).

1.3 Recommendations

1.3.3 Labeling

Below is the recommended language for the aforementioned sections of the prescribing information.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited clinical data are available from a Pregnancy Registry conducted with adalimumab. Excluding lost-to follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups [see Data]. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the in-utero exposed infant [see Clinical Considerations]. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced

exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [ABP-TRADENAME] and any potential adverse effects on the breastfed child from [ABP-TRADENAME] or from the underlying maternal condition.

12.1 Mechanism of Action

Adalimumab products bind specifically to TNF-alpha and block its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab products also lyse surface TNF expressing cells in vitro in the presence of complement. Adalimumab products do not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In Ps, treatment with [ABP-TRADENAME] may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab products exert their clinical effects is unknown.

Adalimumab products also modulate biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of $1-2 \times 10^{-10}M$).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of adalimumab products have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

2 Drug Information

2.1 Drug

CAS Registry Number: 1446410-95-2

Proper Name: To be determined

Code Name: ABP 501

Chemical Name: anti-TNF alpha monoclonal antibody

Molecular Formula/Molecular Weight

Heavy chain: $C_{2191}H_{3392}N_{582}O_{677}S_{15}$ (not including N-linked glycans)

Light chain: $C_{1027}H_{1610}N_{282}O_{332}S_6$

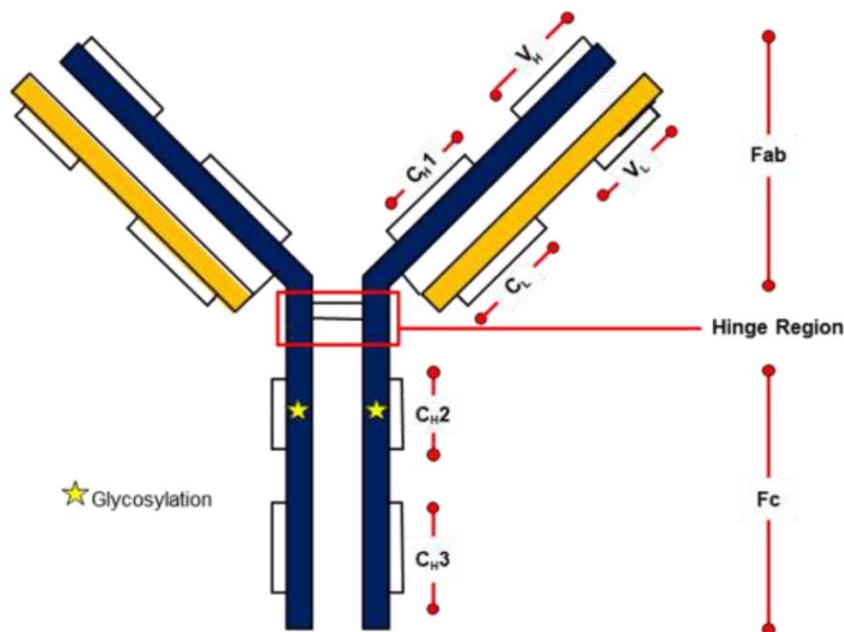
Molecular weight: 145,192 Da (not including N-linked glycans)

Molecular weight: 148,081 Da (glycosylated)

Structure or Biochemical Description

ABP 501 is a fully human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass, expressed in the Chinese hamster ovarian (CHO) cell line. ABP 501 contains 2 heavy chains and 2 light chains of the kappa subclass. Figure 1 below (excerpted from the sponsor's submission) presents ABP 501 structure.

Figure 1: ABP 501 Structure.



Heavy chains are shown in blue and light chains are shown in orange.

Black lines represent disulfide bonds.

V_H is the variable domain of the heavy chain.

C_{H1} , C_{H2} , and C_{H3} are the constant domains of the heavy chain.

V_L is the variable domain of the light chain.

C_L is the constant domain of the light chain.

Pharmacologic Class: anti-TNF alpha monoclonal antibody (IgG1 kappa)

3 Studies Submitted

3.3 Previous Reviews Referenced

Pharm/Tox review dated August 22, 2016

11 Integrated Summary and Safety Evaluation

The original 351(k) BLA was submitted by Amgen, Inc. on November 25, 2015. However, revised labeling language was submitted subsequently, after the approved

label for US-licensed Humira® was updated to conform to the Pregnancy and Lactation Labeling Rule (PLLR) that went into effect on June 30, 2015.

The language of the nonclinical sections of the proposed label [i.e., sections 8.1 “Pregnancy” (only the “Risk Summary” and “Animal Data”), 8.2 “Lactation”, 12.1 “Mechanism of action”, and 13 “Nonclinical Toxicology”] was reviewed and is generally consistent with the approved labeling for US-licensed Humira. However, certain references to “adalimumab” were revised to “adalimumab products” as appropriate. The term “adalimumab” was used where specific data derived from Humira were presented. The term “adalimumab products” was used when the information or the overall risk-benefit profile of Humira is relevant to ABP 501.

Since the prescribing information was submitted in PLLR format, a review was also conducted by the Division of Pediatric and Maternal Health (DPMH). Recommended language for sections 8.1 “Pregnancy” and 8.2 “Lactation” is based on agreement between DPMH and DPARP and is consistent with current thinking. Below is the proposed labeling text with recommended edits. Deleted text is shown as strikethrough text and inserted text is shown in underlined red font. An explanation for the proposed changes is included in *italics* under “Rationale for Changes”.

LABELING EDITS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited clinical data are available from a Pregnancy Registry conducted with adalimumab. Excluding lost-to follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups [see Data]. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the in-utero exposed infant [see Clinical Considerations]. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [ABP-TRADENAME] and any potential adverse effects on the breastfed child from [ABP-TRADENAME] or from the underlying maternal condition.

Rationale for Changes in Section 8

No changes are recommended for Sections 8.1 "Pregnancy" or 8.2 "Lactation". The above language is identical as the US-licensed Humira® label approved on June of 2016.

12.1 Mechanism of Action

Adalimumab (b) (4) **products** bind (b) (4) specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab (b) (4) **products** also lyse surface TNF expressing cells in vitro in the presence of complement. Adalimumab **products** do (b) (4) not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In Ps, treatment with [ABP-TRADENAME] may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab (b) (4) **products** exert (b) (4) **their** clinical effects is unknown.

Adalimumab (b) (4) **products** also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC₅₀ of 1-2 X 10⁻¹⁰M).

Rationale for Changes in Section 12.1

The proposed generic name of adalimumab-^{(b) (4)} was removed since the Agency's review of the proposed suffix has not been finalized. In addition, certain references to "adalimumab" were revised to say "adalimumab products" as appropriate to indicate that the information is relevant to both US-licensed Humira[®] and ABP 501.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of adalimumab **products** have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

Rationale for Changes in Section 13.1

The reference to "adalimumab" was revised to "adalimumab products" to indicate that no studies have been conducted with US-licensed Humira[®] or ABP 501.

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/s/

CAROL M GALVIS
09/20/2016

TIMOTHY W ROBISON
09/20/2016
I concur

Pharmacology and Toxicology Secondary Review for BLA 761024

TO: BLA 761024
ABP-501 (a proposed biosimilar to US-licensed Humira® [adalimumab])

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Pharmacology and Toxicology Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: August 25, 2016

BLA 761024 was submitted by Amgen, Inc. on November 25, 2015 under section 351(k) of the Public Health Service Act (PHS Act) to support licensure of ABP-501 as a biosimilar to US-licensed Humira® (adalimumab). Humira® was approved on December 31, 2002 under BLA 125057 and is currently approved for the following indications: Rheumatoid arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease (pediatric and adult), Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, and Uveitis. Amgen, Inc. is seeking approval of ABP-501 for the following indications: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis (4 years of age and older), Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, and Plaque Psoriasis.

Dr. Carol Galvis' review dated August 22, 2016 focused on two nonclinical studies submitted in support of a demonstration of biosimilarity of ABP-501 to US-licensed Humira®: (1) a toxicokinetic (TK) study in cynomolgus monkeys comparing ABP 501 vs. US-licensed Humira® and (2) a 4-week toxicology/TK study in Cynomolgus monkeys comparing ABP 501 vs. US licensed Humira®.

In the 4-week toxicology study with Cynomolgus monkeys, ABP-501 and US-licensed Humira® were studied at a dose of 157 mg/kg/week; this dose in a 4-week toxicology study with US-licensed Humira® in Cynomolgus monkeys had been found to produce pharmacodynamic effects of decreased cellularity of B cells (CD21) in the splenic follicles. In the 4-week study with ABP-501 and US-licensed Humira, there were similar findings of decreased size/number of germinal centers in lymph nodes and spleen as well as similar staining of CD20 and CD21 lymphocytes in the spleen for both agents.

The totality of the nonclinical toxicokinetic and repeat-dose toxicology data submitted in the BLA support a demonstration of biosimilarity (i.e., comparable systemic exposures and safety profiles) between ABP-501 and US-licensed Humira® from the nonclinical Pharmacology and Toxicology perspective.

I concur with Dr. Galvis' review dated August 22, 2016 that recommended approval of ABP-501 from the nonclinical Pharmacology and Toxicology perspective. A labeling review will follow.

Recommendation: From the nonclinical perspective, approval of the application is recommended.

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/s/

TIMOTHY W ROBISON
08/29/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: BLA 761024
Supporting document/s: SD#1
Applicant's letter date: November 25, 2015
CDER stamp date: November 25, 2015
Product: ABP 501 (a proposed biosimilar to US-licensed Humira®)
Proposed Indications: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)
Applicant: Amgen, Inc.
Review Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer: Carol M. Galvis, PhD
Supervisor/Team Leader: Timothy Robison, PhD, DABT
Division Director: Badrul A. Chowdhury, MD, PhD
Project Manager: Sadaf Nabavian

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1 Executive Summary

1.1 Introduction

This review evaluates the nonclinical pharmacology and toxicology data supporting a demonstration that ABP 501, is biosimilar to US-licensed Humira® (adalimumab). Amgen, Inc. submitted a Biologics License Application (BLA) on November 25, 2015 under section 351(k) of the Public Health Service Act (PHS Act) to support licensing of ABP 501 as a biosimilar product to US-licensed Humira® (adalimumab). Adalimumab is a monoclonal antibody that targets tumor necrosis factor (TNF)-alpha and works by blocking TNF-alpha interaction with cell surface TNF receptors.

Humira® was approved in 2002 under BLA 125057 (Abbot Laboratories, now AbbVie) and is currently approved for the following indications: Rheumatoid arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease (pediatric and adult), Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, and Uveitis. Amgen, Inc. seeks approval of ABP 501 for the following indications: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis (4 years of age and older), Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical development program for ABP 501 consisted of two nonclinical studies: a toxicokinetic (TK) study in cynomolgus monkeys comparing ABP 501 vs. US-licensed Humira and 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 totality of the nonclinical pharmacokinetic and repeat-dose toxicity data submitted in the BLA support a demonstration of biosimilarity (i.e., comparable systemic exposures and safety profiles) between ABP 501 and US-licensed Humira from the nonclinical Pharmacology and Toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

BLA 761024 is recommended for approval from the nonclinical Pharmacology and Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

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

1.3.3 Labeling

A separate labeling review will be completed for the nonclinical section of the labeling.

2 Drug Information

2.1 Drug

CAS Registry Number: 1446410-95-2

Proper Name: To be determined

Code Name: ABP 501

Chemical Name: anti-TNF alpha monoclonal antibody

Molecular Formula/Molecular Weight

Heavy chain: $C_{2191}H_{3392}N_{582}O_{677}S_{15}$ (not including N-linked glycans)

Light chain: $C_{1027}H_{1610}N_{282}O_{332}S_6$

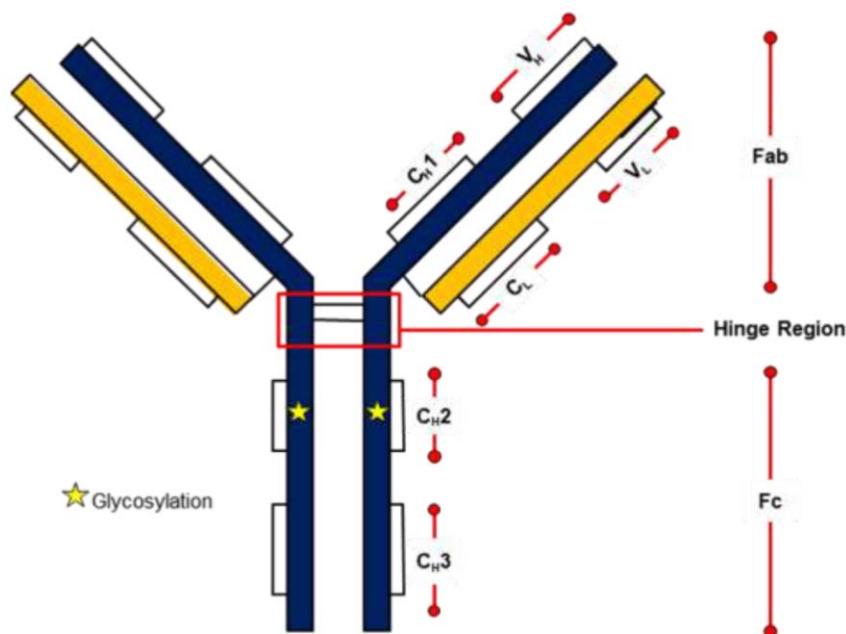
Molecular weight: 145,192 Da (not including N-linked glycans)

Molecular weight: 148,081 Da (glycosylated)

Structure or Biochemical Description¹

ABP 501 is a fully human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass, expressed in the Chinese hamster ovarian (CHO) cell line. ABP 501 contains 2 heavy chains and 2 light chains of the kappa subclass. Figure 1 below (excerpted from the sponsor's submission) presents ABP 501 structure.

Figure 1: ABP 501 Structure.



Heavy chains are shown in blue and light chains are shown in orange.

Black lines represent disulfide bonds.

V_H is the variable domain of the heavy chain.

C_H1, C_H2, and C_H3 are the constant domains of the heavy chain.

V_L is the variable domain of the light chain.

C_L is the constant domain of the light chain.

Pharmacologic Class: anti-TNF alpha monoclonal antibody (IgG1 kappa)

2.2 Relevant INDs, NDAs, BLAs and DMFs

ABP 501 was developed under IND 111,714.

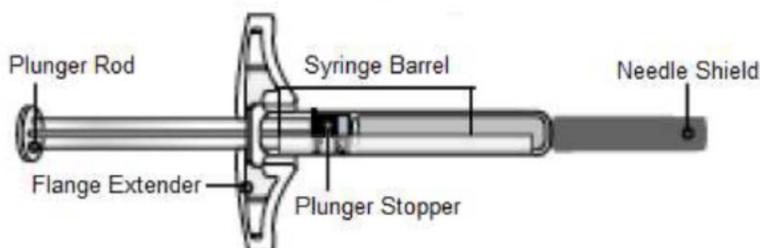
2.3 Drug Formulation

ABP 501 is proposed in two different container closure systems: a pre-filled syringe (PFS) and an auto-injector (AI) integrated with a PFS.

¹ Excerpted from the sponsor's submission

The PFS drug product is supplied as a sterile, single-use, preservative-free solution for SC injection in a pre-filled syringe. The PFS contains 0.4 mL (20 mg ABP 501) or 0.8 mL (40 mg ABP 501) of deliverable volume of 50 mg/mL ABP 501 in 10 mM acetate, 9% (w/v) sucrose, 0.1% Polysorbate 80, pH=5.2. The PFS container closure system consists of a Type 1 glass barrel (1 mL) with a stainless steel staked-in-place needle, a plunger stopper made of (b) (4) on the product contact surface, an (b) (4) needle shield, a plastic plunger rod, and a plastic flange extender. Figure 2 below, excerpted from the sponsor's submission, presents ABP 501 PFS.

Figure 2: ABP 501 Pre-filled Syringe.



The AI drug product is supplied as a sterile, preservative-free solution for SC injection in a single-use, disposable, handheld, mechanical (b) (4) pre-assembled AI. The AI contains a 27-gauge pre-filled syringe with a deliverable volume of 0.8 mL of 50 mg/mL ABP 501 (40 mg ABP 501) in 10 mM acetate, 9% (w/v) sucrose, 0.1% (w/v) Polysorbate 80, pH=5.2. The proposed AI device is an Amgen platform device (SureClick®) that is also used for Enbrel®. Figure 3 below, excerpted from the sponsor's submission, presents ABP 501 AI.

Figure 3: ABP 501 Autoinjector.

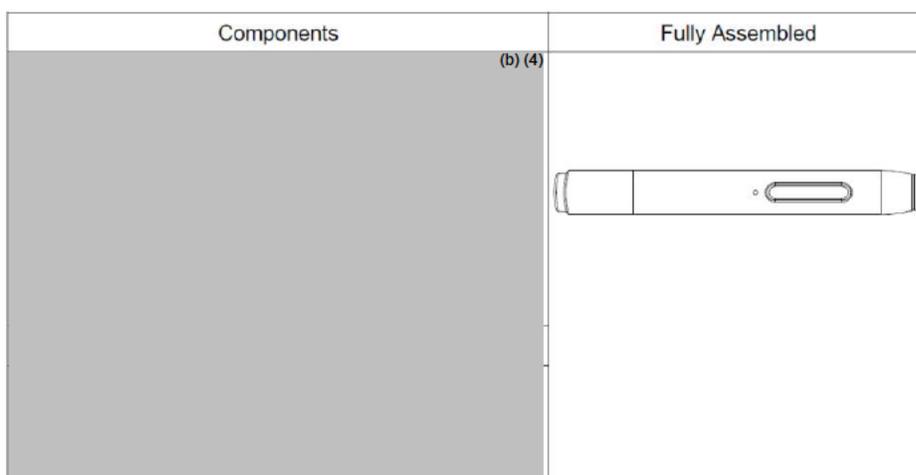


Table 1 below, excerpted from the sponsor's submission, includes the quantitative and qualitative composition of ABP 501 drug product.

Table 1: Qualitative and Quantitative Composition of ABP 501 Drug Product.

Component	Grade	Function	Quantity (0.4 mL)	Quantity (0.8 mL)	Concentration
ABP 501	In house ^a	Active ingredient	20 mg	40 mg	50 mg/mL
Sucrose	NF, PhEur, JP	(b) (4)	36 mg	72 mg	9.0% (w/v)
Polysorbate 80	NF, PhEur, JP	(b) (4)	0.4 mg	0.8 mg	0.10% (w/v)
Glacial acetic acid ^b	USP, PhEur, JP	(b) (4)	0.24 mg	0.48 mg	10 mM
Sodium hydroxide ^c	NF, PhEur, JP	pH adjustment	qs to target pH	qs to target pH	qs to target pH
Water for injection	USP, PhEur, JP	(b) (4)			(b) (4)

qs = quantum sufficit

^a Tested to internal specifications (3.2.S.4.1. Specification)

^b Glacial acetic acid is used in the (b) (4). 10 mM represents the acetate concentration. Sodium is the counter ion upon pH adjustment with sodium hydroxide.

^c The sodium hydroxide solution may be used to adjust pH. The supplier tests sodium hydroxide (b) (4) to NF, PhEur, and JP standards.

2.4 Comments on Novel Excipients

There are no novel excipients in ABP 501 drug product.

2.5 Comments on Impurities/Degradants of Concern

There were no impurities issues identified that impacted the nonclinical safety program. For additional information with drug substance and drug product impurities, refer to the Drug Quality review.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indications are based on those currently approved for Humira[®]. The proposed indications include Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps).

ABP 501 is proposed to be administered by SC injection at the following dosing regimens:

- For RA, PsA, AS: 40 mg every other week (or 40 mg every week for patients with RA not receiving methotrexate).
- For JIA: 20 mg every other week for patients 15 kg to 30 kg or 40 mg every other week for patients \geq 30 kg.
- For CD and UC: 160 mg initial dose (four 40 mg injections in one day or two 40 mg injections each day for two consecutive days), followed by a second dose of 80 mg two weeks later, and then a maintenance dose of 40 mg every other week.

- For Ps: 80 mg initial dose, followed by 40 mg every other week starting one week after the initial dose.

2.7 Regulatory Background

ABP 501 was developed by Amgen, Inc. under IND 111,714. A pre-IND meeting was held with Amgen on August 24, 2011 to discuss the adequacy of their proposed development plan, including the nonclinical requirements. The Division recommended a well-designed toxicity study in monkeys, consistent with biosimilar nonclinical requirements at the time. A second pre-IND meeting was held with Amgen on April 18, 2012 to discuss the adequacy of the analytical package for an IND submission. No nonclinical issues were discussed at this meeting. IND 111,714 was originally submitted on May 25, 2012 and the 2 nonclinical studies conducted with ABP 501 were reviewed to support safety for the opening IND clinical study (refer to Attachment 1, PharmTox review by Dr. Grace Lee, dated June 28, 2012). Additional meetings were held with Amgen during the IND phase, but no nonclinical issues were identified or discussed. A BPD Type 4 meeting was held with Amgen on June 10, 2015 to discuss the structure, format, and content for a proposed BLA for ABP 501 under section 351(k). The nonclinical program was considered adequate.

3 Studies Submitted

3.1 Studies Reviewed

- Study #114832, ABP501: 1-Month Subcutaneous Toxicology Study in the Male Cynomolgus Monkey.
- Study #115674, ABP501: 1-Month Subcutaneous Toxicology Study in the Cynomolgus Monkey.

3.2 Studies Not Reviewed

Not applicable

3.3 Previous Reviews Referenced

- PharmTox review dated June 28, 2012 by Dr. Grace S. Lee.

4 Pharmacology

4.1 Primary Pharmacology

Adalimumab is a monoclonal antibody that targets tumor necrosis factor (TNF)-alpha. Adalimumab works by blocking TNF-alpha interaction with cell surface TNF receptors and interfering with downstream signaling. ABP 501 was developed by Amgen, Inc. as a biosimilar to US-licensed Humira (adalimumab). A number of studies were conducted by Amgen to characterize the biological activity and immunochemical properties of ABP 501 relative to US-licensed Humira. Refer to the Product Quality review for a detailed description of these studies. No issues were identified that would affect the nonclinical safety assessment for ABP 501.

4.2 Secondary Pharmacology

Secondary pharmacology studies were not submitted with this BLA.

4.3 Safety Pharmacology

Safety pharmacology studies were not submitted with this BLA.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

See below under Section 6.2 "Repeat-Dose Toxicity".

5.2 Toxicokinetics

See below under Section 6.2 "Repeat-Dose Toxicity".

6 General Toxicology

6.1 Single-Dose Toxicity

Single-dose toxicity studies were not submitted with this BLA.

6.2 Repeat-Dose Toxicity

Study title: ABP 501: 1-Month Subcutaneous Toxicology Study in the Male Cynomolgus Monkey.

Study no.:	114832
Study report location:	EDR
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	July 19, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ABP 501, Lot #0010085288, 98.9-99.6% pure US-Humira [®] , Lot#042212E (expiration date: December 2012)

Key Study Findings

- This study was designed as a 4-week toxicity study. However, the study was terminated on study day 10 after the animals were administered two weekly doses.

- Toxicokinetic analysis showed that systemic exposure to ABP 501 and US-licensed Humira[®] is similar after a single SC dose.

Methods

Doses:	32 mg/kg ABP501 or US-licensed Humira [®]
Frequency of dosing:	Once weekly (2 doses only)
Route of administration:	Subcutaneous
Dose volume:	0.64 mL/kg/dose
Formulation/Vehicle:	10 mM sodium acetate, 9% (w/v) sucrose, 0.1% (w/v) Polysorbate 80, pH=5.2
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	5 Males/group
Age:	2.3-3.6 years old
Weight:	Not provided (target 2-5 kg)
Satellite groups:	None
Unique study design:	This study was designed as a 4-week study; however, the study was terminated on study day 10 after the animals were administered two weekly doses per sponsor's directive because the study design was not considered adequate to support clinical dosing.
Deviation from study protocol:	Deviations from the protocol were reviewed and judged not to affect the quality of study data.

Observations and Results

Mortality

Animals were observed twice daily, once in the morning and once in the afternoon, for general health and mortality or moribundity. There were no mortalities reported in the study.

Clinical Signs

Cageside observations were performed once daily in the morning. In addition, animals were observed twice daily for clinical signs of toxicity (general appearance and behavior) once pre-study and weekly thereafter.

There were no clinical signs of concern during the study.

Body Weights

Body weights were measured at least twice pre-study and weekly thereafter starting on study day 1. There were no drug-related changes in body weights in the study.

Feed Consumption

Food consumption was measured once daily in conjunction with the morning cageside observations by observing the number of biscuits remaining from the previous days feed ration. No drug-related effects were observed in food consumption.

Ophthalmoscopy

Not conducted

ECG

Not conducted

Clinical Pathology

Blood samples were collected from all animals for clinical pathology endpoints by venipuncture at pre-study and on study day 4. Urine was collected by drainage from special stainless steel cage pans at pre-study and on study day 4. Animals were fasted for clinical chemistry blood collections. Because a control group was not included in the study, the comparison was only made for ABP 501 versus US-Humira® and from study day 4 versus pre-study.

Hematology and Coagulation

There were no drug-related changes in hematology or coagulation parameters.

Clinical Chemistry

There were no drug-related changes in clinical chemistry parameters.

Urinalysis

There were no effects on urine volume, the only urinalysis parameter measured.

Gross Pathology

Not conducted

Organ Weights

Not conducted

Histopathology

Not conducted

Special Evaluation

None

Toxicokinetics

Blood samples were collected from both treatment groups for toxicokinetic analysis at pre-dose and at approximately 4, 24, 48, 72, 96, and 168 hours after the first dose. Adalimumab (ABP 501 or Humira[®]) concentration was measured in serum using a validated ELISA method (LLOQ = 100 ng/mL). Because the study was terminated on after the second dose, toxicokinetic evaluation was limited to single-dose information. Anti-drug antibodies were not analyzed.

Table 2 below, excerpted from the sponsor's submission, presents the mean TK parameters for ABP 501 and Humira[®] following a single-dose on study day 1. As shown, T_{max} was observed at 48 hours or 72 hours post-dose, except for one animal in the ABP 501 group. Systemic exposure to ABP 501 or US-licensed Humira[®] was similar after a single-dose of 32 mg/kg SC.

Table 2: Mean Toxicokinetic Parameters for ABP 501 and US-licensed Humira[®] Following a Single-Dose on Study Day 1.

Dosing.Info (mg/kg)	Treatment. Desc	N	t_{max} (hr) ¹	C_{max} (ug/mL)	AUC_{0-t} (ug*hr/mL)
32	adalimumab (Humira [®])	5	48.00 (48.00- 72.00)	280 (23.0)	38300 (4210)
	ABP 501	5	48.00 (48.00- 168.00)	244 (42.9)	34100 (5560)

¹ t_{max} (hr) is Median (min - max)

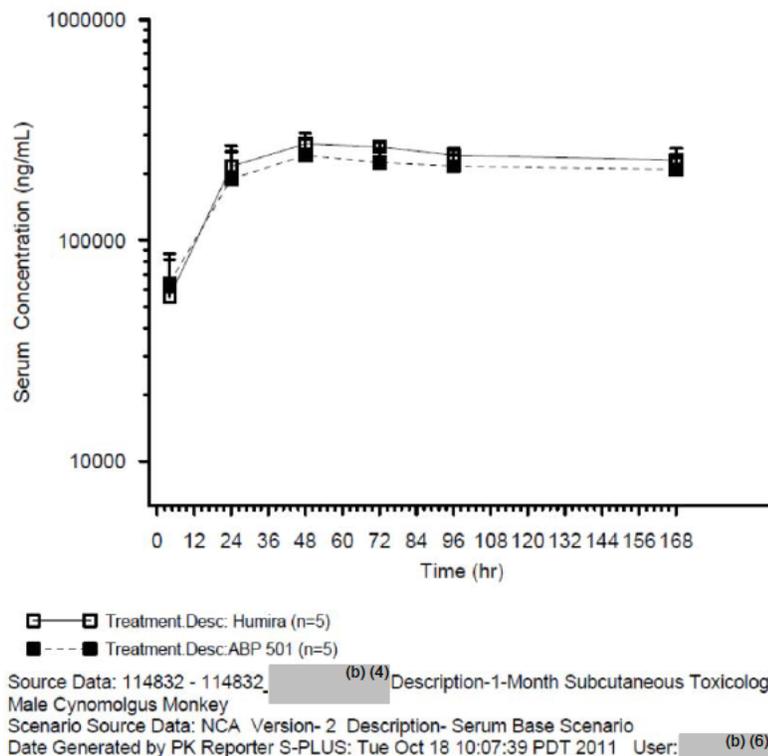
Source Data: 114832 - 114832_ (b) (4) Description-1-Month Subcutaneous Toxicology Study in the Male Cynomolgus Monkey

Scenario Source Data: NCA Version- 2 Description- Serum Base Scenario

Date Generated by PK Reporter S-PLUS: Tue Oct 18 10:07:42 PDT 2011 User: (b) (6)

Figure 4, excerpted from the sponsor's submission, presents the mean serum adalimumab (ABP 501 or Humira[®]) concentration-time profiles on study day 1. As shown, the mean concentration-time profiles were similar between ABP 501 and US-licensed Humira[®] after a single-dose.

Figure 4: Concentration-Time Profiles for ABP 501 and US-licensed Humira® after a Single-Dose on Study Day 1.



Dosing Solution Analysis

The test articles were administered as received by the sponsor. The sponsor provided the relevant information for ABP 501 identity, purity, strength, composition, and stability. The study report claims that the test article was stable under the conditions of the study. However, no data were provided in the study report for review.

Study title: ABP 501: 1-Month Subcutaneous Toxicology Study in the Cynomolgus Monkey.

Study no.: 115674
Study report location: EDR
Conducting laboratory and location:  (b) (4)
Date of study initiation: September 16, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: ABP 501, Lot #0010085288, 98.9-99.6% pure
US-licensed Humira[®], Lots #042212E (expiration date: December 31, 2012) and 031622E (expiration date: November 30, 2012)

Key Study Findings

- Cynomolgus monkeys received 0, 157 mg/kg ABP 501 or 157 mg/kg US-licensed Humira (US-Humira) once weekly for 4 consecutive weeks via SC administration.
- There were similar increases in white blood cells, neutrophils, and fibrinogen in animals treated with both ABP 501 and US-licensed Humira.
- The following findings were observed with similar incidence in animals treated with US-licensed Humira and ABP 501: decreased size/number of germinal centers in lymph nodes and spleen, and fibroplasia/fibrosis and inflammatory cell infiltration at the injection sites.
- Similar staining was observed for CD20 and CD21 in spleens collected from animals treated with US-licensed Humira or ABP 501.
- The TK profile and systemic exposure (C_{max} and AUC) of ABP 501 was comparable to US-licensed Humira on study days 1 and 22.

Methods

Doses: 0, 157 mg/kg ABP 501, or 157 mg/kg US-licensed Humira®
 Frequency of dosing: Once weekly for 4 consecutive weeks
 Route of administration: Subcutaneous
 Dose volume: 3.14 mL/kg/dose
 Formulation/Vehicle: 10 mM sodium acetate, 9% (w/v) sucrose, 0.1% (w/v) Polysorbate 80, pH=5.2
 Species/Strain: Cynomolgus monkey
 Number/Sex/Group: 3/sex/group
 Age: Males: 3-3.7 years of age
 Females: 3-4 years of age
 Weight: Males: 2.5-3.5 kg
 Females: 2.6-3 kg
 Satellite groups: None
 Unique study design: None
 Deviation from study protocol: Protocol deviations were reviewed and judged to not affect the quality or integrity of study data.

Per Division's request, this study included both genders (males and females), included a vehicle control group, and included a higher dose of both ABP 510 and US-licensed Humira®. Table 3 below, excerpted from the study report, includes a summary of the study design.

Table 3: Study 115674 Experimental Design.

Group No.	No. of Animals ^a (Male/Female)	Test Material	Dose Level (mg/kg/dose)	Dose Concentration (mg/mL)	Dose Volume (mL/kg/dose)
1	3/3	Control for ABP 501	0	0	3.14
2	3/3	ABP 501	157	50	3.14
3	3/3	Humira®	157	50	3.14

^a Terminal necropsy on Day 29

Observations and Results

Mortality

Animals were observed twice daily, in the morning and in the afternoon, for general health and mortality/moribundity.

There were no drug-related effects on mortality. All the animals survived until the scheduled necropsy.

Clinical Signs

Animals were observed for clinical signs of toxicity once prior to initiation of dosing and weekly starting on study day 1 during the dosing period. A final detailed clinical observation was performed for each animal on the day of scheduled necropsy. In addition, cageside observations were performed once daily in the morning starting pre-study and continuing through the day of necropsy.

There were no drug-related effects observed.

Body Weights

Body weights were recorded twice prior to initiation of dosing and weekly during the dosing period. A final fasted body weight was recorded on the day of euthanasia for calculation of organ-to-body weight ratios.³

There were no drug-related effects on body weights.

Feed Consumption

Food consumption was qualitatively evaluated once daily in the morning starting pre-study and continuing through the day of necropsy.

There were no drug-related effects on food consumption.

Ophthalmoscopy

Ophthalmic examinations were conducted by a certified veterinary ophthalmologist once prior to dosing and on study day 26. Slit-lamp biomicroscopy was performed to examine the anterior segment of the eye, lens, and anterior vitreous. The lids and conjunctiva, cornea and tear film, anterior chamber, iris, and pupil were included in the examination of the anterior segment. Indirect ophthalmoscopy was performed to examine the vitreous, retina, optic disc, and choroid.

There were no drug-related effects on ophthalmic examinations.

ECG

ECGs were recorded once prior to dosing and on study days 3 and 24. Monkeys were temporarily restrained outside their cages, but were not sedated. The evaluation consisted of qualitative examination of each tracing for abnormalities as well as a quantitative measurement of the PR, QRS, QT, and RR intervals from an average of 10 complexes in each recording. QTc was derived using Bazett's formula.

There were no drug-related effects observed on ECG examinations.

Clinical Pathology

Blood samples were collected from all animals by venipuncture. Urine was collected by drainage from special stainless steel cage pans. Animals were fasted for clinical chemistry blood sample collections. Samples were collected prior to dosing and on study days 4 and 29.

Hematology and Coagulation

A full battery of hematology parameters was evaluated. The following coagulation parameters were evaluated: fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (APTT).

Similar increases in white blood cells, neutrophils, and fibrinogen were observed in males and females on days 4 and 29 with both ABP 501 and US-licensed Humira (Table 4).

Table 4: Summary of Changes in Hematology and Coagulation Parameters.

Dose Group		Males			Females		
		Veh	ABP	US-Hum	Veh	ABP	US-Hum
WBC($10^3/\mu\text{L}$)	Day 4	10.90	19.87 (+82%)	23.73 (+118%)	12.33	14.00 (+14%)	17.37 (+41%)
	Day 29	9.67	14.70 (+52%)	15.17 (+57%)	9.90	10.13 (+2.3%)	11.17 (+13%)
Neutrophils (μL)	Day 4	3417.3	8122.0 (+138%)	12705.7 (+272%)	5375.3	8329.7 (+55%)	10611.3 (+97%)
	Day 29	3766.0	5982.3 (+59%)	6925.7 (+84)	4991.7	5250.3 (+5.2%)	6145 (+23%)
Fibrinogen (mg/dL)	Day 4	271	345 (+27%)	474 (+75%)	244	273 (+12%)	281 (+15%)
	Day 29	205	165 (-20%)	219 (+6.8%)	211	203 (-3.8%)	175 (-17%)

Clinical Chemistry

A full battery of clinical chemistry parameters was evaluated in serum.

There were no drug-related effects observed.

Urinalysis

A full battery of urinalysis parameters was evaluated.

There were no drug-related effects observed.

Gross Pathology

Animals were euthanized using Beuthanasia[®]-D injection, followed by exsanguination. The animals were necropsied and urine was collected using a cage pan collection. Main study animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic

cavities with their associated organs and tissues. Necropsy examinations were conducted under the supervision of a veterinary pathologist.

There were no drug-related findings observed.

Organ Weights

At scheduled necropsies, the following organs were weighed: brain, epididymis, adrenal gland, pituitary gland, prostate gland, thyroid gland, heart, kidney, liver, lung, spleen, testis, and thymus. Paired organs were weighed together. Organ-to-body weight ratios were calculated using the terminal body weights. In addition, organ-to-brain ratios were also calculated.

There were no drug-related effects observed.

Histopathology

Adequate Battery

A full battery of tissues was collected from all animals at necropsy. The following table, excerpted from the study report, presents a list of tissues/organs collected at necropsy.

Table 5: List of Organs and Tissues Collected at Necropsy – Study #115674.

Administration site	Large intestine, colon
Animal identification	Large intestine, rectum
Artery, aorta	Liver
Bone marrow smear	Lung
Bone marrow, femur	Lymph node, axillary
Bone marrow, sternum	Lymph node, mesenteric
Bone, femur	Muscle, skeletal psoas
Bone, sternum	Nerve, optic ^a
Brain	Nerve, sciatic
Cervix	Ovary
Epididymis	Oviduct
Esophagus	Pancreas
Eye ^a	Skin
Gallbladder	Small intestine, duodenum
Gland, adrenal	Small intestine, ileum
Gland, mammary	Small intestine, jejunum
Gland, parathyroid	Spinal cord
Gland, pituitary	Spleen
Gland, prostate	Stomach
Gland, salivary mandibular	Testis ^b
Gland, seminal vesicle	Thymus
Gland, thyroid	Tongue
Gross lesions/masses	Tonsils
Gut-associated lymphoid tissue	Trachea
Heart	Ureter
Kidney	Urinary bladder
Large intestine, cecum	Uterus
	Vagina

^a Preserved in Davidson’s fixative.

^b Preserved in Modified Davidson’s fixative.

Peer Review

A peer pathologist review was conducted on all the pathology data by a pathologist from Amgen at the test facility. The peer review was documented (review certificate) in the study report.

Histological Findings

A summary of histological observations is presented in Table 6 below. The following findings were observed with similar incidence in animals that received US-licensed Humira or ABP 501: decreased size/number of germinal centers in lymph nodes and spleen, and fibroplasia/fibrosis and inflammatory cell infiltration at the injection sites.

Table 6: Summary of Histological Observations (Incidence and Severity).

Dose Group No. animals examined	Males			Females		
	Veh 3	ABP 3	Hum 3	Veh 3	ABP 3	Hum 3
Axillary lymph nodes Decreased size/number germinal						

centers						
Mild	1	1	1	0	1	1
Moderate	0	0	0	0	1	2
Mesenteric lymph nodes						
Decreased size/number germinal centers						
Mild	0	1	0	1	1	0
Moderate	0	0	2	0	2	3
Spleen						
Decreased size/number germinal centers						
Mild	1	0	1	0	1	1
Moderate	1	1	0	0	1	2
Injection site, upper						
Fibroplasia/fibrosis, focal						
Minimal	1	0	0	0	1	0
Mild	0	0	1	0	0	1
Infiltrate, mononuclear cell, focal						
Minimal	0	1	0	0	0	1
Injection site, lower						
Fibroplasia/fibrosis, focal, minimal	0	1	1	0	0	0
Infiltrate, mixed cell, focal, minimal	0	1	0	0	0	1

Special Evaluation

Immunohistochemistry

A representative section of the spleen was collected at necropsy after the spleen was weighed but prior to placement in formalin for immunohistochemistry (IHC) using antibodies specific for CD20, CD21, and mouse IgG (negative control) and flow cytometry analysis.

Similar staining was observed for both CD20 and CD21 in spleens collected from animals treated with US-licensed Humira or ABP 501 (Tables 7 and 8 below).

Table 7: Immunohistochemistry of CD20 in Spleen Tissue *Ex vivo*.

Dose Group No. animals examined		Males			Females		
		Veh 3	ABP 3	Hum 3	Veh 3	ABP 3	Hum 3
Spleen – Follicle	Frequent	2	2	2	3	1	1
	Occasional	1	1	1	0	1	2
	Rare	0	0	0	0	1	0
Spleen – PALS	Very rare	3	3	3	3	3	3
Spleen – Red pulp	Very rare	3	3	3	3	3	3

Table 8: Immunohistochemistry of CD21 in Spleen Tissue *Ex vivo*.

Dose Group	Males			Females		
	Veh	ABP	Hum	Veh	ABP	Hum

No. animals examined		3	3	3	3	3	3
Spleen – Follicle	Frequent	2	0	1	3	0	1
	Occasional	1	3	2	0	2	2
	Rare	0	0	0	0	1	0
Spleen – PALS	Negative	3	3	3	3	3	3
Spleen – Red pulp	Negative	3	3	3	3	3	3

Toxicokinetics and ADA

Blood samples were collected from all groups at the following time points, relative to day 1 or 15 dosing: pre-dose and 4, 24, 48, 72, 96, 168 hours post-dose; for toxicokinetic analysis. Samples were collected into serum separator tubes without additives or anticoagulant for serum separation. ABP 501 and US-Humira® concentrations in serum were quantitated using a validated immunoassay. A portion of the samples collected were also used for incurred sample reanalysis (ISR).

Blood samples were also collected by venipuncture at pre-dose, on study days 1 and 15, and at terminal necropsy for anti-drug antibodies (ADA) analysis. Animals were not fasted prior to blood collection.

Table 9, excerpted from the study report, presents a summary of the mean TK parameters of ABP 501 and US-licensed Humira on study days 1 and 22 (males and females combined). The TK profile and systemic exposure (C_{max} and AUC) of ABP 501 was comparable to US-licensed Humira on study days 1 and 22.

Table 9: Mean Toxicokinetic Parameters of ABP 501 and US-licensed Humira® on Day 1 and Day 22 Following Subcutaneous Administration to Monkeys.

Route	Treatment Desc	Day	N	t_{max} (hr) ¹	C_{max} (ug/mL)	AUC _{0-t} (ug*hr/mL)	AR
SC	ABP 501	1	6	48.00 (48.00-96.00)	1030 (162)	145000 (24800)	NC
		22	6	36.00 (24.00-72.00)	2660 (406)	380000 (59600)	2.65 (0.300)
	Humira®	1	6	48.00 (24.00-72.00)	1130 (160)	154000 (15800)	NC
		22	6	36.00 (24.00-48.00)	2640 (526)	380000 (68100)	2.47 (0.396)

¹ t_{max} (hr) is Median (min - max)

Source Data: 115674 - 115674 (b)(4) Description-ABP 501: 1-Month Subcutaneous Toxicology

Study in the Cynomolgus Monkey

Scenario Source Data: NCA Version- 3 Description- Serum Base Scenario

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Dosing Solution Analysis

Test article, US-licensed Humira[®], and vehicle control formulations were used as received from the sponsor. Pre-filled syringes were removed from the refrigerator and formulations were slowly injected into a sterile container used for administration, then allowed to warm to room temperature for at least 30 minutes prior to administration. For ABP 501 and the vehicle control, the sponsor provided documentation of the identity, strength, purity, and stability. The certificates of analysis were included in the study report. Characterization of US-licensed Humira[®] was documented in the product insert. No additional characterization was conducted at the test site.

7 Genetic Toxicology

Genetic toxicology studies were not submitted with this BLA.

8 Carcinogenicity

Carcinogenicity studies were not submitted with this BLA.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were not submitted with this BLA.

10 Special Toxicology Studies

There were no special toxicology studies submitted for review with this BLA.

11 Integrated Summary and Safety Evaluation

Amgen, Inc. submitted this BLA 761024 under section 351(k) of the PHS Act to support licensing of ABP 501 as a biosimilar product to US-licensed Humira[®] (adalimumab). Adalimumab is a monoclonal antibody that targets TNF-alpha. Humira[®] was originally approved in 2002 under BLA 125057 (Abbott Laboratories, now AbbVie). Humira[®] is approved for the following indications: Rheumatoid arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease (pediatric and adult), Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, and Uveitis. Amgen, Inc. seeks approval of ABP 501 for the following indications: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis (4 years of age and older), Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis.

The nonclinical development program for ABP-501 included two studies: (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 profile of ABP 501 in cynomolgus monkeys was considered comparable to that of US-licensed Humira (Table 10).

Table 10: Mean Toxicokinetic Parameters of ABP 501 and US-licensed Humira[®] Following Subcutaneous Administration to Cynomolgus Monkeys.

	Dose Levels (mg/kg)	N	Study Day	T _{max} (hr)	C _{max} (µg/mL)	AUC _{0-t} (µg·hr/mL)	AR
ABP 501	32	5 Males	1	48	244 (42.9)	34100 (5560)	
	157	3 M, 3 F	1	48	1030 (162)	145000 (24800)	
			22	36	2660 (406)	380000 (59600)	2.65
US-Humira	32	5 Males	1	48	280 (23.0)	38300 (4210)	
	157	3 M, 3 F	1	48	1130 (160)	154000 (15800)	
			22	36	2640 (526)	380000 (68100)	2.47

N = number of animals, M = males, F = females, AR = accumulation ratio

The totality of the nonclinical pharmacokinetic and repeat-dose toxicity data submitted in the BLA (i.e., comparable systemic exposure and safety profile in a repeat-dose toxicity study) support a demonstration of biosimilarity between ABP 501 and US-licensed Humira from the nonclinical Pharmacology and Toxicology perspective. It is considered that the results of these animal studies can be taken together with the data from the analytical bridging studies (refer to the Drug Product Quality review for details) to support a demonstration that ABP 501 is biosimilar to US-licensed Humira[®].

No residual uncertainties have been identified by this discipline and there are no outstanding issues from the nonclinical Pharmacology and Toxicology perspective. Therefore, the BLA is recommended for approval from the nonclinical perspective.

12 Appendix/Attachments

Attachment 1: PharmTox review under IND 111,714 dated June 28, 2012.

DIVISION OF PULMONARY, ALLERGY AND RHEUMATOLOGY PRODUCTS
PRELIMINARY PHARMACOLOGY SAFETY REVIEW

IND: 111,714

Drug: ABP 501

Drug Category: Biosimilar to adalimumab [Humira[®]]; a TNF blocker

Intended clinical population: The proposed indications for ABP 501 are the same as all of those approved for FDA-licensed adalimumab: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, and Plaque Psoriasis

Review completion date: June 28, 2012

The IND opening study is a randomized, single-blind, single-dose, 3-arm, parallel group phase 1 bioequivalence study in healthy adult male and female subjects (between 18 to 45 years of age). The primary objectives of the study are to demonstrate bioequivalence (as assessed principally by AUC_{inf} and C_{max}) of ABP 501 following a 40 mg SC injection relative to that from a 40 mg SC injection of Humira[®] (US) or Humira[®] (EU). The secondary objective is to determine the safety, tolerability, and immunogenicity in healthy adult subjects of ABP 501 compared with Humira[®] (US) or Humira[®] (EU). The phase 1 bioequivalence study will enroll subjects from both the US and Europe. Subjects in the US will receive ABP 501 or Humira[®] (US), and subjects in Europe will receive ABP 501 or Humira[®] (EU). Data from all subjects who received ABP 501, and US subjects who received Humira[®] (US), will be used to demonstrate the pharmacokinetic comparability of ABP 501 to Humira[®] (US). Similarly, data from all subjects who received ABP 501 and EU subjects who received Humira[®] (EU) will be used to demonstrate the pharmacokinetic comparability of ABP 501 to Humira[®] (EU).

Men and women of reproductive potential must use a highly effective method of birth control for the duration of the study and continuing 4 months following treatment with the investigational product or until the scheduled end of study (whichever is longer). Male subjects must agree not to donate sperm during the study and for 4 months following treatment with investigational product or until the scheduled end of the study (whichever is longer).

ABP 501 medicinal product has the same strength as the 40-mg prefilled syringe presentation of Humira[®] (US and EU), but is formulated differently from Humira[®] (US and EU). The excipients of ABP 501 includes with 10 mM sodium acetate, 9.0% (w/v) sucrose, 0.1% (w/v) polysorbate 80, pH 5.2, whereas Humira[®] (US and EU) contains (b) (4) [redacted]. The excipients used in the ABP 501 formulation are all used at comparable or higher levels for other injectable drug products approved in the US.

ABP 501 is a humanized IgG1 monoclonal antibody that is being developed as a biosimilar product to Humira[®] (adalimumab). The primary amino acid sequence for adalimumab in ABP 501 and in Humira[®] is identical. ABP 501 binds to TNF α , prevents it from binding to and activating TNF receptor superfamily 1A (p55) and 1B (p75), and consequently interferes downstream signaling.

In support of the clinical protocol, the sponsor conducted comparative in vitro studies, two repeat dose PK studies in male monkeys and 1-month SC toxicity study in monkeys.

(b) (4) analysis showed that comparable binding affinities to both recombinant human TNF α and recombinant cynomolgus monkey TNF α were observed for ABP 501, US-Humira[®] and EU-Humira[®] (using 3 lots per each product). Equilibrium binding constants for all three lots of all three mAbs were comparable. The affinity of each of the three anti-TNF α mAbs for nonhuman primate TNF α (e.g., K_d = 70 pM for ABP 501) was slightly lower than those for human TNF α (e.g., K_d = 50 pM for ABP 501), which was observed in all three lot sets tested.

All three mAb products (ABP 501, US-Humira[®] and EU-Humira[®]) were shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in the presence of cells expressing membrane-bound human TNF α , with similar binding of three products to Fc γ RIIIa, which is one of the critical steps for ADCC induction. Comparable binding to FcRn was also shown with all three products.

As compared to those of US-Humira[®] and EU-Humira[®], ABP 501 showed similar inhibitory effects on human TNF α -induced biological responses in comparative *in vitro* studies. These studies assessed the following biological responses: inhibition of TNF α -induced apoptosis in U-927 cells, neutralization of TNF α -induced secretion of IL-8 in human umbilical vein endothelial cells (HUVEC), lack of neutralization of lymphotoxin α -induced secretion of IL-8 in HUVEC, inhibition of TNF α -induced death of actinomycin D-sensitized L929 cells, and inhibition of TNF α -induced chemokine production in human whole blood.

In addition to inhibitory effects of ABP 501 on human TNF α -induced biological responses, inhibitory effects of ABP 501 on cynomolgus monkey TNF α -induced biological responses were examined in cynomolgus monkey TNF α -induced death of actinomycin D-sensitized murine L929 cells and chemokine production using cynomolgus monkey whole blood as compared to those of US-Humira[®] and EU-Humira[®] (using 3 lots per each product). The results showed similar activity of ABP 501 and Humira[®] (US and EU), however, due to large variability in these assays, these data along with binding affinity data to monkey TNF α could only demonstrate that cynomolgus monkeys are pharmacologically relevant species.

In a monkey PK study [Amgen Study No. 114832], ABP 501 or US-Humira[®] were administered at 32 mg/kg via subcutaneous (SC) injection once weekly to male cynomolgus monkeys (5/group), and the study was terminated on Day 10 after the animals were administered two weekly doses. After a single SC dose of 32 mg/kg, mean C_{max} and AUC of ABP 501 and Humira[®]-dosed groups were similar (see Table 5).

In a 4-week toxicology study [Amgen Study No. 115674], cynomolgus monkeys (3/sex/group) were weekly administered at SC doses of 0 (ABP 501 placebo: 10 mM Na acetate, 9% (w/v) sucrose, 0.1% (w/v) polysorbate 80 at pH 5.2; Group 1), 157 (ABP 501; Group 2) and 157 (US-Humira[®]; Group 3) mg/kg/week. Monkeys were dosed on Days 1, 8, 15 and 22 and then sacrificed on Day 29. There was no mortality in the study. There was an increase in mean counts of white blood cells and neutrophils and mean levels of fibrinogen in both ABP 501- and Humira[®]-dosed groups (Table 1). ABP-501 and Humira[®]-related histopathological changes were comparable and limited to the lymphoid tissues, and were characterized by higher incidences of decreased size and number of germinal centers present in axillary lymph node, mesenteric lymph node, and tonsil (Table 2). Higher incidences of mild to moderate decreased

size and number of germinal centers were observed in the axillary lymph node of females in ABP 501- and Humira®-dosed groups. Increased incidences of decreased size and number of germinal centers were also present in mesenteric lymph node of males and females administered with ABP 501 and Humira® and tonsil of males and females administered with ABP 501, and females administered with Humira®. Immunohistochemical staining of spleen tissue for CD20 and CD21 showed comparable effects of both ABP 501 and Humira® (Tables 3 and 4). A slightly higher incidence of decreased staining frequency of CD20+ cells in lymphoid follicles was observed in females in ABP 501- and Humira®-dosed groups. A slightly higher incidence of decreased staining frequency of CD21+ cells in lymphoid follicles was also present in males and females in ABP 501- and Humira®-dosed groups.

Table 1 Changes in the hematology parameters from the 1-month toxicity study in monkeys

Dose Group		Male			Female		
		G1 vehicle	G2 ABP 501	G3 Humira®	G1 vehicle	G2 ABP 501	G3 Humira®
WBC (10 ³ /μL)	Day 4	10.90	19.87 (+82%)	23.73 (+118%)	12.33	14.00 (+14%)	17.37 (+41%)
	Day 29	9.67	14.70 (+52%)	15.17 (+57%)	9.90	10.13 (+2.3%)	11.17 (+13%)
Neutrophil (/μL)	Day 4	3417.3	8122.0 (+138%)	12705.7 (+272%)	5375.3	8329.7 (+55%)	10611.3 (+97%)
	Day 29	3766.0	5982.3 (+59%)	6925.7 (+84%)	4991.7	5250.3 (+5.2%)	6145 (+23%)
Fibrinogen (mg/dL)	Day 4	271	345 (+27%)	474 (+75%)	244	273 (+12%)	281 (+15%)
	Day 29	205	165 (-20%)	219 (+6.8%)	211	203 (-3.8%)	175 (-17%)

Table 2 Histopathological Findings from the 1-month SC toxicity study in monkeys

Dose Group		Males			Females		
		G1 vehicle	G2 ABP 501	G3 Humira®	G1 vehicle	G2 ABP 501	G3 Humira®
Organ/Tissue							
Axillary lymph node							
Decreased size/no. germinal center	Total	1/3	1/3	1/3	0/3	2/3	3/3
	Mild	1	1	1	0	1	1
	moderate	0	0	0	0	1	2
Mesenteric lymph node							
Decreased size/no. germinal center	Total	0/3	1/3	2/3	1/3	3/3	3/3
	Mild	0	1	0	1	1	0
	moderate	0	0	2	0	2	3
Tonsil							
Decreased size/no. germinal center	Total	0/3	1/3	0/3	0/3	1/3	2/3
	Mild	0	1	0	0	1	1
	moderate	0	0	0	0	0	1

Table 3 Immunohistochemistry of CD20 with the spleen of cynomolgus monkeys *ex vivo*

Dose Group		Male			Female		
		G1 vehicle	G2 ABP 501	G3 Humira®	G1 vehicle	G2 ABP 501	G3 Humira®
Follicle	Frequent	2	2	2	3	1	1*
	Occasional	1	1	1	0	1	2
	Rare	0	0	0	0	1	0
Pals	Very rare	3	3	3	3	3	3
Red Pulp	Very rare	3	3	3	3	3	3

*mild in intensity, all other findings were moderate in intensity

Table 4 Immunohistochemistry of CD21 with the spleen of cynomolgus monkeys *ex vivo*

Dose Group		Male			Female		
		G1 vehicle	G2 ABP 501	G3 Humira®	G1 vehicle	G2 ABP 501	G3 Humira®
Follicle	Frequent	2	0	1	3	0	1
	Occasional	1	3	2*	0	2*	2*
	Rare	0	0	0	0	1	0
Pals	Negative	3	3	3	3	3	3
Red Pulp	Negative	3	3	3	3	3	3

* One female in Group 2, one male in Group 3, and 2 females in Group 3 had occasional staining with mild in intensity in the follicle, and all other findings were moderate in intensity

TK data showed similar systemic exposure in monkeys dosed either ABP 501- or Humira® (see Table 5). There was no sex difference, but accumulation in exposure was observed on Day 22 with an AR of 2.65 for ABP 501 and 2.47 for Humira®.

Table 5 Mean (SD) Values of TK parameters from 2 repeat-dose and 1-month toxicity studies in monkeys [Amgen Study Nos. 114832 and 115674, respectively]

	Dose Levels	N	Day	T _{max} (hr)	C _{max} (µg/mL)	AUC _{0-t} (µg*hr/mL)	AR
ABP 501	32	5 ♂	1	48	244 (42.9)	34100 (5560)	
	157	3 ♂ & 3 ♀	1	48	1030 (162)	145000 (24800)	
			22	36	2660 (406)	380000 (59600)	2.65
Humira®	32	5 ♂	1	48	280 (23.0)	38300 (4210)	
	157	3 ♂ & 3 ♀	1	48	1130 (160)	154000 (15800)	
			22	36	2640 (526)	380000 (68100)	2.47

AR = accumulation ratio

Overall, the Sponsor provided adequate evidence for comparability between ABP 501 and US-Humira[®] in monkey studies in term of PK/TK and PD parameters and there is no safety concern for ABP 501 from the nonclinical perspective.

Recommendation: It is safe to proceed from the nonclinical perspective.

Non-hold Comment: None

To the PM: A more comprehensive review will be followed.

Grace S. Lee, Ph.D.

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/s/

GRACE S LEE
06/28/2012

TIMOTHY W ROBISON
06/28/2012
I concur

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

/s/

CAROL M GALVIS
08/22/2016

TIMOTHY W ROBISON
08/22/2016
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 761-024

Applicant: Amgen, Inc.

Stamp Date: 11/24/2015

Drug Name: ABP 501 (proposed biosimilar to US-Humira) **NDA/BLA Type: Original application**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		This is a 351(k) application for a proposed biosimilar to US-licensed Humira. Therefore, the nonclinical program is an abbreviated program. Only a comparative toxicity study and a PK study in monkeys were conducted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		The pivotal toxicity study was conducted in compliance with GLP regulations.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		Section 8 follows the new PLLR format. A consult to the Maternal Health staff will be requested to discuss the language.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)			There were no issues identified during the IND review and no issues identified to date.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			This is not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			This is not applicable. This is a 351(k) application for a proposed biosimilar to US-licensed Humira.

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION
FILEABLE? ___ Yes ___**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

BLA 761-024 is fileable from the Pharmacology/Toxicology perspective.

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

There are no comments for the applicant.

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

/s/

CAROL M GALVIS
01/12/2016

MARCIE L WOOD
01/12/2016