CLINICAL PHARMACOLOGY REVIEW

BLA	761024
Submission Date:	11/25/2015
Proposed Brand Name:	(b) (4)
Nonproprietary Name:	ABP 501 (adalimumab-xxxx)[1]
Clinical Pharmacology Reviewer:	Jianmeng Chen, M.D., Ph.D.
Clinical Pharmacology Team Leader :	Anshu Marathe, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor:	Amgen
Submission Type; Code:	351(k); standard review
Formulation; Strength(s)	Single-use prefilled syringe 40 mg/0.8 mL and 20 mg/0.4 mL; Autoinjector (SureClick): 40 mg/0.8 mL
Proposed Indications:	Rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (PJIA) in patients 4 years and older, ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis (PsO), adult Crohn's disease (CD), adult Ulcerative colitis (UC)
Proposed Dosage Regimens:	Same as Humira

[1] In this document, FDA generally refers to Amgen's proposed product by the Amgen descriptor "ABP 501." FDA has not yet designated a nonproprietary name for Amgen's proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products).

1. Executive Summary

Amgen submitted a Biologic License Application (BLA) for ABP501, a recombinant human immunoglobulin G1(IgG1) monoclonal antibody that binds to human tumor necrosis factor alpha (TNFα), under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for ABP501 as a biosimilar to US-licensed Humira (BLA 125057) and licensure for seven indications currently approved for US-licensed Humira, which are Rheumatoid Arthritis (RA), juvenile idiopathic arthritis (PJIA) in patients 4 years of age and older, Psoriatic Arthritis (PA), Ankylosing Spondylitis (AS), adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (PsO). ABP501 drug product is supplied as a single-use pre-filled syringe (40 mg/0.8 mL, 20 mg/0.4mL) or a single use autoinjector (40 mg/0.8 mL) for subcutaneous injection.

The clinical development for ABP501 relevant to US submission included three clinical studies.

Pharmacokinetic (PK) similarity of ABP501 to US-licensed Humira was evaluated with the pivotal three-way PK similarity study to compare the PK, safety, tolerability, and immunogenicity of ABP501, EU-approved Humira and US-licensed Humira in healthy subjects (Study 217). PK and immunogenicity were also assessed in study 262 to compare ABP 501 and US-licensed Humira in RA patients (with concomitant use of methotrexate), and study 263 in psoriasis patients to compare ABP501 and EU-approved Humira (administered as monotherapy).

PK similarity was demonstrated between ABP501, EU-approved Humira, and US-licensed Humira in healthy subjects (study 217). In this study, the pairwise comparisons of ABP501, US-licensed Humira and EU-approved Humira met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%), thus establishing the PK similarity and providing the PK bridging data in addition to the analytical bridging data, to justify the relevance of the comparative data generated using EU-approved Humira.

In addition, similar trough concentrations were demonstrated for ABP501 and US-licensed Humira in patients with RA (with concomitant use of methotrexate, Study 262), and for ABP501 and EU-approved Humira in patients with PsO (administered as monotherapy, Study 263).

The incidence of binding anti-drug antibody (ADA) formation on Day 63 in healthy subjects was 43%, 51%, and 50% for ABP501, EU-approved Humira, and US-licensed Humira, respectively. While the development of ADAs appears to increase clearance of the products, the impact of ADAs on PK was similar between these three treatment groups. After multiple doses, the ADA incidence increased over time in all arms in Study 262 and 263, and was comparable between ABP501 and US-licensed Humira in patients with RA (Study 262), and ABP501 and EU-approved Humira in patients with PsO (Study 263).

Overall, the PK similarity has been demonstrated between ABP501 and the US-licensed Humira. PK data also support the scientific bridge between the US-licensed Humira and EU-approved Humira to justify the relevance of comparative data generated using EU-approved Humira. The PK results add to the totality of evidence to support a demonstration of biosimilarity of ABP501 and US-licensed Humira.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that PK similarity has been demonstrated between ABP501 and US-licensed Humira, and the PK results support a demonstration of no clinically meaningful differences between ABP501 and US-licensed Humira.

Labeling Recommendations

Please refer to Section 3 – Detailed Labeling Recommendations.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The clinical development for ABP501 relevant to US submission included three clinical studies. Pharmacokinetic (PK) similarity of ABP501 to US-licensed Humira was evaluated with the pivotal three-way PK similarity study to compare the PK, safety, tolerability, and immunogenicity of ABP501, EU-approved Humira and US-licensed Humira in healthy subjects (Study 217). PK and immunogenicity were also assessed in study 262 to compare ABP 501 and US-licensed Humira in RA patients (with concomitant use of methotrexate), and study 263 in psoriasis patients to compare ABP501 and EU-approved Humira (administered as monotherapy).

In the dedicated PK study 217, the pairwise comparisons of ABP501, US-licensed Humira and EU-approved Humira met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUCinf, AUClast, and Cmax, within the interval of 80% to 125%) as summarized in Table 1. These data establish the PK similarity between ABP501 and US-licensed Humira. These data also establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP501 to US-licensed Humira.

Table 1. Statistical Analysis of PK parameters in Study 217

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

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

The incidence of binding anti-drug antibody (ADA) formation on Day 63 in healthy subjects was 43%, 51%, and 50% for ABP501, EU-approved Humira, and US-licensed Humira, respectively. While the development of ADAs appears to increase clearance of the products, the impact of ADAs on PK was similar between these three treatment groups. After multiple doses, the ADA incidence increased over time in all arms in Study 262 and 263, and was comparable between ABP501 and US-licensed Humira in patients with RA (Study 262), and ABP501 and EU-approved Humira in patients with PsO (Study 263).

Overall, from the clinical pharmacology perspective, the submitted clinical pharmacology studies support a demonstration of PK similarity among ABP501, EU-approved Humira, and US-licensed Humira.

2. Question Based Review

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Amgen is developing ABP501 as a proposed biosimilar to Humira® (adalimumab). Humira® was approved in the United States (US) in 2002 under BLA125057. During the clinical development of ABP501, several key regulatory interactions with Amgen occurred: The first interaction with the FDA on the ABP 501 development program occurred at a Biosimilar Biological Product Development (BPD) meeting held on August 24, 2011 with several follow up interactions that included a BPD Type 4 meeting held on June 10, 2015. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP). During the pre-submission interactions, FDA provided product quality, nonclinical, and clinical comments, including the recommendations to the applicant regarding demonstration of PK similarity between ABP 501, US-licensed Humira and EU-approved Humira.

OSI inspection was requested for study 20110217 (Study 217), for ICON Clinical Pharmacology (clinical site) and (b) (4) (analytical lab). The Division of New Drug Bioequivalence Evaluation (DNDBE) and Office of Study Integrity and Surveillance (OSIS) recommended that the data were acceptable following evaluation of the inspection findings. See reviews by Dr. Mohsen Rajabi and Dr. Xiaohan Cai dated 7/27/2016.

An advisory committee meeting was held on 7/12/2016 and the committee voted (26yes: 0no: 0abstain) for approval of ABP501. The voting question is:

- Does the totality of the evidence support licensure of ABP501 as a biosimilar product to US-licensed Humira for the following indications for which US-licensed Humira is currently licensed and for which Amgen is seeking licensure (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, adult UC, and PsO)?

The vote result is: 26Y: 0N: 0Abstain

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

ABP501 drug substance is fully human recombinant monoclonal antibody with an amino acid sequence identical to adalimumab. Similar to adalimumab, ABP 501 consists of 2 heavy chains of the immunoglobulin G1 (IgG1) subclass and 2 light chains of the human kappa subclass, which are covalently linked through disulfide bonds. The molecular weight of ABP 501 is approximately 148 kDa. ABP 501 is produced by recombinant DNA technology in a Chinese hamster ovary cell expression system.

The ABP 501 drug product was developed as a single-use pre-filled syringe or a single-use autoinjector in some of the same strengths approved for US-licensed Humira (i.e. 40 mg/0.8 mL); and it also has the same dosage form and route of administration as those approved for US-licensed Humira. The ABP 501 drug product formulation has different inactive ingredients than US-licensed Humira. The composition of ABP 501 drug product is presented below in Table 2.

Table 2. Formulation Ingredients and Composition of ABP 501 Drug Product

Component	Function	Quantity (0.4 mL)	Quantity (0.8 mL)	Concentration
ABP 501	Active Ingredient	20 mg	40 mg	50 mg/mL
Sucrose	(b) (4)	36 mg	72 mg	9.0% (w/v)
Polysorbate 80		0.4 mg	0.8 mg	0.10% (w/v)
Glacial Acetic Acid		0.24 mg	0.48 mg	10 mM
Sodium Hydroxide	pH adjustment	qs to Target	qs to Target	qs to Target
Water for Injection				(b) (4)

(Source: Table 1, section 3.2.P.1)

Adalimumab (US-licensed Humira) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Humira was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

US-licensed Humira is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen), as a single-use, 1 mL prefilled glass syringe, or as a single-use institutional use vial. Each 40 mg/0.8 mL prefilled syringe, prefilled pen, or single-use institutional use vial delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains adalimumab 40 mg, citric acid monohydrate 1.04 mg, dibasic sodium phosphate dihydrate 1.22 mg, mannitol 9.6 mg, monobasic sodium phosphate dihydrate 0.69 mg, polysorbate 80 0.8 mg, sodium chloride 4.93 mg, sodium citrate 0.24 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH. Each 20 mg/0.4 mL prefilled syringe delivers 0.4 mL (20 mg) of drug product.

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

ABP501 is an IgG1 kappa monoclonal antibody, with a high affinity and avidity for TNF-α, including both the soluble and membrane-bound forms. It functions primarily via the variable region's complementary determining region (CDR) surface by binding, neutralizing and sequestering excess sTNF-α produced in local inflammatory disease tissue sites. Another potential variable region-mediated mechanism of action is the mediating of reverse signaling via binding and cross-linking mTNF on inflammatory cells or induction of regulatory macrophages. Finally, there are some potential functions dependent on the Fragment crystallizable region (Fc) part of the antibody that may be important. These include antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) of lysis of mTNF+ inflammatory T-cells or other cells associated with particular disease states. The relative importance of merely sequestering sTNF vs. eliciting other effector functions on mTNF+ cells may vary between disease states.

ABP501 is proposed to be used for 7 indications currently licensed for US-licensed Humira, which are Rheumatoid Arthritis (RA), juvenile idiopathic arthritis (PJIA) in patients 4 years of age and older, Psoriatic Arthritis (PA), Ankylosing Spondylitis (AS), adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (PsO).

2.1.4 What are the proposed dosages and routes of administration?

The proposed dosages and routes of administration for ABP501 are identical to those approved for US-licensed Humira (Table 3).

Table 3. Dosage and routes of administration of US-licensed Humira

Indication	Dosage and Administration
RA PA AS	40 mg every other week, Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week
CD UC	• Initial dose (Day 1): 160 mg; • Second dose two weeks later (Day 15): 80 mg; • Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. • For UC only: Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy.
PsO	80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.
PJIA	• 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week • ≥ 30 kg (66 lbs): 40 mg every other week

(Source: Summary from US-licensed Humira Label)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Three studies were conducted to assess PK similarity, including Study 217, a pivotal 3-way PK bridging study in healthy subjects, and two supportive studies for PK assessment in patients: trough concentrations were collected in RA patients in study 262, and in psoriasis patients in study 263 (Table 4). (b) (4)

This clinical pharmacology review primarily focused on the pivotal PK similarity Study 217. We also evaluated the PK and immunogenicity in Studies 262 and 263. The PK findings from these studies are also summarized in the appendix 4.1. Data from (b) (4) was not submitted to this BLA (BLA791024).

Table 4. Summary of ABP501 clinical studies

Study	Objective	Design	Subjects (Planned)	Treatments
20110217	PK similarity, ABP 501, HUMIRA-US, HUMIRA-EU	SC, R, SD, SB, 3-arm parallel	203 healthy subjects	40 mg (PFS) SC SD
20120262	Clinical comparability in RA, ABP 501 vs HUMIRA (US)	SC, R, MD, DB	526 Patients with RA	40 mg SC Q2W+MTX, 26W
20120263	Clinical comparability in Ps, ABP 501 vs HUMIRA (EU)	SC, R, MD, DB, re-randomization at W16 -	350 Patients with Ps -	80 mg SC d1, 40 mg SC Q2W beginning at W2, 52 W
				(b) (4)

(Source: reviewer summary)

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

PK (AUC0-inf, AUC0-t, and Cmax) was assessed as primary endpoint in the Study 217 to evaluate and compare the PK profiles of ABP501, EU-approved Humira and US-licensed Humira in healthy subjects. Safety, tolerability and immunogenicity were the secondary endpoints. The study design elements and the PK similarity assessments were aligned with the Draft FDA guidance for industry *Clinical Pharmacology Data To Support A Demonstration Of Biosimilarity To A Reference Product*", which was published in May 2014.

Study 262 was the clinical comparative study in RA patients. Study 263 was the clinical comparative study in PsO patients. Ctrough was also assessed in these studies, and allowed for the assessment of impact of immunogenicity on PK. For the choice of efficacy endpoints and margins, and the endpoints for safety assessment in Study 262 and 263, see details in the medical review and statistical review.

2.2.3 What are the PK characteristics of the drug?

2.2.3.2 What are the single dose and multiple dose PK characteristics for ABP501?

Single-Dose PK

The pivotal PK similarity Study 217 was a randomized, single-blind, parallel-group single dose clinical study. A total of 203 healthy subjects were enrolled and randomized to 3 parallel arms with 67 to 69 subjects in each arm. All subjects received a single-dose of 40mg of either ABP501 (n=67), US-licensed Humira (n=69) or EU-approved Humira (n=67) through subcutaneous

injection by pre-filled syringe. The PK, safety, tolerability, and immunogenicity of ABP501, EU-approved Humira and US-licensed Humira were assessed. Mean serum concentration-time profiles were similar between the ABP501, EU-approved Humira and US-licensed Humira treatment groups (Figure 1). For the 3-way PK similarity comparisons (ABP501 vs. US-licensed Humira, ABP501 vs. EU-approved Humira and EU-approved Humira vs. US-licensed Humira), the 90% CIs for the geometric mean ratios of Cmax, AUC0-t and AUC0-inf were all contained within the similarity range of 80% –125% (Table 5).

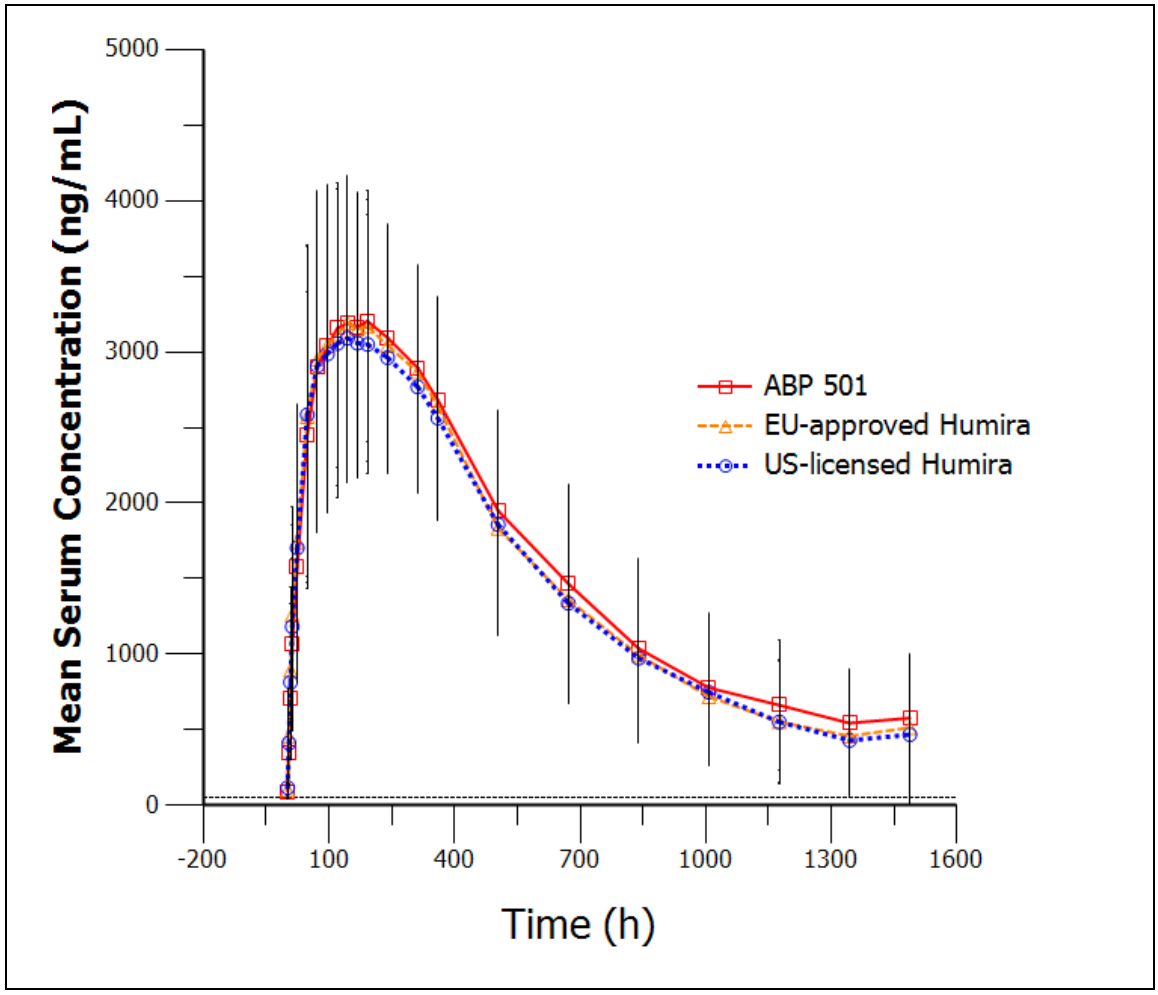


Figure 1. PK Profiles Following a Single SC 40mg Dose of ABP501, EU-approved Humira, or US-licensed Humira in Healthy Subjects (Study 217)

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

Table 5. Statistical Analysis of PK parameters in Study 217

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

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

Multiple-Dose PK

Study 262 was a randomized, double-blind, active comparator-controlled, 26-week study in subjects with moderate to severe RA who had an inadequate response to methotrexate (MTX). Subjects received ABP 501 (n=264) or US-licensed Humira (n=262) at 40 mg SC every 2 weeks (Q2W), and the last dose is at week 22. Trough serum concentrations were assessed for comparison between ABP501 and US-licensed Humira in RA patients. PK samples were collected pre-dose on day 1 and at weeks 2, 4, 12, 24, and at the end of study visit (week 26). As shown in Figure 2, the trough concentrations are comparable at each time point between ABP501 and US-licensed Humira.

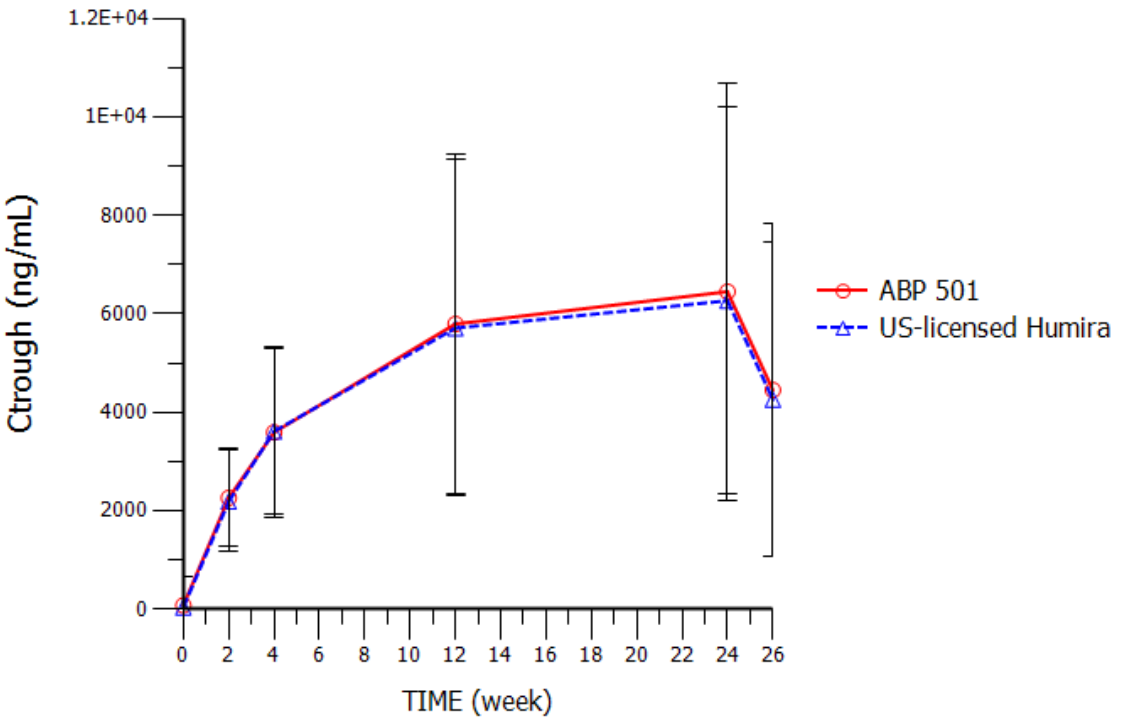


Figure 2. Trough Concentration Following Multiple SC Dosing (40 mg Q2W) of ABP501 (n=264) or US-Licensed Humira (n=262) in RA Patients (Study 262, mean±sd)

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

In addition, the PK of ABP501 was also compared to EU-approved Humira in the comparative efficacy Study 263. This study was a randomized, double-blind, active comparator-controlled study in adult subjects with at least 6 months duration of moderate to severe psoriasis (PsO). Subjects received ABP 501 or EU-approved Humira (1:1 ratio, n=173-174/group) at an initial loading dose of 80 mg SC on week 1/day 1 followed by 40 mg SC every other week starting 1 week after the loading dose. At week 16, eligible subjects who continued treatment beyond week 16 were re-randomized in a blinded fashion such that all subjects initially randomized to ABP 501 continued treatment with ABP 501 (ABP 501/ABP 501), and subjects initially randomized to EU-approved Humira were re-randomized in a 1:1 ratio to either continue treatment with EU-approved Humira or to transition to and continue treatment with ABP 501. Trough serum concentrations were assessed for comparison between ABP501 and EU-approved Humira in PsO patients. Sparse PK samples were collected at pre-dose on day 1 and at weeks 4, 16, 20, 32, and at the end of study visit. Figure 3 showed the trough concentrations for ABP501 and EU-approved Humira at week 4 and 16 before the re-randomization. The trough concentrations are comparable at each time point between ABP501 and EU-approved Humira.

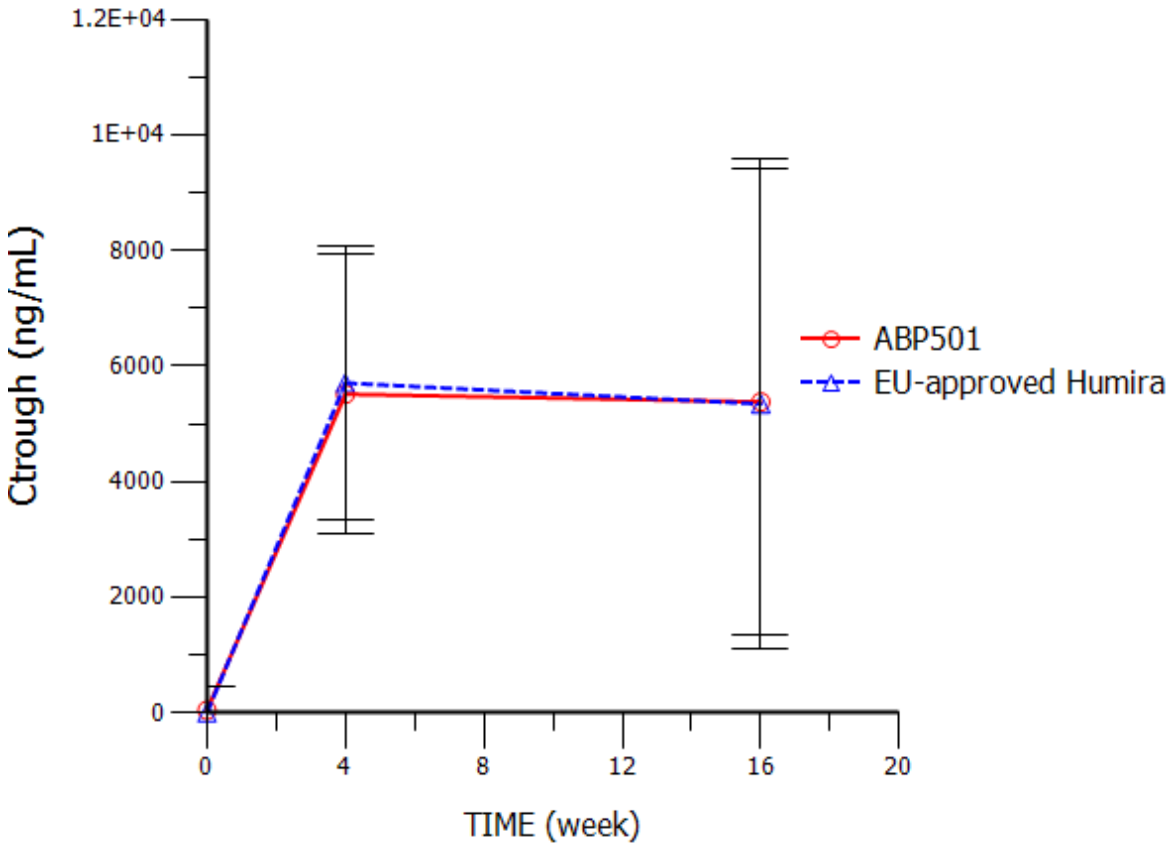


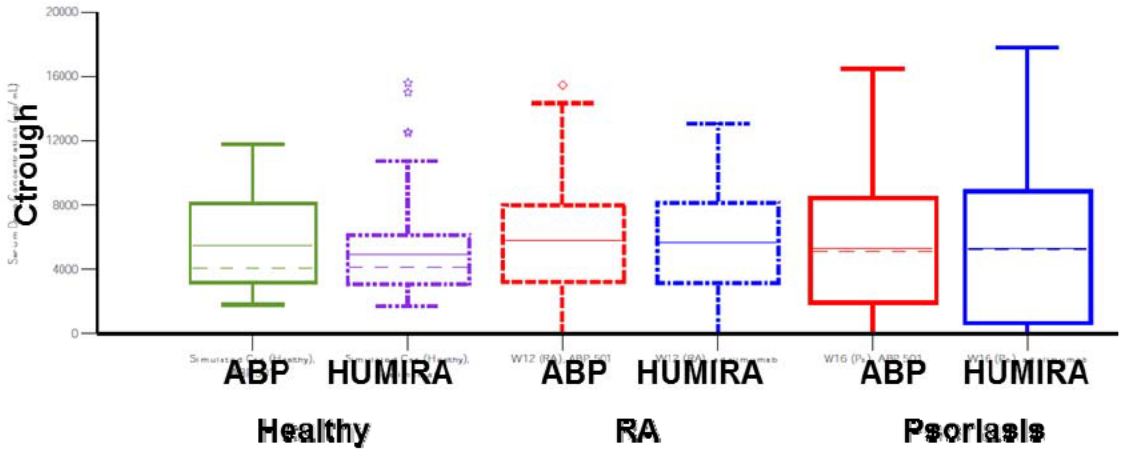
Figure 3. Ctrough at Weeks 4 and 16 Following Multiple SC Doses of ABP501 (n=174) or EU-approved Humira (n=173) in PsO Patients (Study 263, mean±sd)

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

2.2.3.3 How does the PK of ABP501 in healthy adults compare to that in patients with the target disease?

PK similarity was demonstrated between ABP 501 and US-licensed Humira and EU-approved Humira in a pivotal PK study in healthy volunteers (see section 2.2.3.2). Additionally, similar trough concentrations were demonstrated for ABP501 and US-licensed Humira in patients with RA and for ABP501 and EU-approved Humira in patients with PsO (see section 2.2.3.2). As per the product labeling for US-licensed Humira, healthy volunteers and patients with rheumatoid arthritis displayed similar pharmacokinetics. As similarity is established between ABP 501 and US-licensed Humira, it is expected that PK of ABP 501 in healthy adults should be comparable to patients.

In addition, as shown in Figure 4, the trough concentrations derived from the ABP 501 study in healthy subjects are highly consistent with those observed from the ABP 501 studies in RA and PsO subjects as well as between ABP 501 and adalimumab. Furthermore, the observed trough concentrations of ABP 501 and US-licensed Humira and EU-approved Humira in Studies 262 and 263 were within the range of steady state trough concentrations for US-licensed Humira in PsA, UC, CD, RA and PsO.



*Trough concentrations for subjects in Study 20110217 are projected. The overall formula is as follows: 1/(1-exp(-0.693*14/half-life in days)) * C312h.

Figure 4. Steady State Serum Trough Concentration Comparisons (projected for Healthy subjects, Week 12 for RA patients, Week 16 for PsO patients)

(Source: Figure 2, section 2.7.2, Summary of Clin Pharm)

2.2.3.4 What is the variability of the PK parameters in volunteers and patients with the target disease?

The variability of Cmax and AUC evaluated as geometric coefficient of variation (%CV) was 30-60% as shown in Table 6 after single dose administration of 40 mg for all the three products. After multiple dose administration, variability for Ctrough is ~ 210-230% in patients with RA and PsO.

Table 6. Variability of adalimumab exposure

Product	Geometric CV (%)			Dose
	Cmax	AUC0-inf	AUC0-last	
217				
ABP501 (N=67)	30.2	47.4	39.3	40 mg SD
EU-approved Humira (N=67)	30.5	46.7	40.9	40 mg SD
US-licensed Humira (N=69)	32.7	56.6	43.6	40 mg SD
262 (Week 12)				
	Cmin			
US-Licensed Humira (N=239)	211			40 mg SC Q2W
ABP501(N=231)	211			40 mg SC Q2W
263 (Week 16)				
	Cmin			
EU-approved Humira(N=131)	220			80 mg subcutaneous (SC) on week 1/day 1, followed by 40 mg SC every other week starting 1 week after the loading dose
ABP501(N=139)	230			

(Source: reviewer summary)

2.3 Intrinsic Factors

2.3.1 Immunogenicity

2.3.1.1 How was the immunogenicity assessed and what was the incidence of the formation of the anti-drug antibody (ADA)?

In the ABP 501 clinical studies, all samples were screened with a two-tiered approach (screening and specificity) for binding ADA activity using a sensitive and drug-tolerant bridging immunoassay. Samples were also analyzed to detect drug-specific ADA; thus, all samples were tested for binding ADA against ABP 501, US-licensed Humira, and EU-approved Humira. Samples that tested positive in either assay were considered 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. For the assessment of binding ADA and neutralizing ADA assays, see OBP review for more detailed information.

In Study 217, no pre-existing ADAs were detected in subject samples at baseline. The incidence of ADAs throughout the study following a single dose of 40 mg SC of study drug was similar between all three treatment arms. Importantly, the rate of neutralizing ADA was similar between all three treatment arms at 18%, 22%, and 21%, respectively.

Overall, as summarized in Table 7, in studies 262 in RA and 263 in PsO patients, following repeat dosing the rates of immunogenicity, assessed as the proportion of binding and neutralizing ADA-positive patients at any time, were similar between the ABP 501 and US-licensed Humira (Study 262) and EU-approved Humira (Study 263) treatment groups for the duration of the studies. The rates of binding and neutralizing ADA positivity were also similar between patients who underwent a single transition from EU-approved Humira to ABP 501 and those who remained on EU-approved Humira in Study 263 in PsO patients. Further, the titers of neutralizing antibodies were similar between the treatment groups (data not shown).

Table 7. Summary of Binding and Neutralizing ADAs in Healthy Subjects, RA Patients and PsO Patients

	Rheumatoid Arthritis Study 262		**Plaque Psoriasis Study 263 Week 16**		**Plaque Psoriasis Study 263 Post-Week 16**			**Healthy Subjects Study 217 (EOS)**		
	ABP 501 (n=264)	US-Humira (n=262)	ABP 501 (n=174)	EU-Humira (n=173)	Cont'd ABP 501 (n=152)	Cont'd EU-Humira (n=79)	EU-Humira → ABP501 (n=77)	ABP 501 (N=67)	US-Humira (N=69)	EU-Humira (N=67)
ADA (+), n (%)	101 (38)	100 (38)	96 (55)	110 (64)	104 (68)	59 (75)	56 (73)	29 (43)	34 (50)	34 (51)
NAb +, n (%)	24 (9)	29 (11)	17 (10)	24 (14)	21 (14)	16 (20)	19 (25)	12 (18)	15 (22)	14 (21)

ADA: Anti-drug antibodies (binding); NAb: Neutralizing anti-drug antibodies
(Source: FDA AC slide, safety analysis of data from Amgen 351(k) BLA submission by stat/medical reviewer)

2.3.1.2 Does the immunogenicity affect the PK of the therapeutic protein similarly?
The ADA formation affects the PK similarly between ABP501, US-licensed Humira, and EU-approved Humira.

As per the product labeling for US-licensed Humira, patients who were antibody-positive were more likely to have higher rates of clearance of adalimumab. In this submission, the systemic exposures (AUC) of ABP501 or US-licensed Humira or EU-approved Humira in healthy subjects who were binding ADA-positive were about 20-30% lower for all 3 treatments compared to ADA-negative subjects, as summarized in Table 8. While the development of ADAs appears to increase clearance of the products, the impact of ADAs appeared to influence PK similarly following treatment with ABP 501, US-licensed Humira, and EU-approved Humira. As stated in section 2.3.1.1, the incidence of ADA is also similar among all three treatments. Therefore, the ADA formation did not affect the PK similarity between ABP501 and US-licensed Humira.

Table 8. Summary of PK Parameters in Study 217 by the binding ADA Status

Parameter	Cmax (ng/ml) GM [n] (GeoCV%)	AUClast (µg.h/mL) GM [n] (GeoCV%)	AUCinf (µg.h/mL) GM [n] (GeoCV%)
ADA positive			
ABP 501	3237 [36] (31.5%)	1726[36] (36.7%)	1831 [33] (27.3%)
US-licensed Humira	3214 [38] (33.0%)	1759 [38] (40.9%)	1782 [36] (41.6%)
EU-approved Humira	3333 [45] (31.8%)	1846 [44] (41.9%)	1874 [42] (42.9%)
ADA negative			
ABP 501	3311 [31] (29.1%)	2488 [31] (31.4%)	2627 [25] (36.9%)
US-licensed Humira	3172 [31] (32.8%)	2157 [31] (44.4%)	2114 [25] (34.8%)
EU-approved Humira	3059 [22] (28.1%)	2360 [22] (26.8%)	2502 [17] (32.6%)

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

To investigate the potential impact of the ADA on PK in RA and PsO patients, the relationship between ADA and trough concentrations in Study 262 and Study 263 was examined. The overall steady-state trough concentrations by ADA status (Figure 5) were evaluated at the closest comparable time points (i.e., week 12 [Study 262] and week 16 [Study 263]). The overall trough concentrations from week 12 in RA subjects and week 16 in PsO subjects are presented by treatment groups (ABP501 versus US-licensed Humira in Study 262 and ABP501 versus EU-approved Humira in Study 263) and ADA status (negative versus positive) in Figure 5 and Figure 6. While the development of ADAs seems to increase apparent clearance of adalimumab and decrease the serum concentrations of adalimumab, the impact of binding ADAs (Figure 5) or neutralizing ADAs (Figure 6) appeared to influence PK similarly following treatment with ABP 501 versus treatment with US-licensed Humira in study 262 and EU-approved Humira in Study 263. The trough concentrations for ADA-negative and ADA-positive subgroups were consistent between ABP 501 and US-licensed Humira and EU-approved Humira treated groups in each study. In addition, the trough concentrations were consistent between studies (Study 262 and

Study 263) with similar variability.

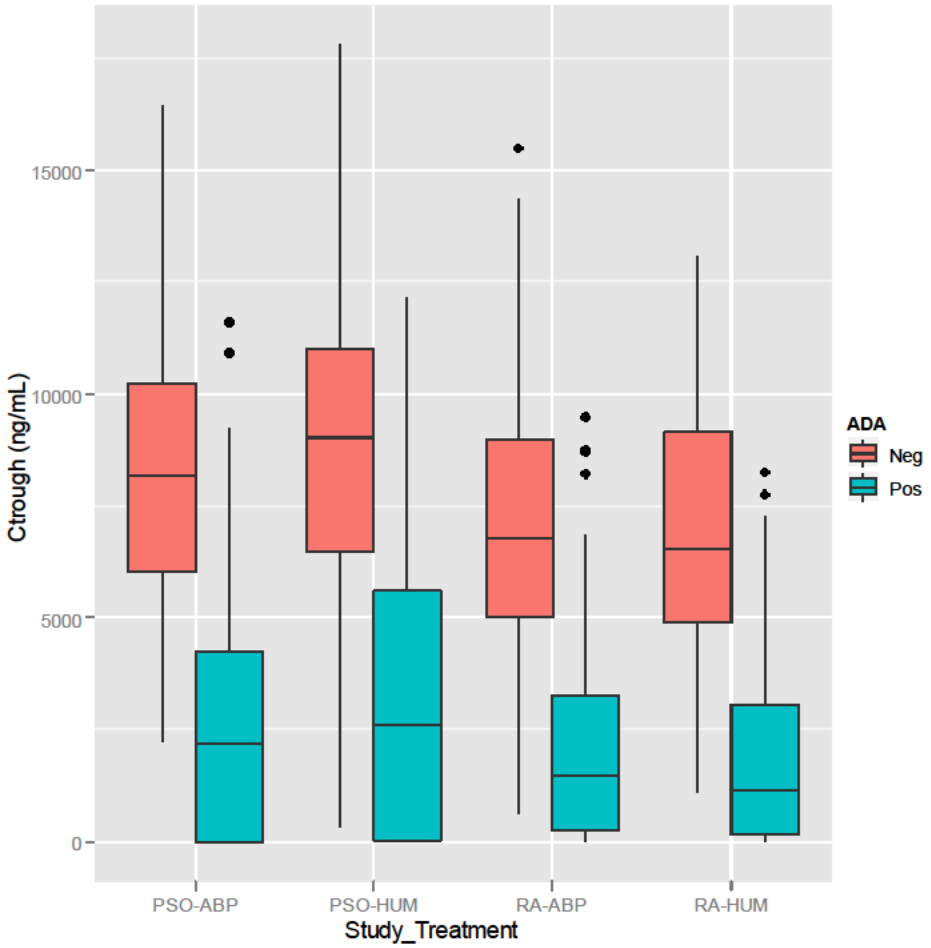


Figure 5. Serum Trough Concentrations by Binding ADA Status (Study 262 and 263)
(Source: FDA analysis of data from Amgen 351(k) BLA submission)

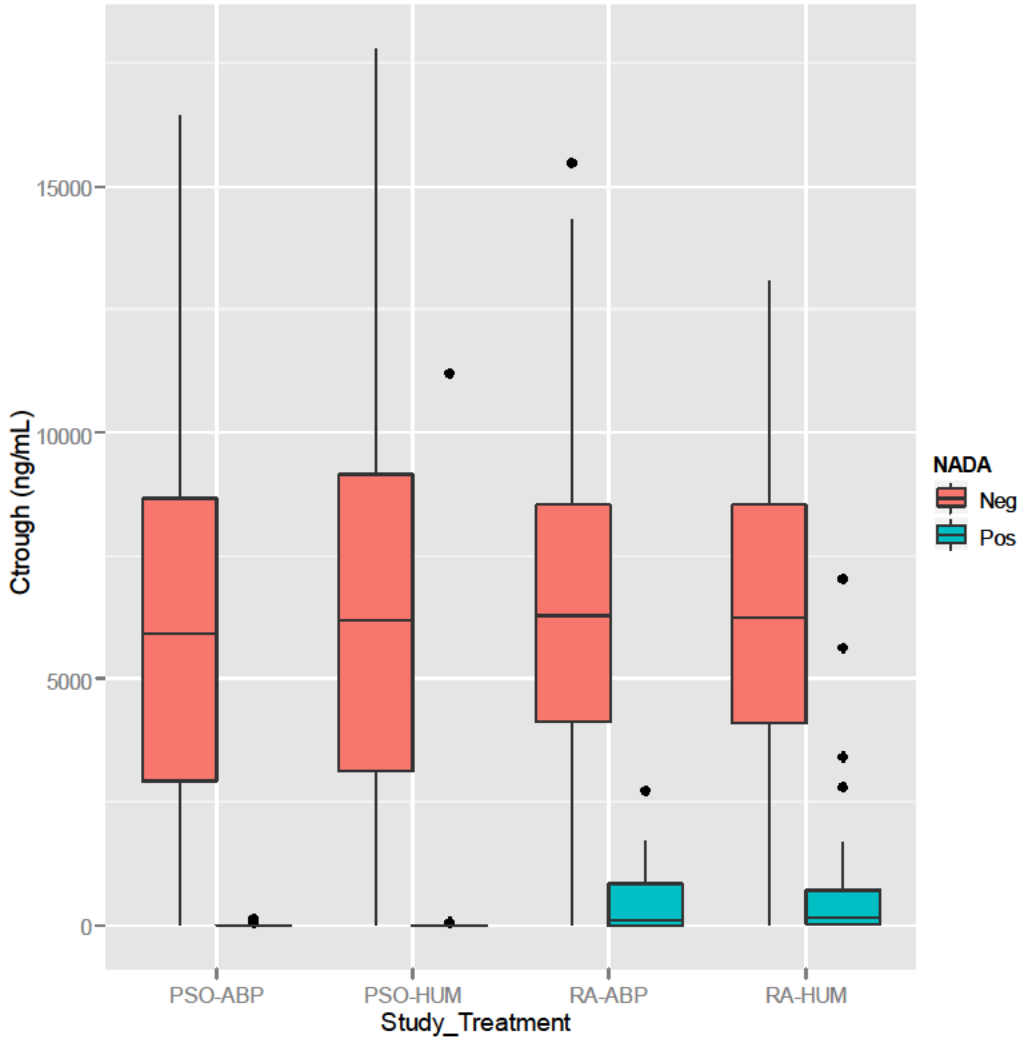


Figure 6. Serum Trough Concentrations by Neutralizing ADA Status (Study 262 and 263)
(Source: FDA analysis of data from Amgen 351(k) BLA submission)

2.3.1.3 Do the anti-drug antibodies have neutralizing activities?

A subgroup of subjects who develop binding ADA also developed neutralizing activities. The proportion of neutralizing ADA-positive patients at any time, were similar between the ABP 501 and US-licensed Humira (Study 262) and EU-approved Humira (Study 263) treatment groups for the duration of the studies (Table 7). Neutralizing ADAs had a great impact on PK and further reduced the adalimumab exposure compared to binding ADAs, as shown in Figure 6 and Figure 5.

2.3.1.4 Does the immunogenicity affect the efficacy comparison of the therapeutic protein?

The binding ADA does not appear to affect the efficacy similarity between ABP501, US-licensed Humira and EU-approved Humira (Table 11, Table 12). Of note, in the NAb positive subpopulations, the clinical responses were numerically lower in ABP 501 arms compared to comparator arms. However, the the apparent numerical differences in clinical responses does not

preclude a finding of no clinically meaningful differences between ABP 501 and US-licensed Humira.

The apparent differences in the treatment responses between ABP501 and Humira were observed as early as Week 4 in the subgroup of patients who were eventually NAb positivie (by Week 24 in Study 262 and by Week 16 in Study 263, Table 9 and Table 10). Most of these subjects who would be NAb positive later on (by Week 24 in Study 262 and by Week 16 in Study 263) were still NAb negative at Week 4. The treatment response difference was observed before the development of NAb in patients, indicating that these efficacy differences were not caused by NAb status. Also, there were no differences in NAb titers between ABP 501 and US-licensed Humira in Study 262, and between ABP 501 and EU-approved Humira in Study 263. In addition, the incidence of Nab and the impact of NAb is similar on PK for ABP501, EU-approved Humira, and US-licensed Humira. Additionally, the analysis is limited by the small sample sizes within subgroups and the non-randomized nature of comparisons, as ADA status is a post randomization variable and observed differences (or lack thereof) could be attributable to ADA formation or to other confounding variables. Overall, the apparent numerical differences in clinical responses does not preclude a finding of no clinically meaningful differences between ABP 501 and US-licensed Humira. Please also refer to medical review for details.

Table 9. Impact of Neutralizing Antibodies on Efficacy (Study 262)

		ACR20 (%)					
		Week 2	**Week 4**	**Week 8**	**Week 12**	**Week 18**	**Week 24**
NAb + *	**ABP501 (n=24)**	45.8	41.7 (5/24 NAb+)**	45.8	58.3	66.7	66.7 (24/24 NAb+)*
	HUMIRA (n=29)	25	51.7 (4/29 NAb+)**	62.1	55.2	86.2	72.4 (29/29 NAb+)*
NAb-	**ABP501 (n=240)**	34.3	52.5	65.3	76.3	78.4	75.4
	HUMIRA (n=233)	24.5	44.2	62.5	66.8	74.6	72.4

*Subgroup of patients who had NAb+ anytime post baseline to Week 24.
** Number of patients who had NAb+ anytime post baseline to Week 4.
(Source: Table 14-4.4.5, study report 262)

Table 10. Impact of Neutralizing Antibodies on Efficacy (Study 263)

			PASI Percent Improvement from base line (mean)			
		Baseline PASI Score	**Week 4**	**Week 8**	**Week 12**	**Week 16**
NAb +*	**ABP501 (n=17)**	19.62	40.76 (0/17 NAb+)**	50.59	47.64	48.46 (17/17 NAb+)*
	HUMIRA (n=24)	19.96	52.02 (1/24 NAb+)**	66.57	64.07	61.91 (24/24 NAb+)*
NAb-	**ABP501 (n=157)**	19.69	45.57	70.07	79.85	84.47
	HUMIRA (n=149)	20.57	43.95	70.17	81.97	86.47

*Subgroup of patients who had NAb+ anytime post baseline to Week 24.
** Number of patients who had NAb+ anytime post baseline to Week 4.
(Source: Table 14-4.5.7, study report 263)

2.3.1.5 Does the immunogenicity affect the safety comparison of the therapeutic protein?
No, the immunogenicity does not appear to affect the safety comparison between ABP501, US-licensed Humira, and EU-approved Humira.

Within each ADA subpopulation there were no notable differences between ABP 501 and US-licensed Humira (Study 262), and ABP 501 and EU-approved Humira (Study 263) in hypersensitivity and injection site reactions. Overall, the incidence of hypersensitivity reactions and injection site reactions is low and appears similar between ADA+ and ADA- patients (Table 11 and Table 12). Please also refer to medical review for details.

Table 11. Incidence of Clinical Responses and Safety Outcomes of Interest by ADA and Neutralizing ADA Status in Study 262 in RA at Week 24

	ABP 501 n/N (%)	US-licensed Humira n/N (%)	Difference (95% CI)
Binding ADA positive			
ACR20 response	74/101 (73)	69/100 (69)	4.3% (-8.2%, 16.8%)
Hypersensitivity reactions	7/101 (7)	1/100 (1)	5.9% (0.6%, 11.3%)
Injection site reactions	2/101 (2)	7/100 (7)	-5.0% (-10.7%, 0.7%)
Binding ADA negative			
ACR20 response	114/160 (71)	120/160 (75)	-3.8% (-13.5%, 6.0%)
Hypersensitivity reactions	7/160 (4)	9/160 (6)	-1.3% (-6.0%, 3.5%)
Injection site reactions	4/160 (3)	6/160 (4)	-1.3% (-5.1%, 2.6%)
Neutralizing ADA positive			
ACR20 response	15/24 (63)	21/29 (72)	-9.9% (-35.2%, 15.4%)
Hypersensitivity reactions	2/24 (8)	2/29 (7)	1.4% (-13.0%, 15.8%)
Injection site reactions	0/24 (0)	1/29 (3)	-3.4% (-10.1%, 3.2%)
Neutralizing ADA negative			
ACR20 response	173/237 (73)	168/231 (73)	0.3% (-7.8%, 8.3%)
Hypersensitivity reactions	12/237 (5)	8/231 (3)	1.6% (-2.1%, 5.3%)
Injection site reactions	6/237 (3)	12/231 (5)	-2.7% (-6.2%, 0.8%)
Source: FDA analysis of data from Amgen 351(k) BLA submission			

(Source: FDA AC briefing document, summary of data from Amgen 351(k) BLA submission by stat/medical reviewer)

Table 12. Incidence of Clinical Responses and Safety Outcomes of Interest by ADA and Neutralizing ADA Status in Study 263 in PsO at Week 16

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

(Source: FDA AC briefing document, summary of data from Amgen 351(k) BLA submission by stat/medical reviewer)

2.4 General Biopharmaceutics

2.4.1 What is the *in vivo* relationship of the proposed to-be-marketed formulation to the

pivotal clinical trial formulation in terms of comparative exposure?

The clinical formulation was the same as the proposed to-be-marketed formulation; therefore, no bridging study is needed.

2.5 Analytical Section

2.5.1 What are the analytical methods used to measure ABP501 or Humira in serum?

The serum concentrations of ABP501, EU-approved Humira and US-licensed Humira from Study 20110217 were quantified by a validated electrochemiluminescent (ECL) assay. The method was developed at Amgen Inc., Seattle, WA. The method was validated and the analysis of study samples was conducted at (b) (4). Based on the inspection report, the bioanalytical portions of Study 20110217are acceptable (reviews by Dr. Mohsen Rajabi and Dr. Xiaohan Cai dated 7/27/2016). This same method was used for determining ABP 501 and adalimumab serum concentrations in the phase 3 studies (Study 262 and Study 263) as well.

(b) (4)

Table 13. Summary of Bioanalytical and Analytical Reports Related to Pharmacokinetics for ABP501 Studies

Study Reference No.	Purpose	Site of Analysis	Analyte Measured	Biomatrix	Method Type	Assay Range (Drug Tolerance)
MVR-115225 Amendment 1 and Addendum 1	PK method validation	(b) (4)	ABP 501, adalimumab (US), adalimumab (EU)	Serum	Electrochemi-luminescent	50 to 12800 ng/mL
20110217 Bioanalytical Clinical Report (178052)	Determination of ABP 501 and adalimumab (US), adalimumab (EU) concentration in human samples collected in Study 20110217		ABP 501, adalimumab (US), adalimumab (EU)	Serum	Electrochemi-luminescent	50 to 12800 ng/mL
20120262 Bioanalytical Clinical Report (180825)	Determination of ABP 501 and adalimumab (US) concentration in human samples collected in Study 20120262	(b) (4)	ABP 501, adalimumab (US)	Serum	Electrochemi-luminescent	50 to 12800 ng/mL
20120263 Bioanalytical Clinical Report (180826)	Determination of ABP 501 and adalimumab (EU) concentration in human samples collected in Study 20120263	(b) (4)	ABP 501, adalimumab (EU)	Serum	Electrochemi-luminescent	50 to 12800 ng/mL

(source: Table 6, section 2.7.1, summary of biopharm)

The assay validation (MVR-115225) was described as below.

Intra-run and inter-run precision and accuracy (ABP501)

In each of nine analysis runs (performed over two days by three analysts), two replicates of QC samples at five concentrations (12800, 9600, 1250, 150, 50.0ng/mL in 100% human serum) were analyzed for ABP 501, US-licensed Humira, and EU-approved Humira. The nominal concentrations of the STD levels included (12800, 6400, 3200, 1600, 800, 400, 200, 100, 50.0 ng/mL) of ABP 501. Precision of the method, defined by the percent coefficient of variation (%CV = [(standard deviation / mean) x 100]), was determined from the interpolated (observed) results. Accuracy of the method was defined by the percent relative error (%Diff = [100 x (mean observed concentration-nominal concentration) / nominal concentration]%). Total error was reported as the sum of absolute value of inter-run % Bias and inter-assay % CV. The QC samples met the acceptance criteria: the intra-run or inter-run accuracy should not deviate by more than ± 20.0% of the nominal value (± 25.0% at the lower limit of quantitation (LLOQ)) and the intra-run or inter-run precision should not deviate by more than 20.0% (25.0% at LLOQ).

For STDs, the %Diff ranged from -1% to 1%. The variability ranged from 1% to 2% (Table 14).

Table 14: Accuracy and Precision of ABP501 standards

Standards Conc. (excluding anchor points) (ng/mL)	Average %Diff	Mean %CV	%CV of individual replicates
50.0 to 12800 ng/mL	-1% to 1%	1% to 2%	0% to 4%

(Precision: %CV = [(standard deviation / mean) x 100]%), Accuracy: %Diff = [100 x (mean observed concentration-nominal concentration) / nominal concentration]%).
(source: Table 2 on page 16, validation report MVR115225)

For ABP 501 QC, the mean intra-assay variability ranged from 1% to 3%, and the inter-assay variability ranged from 3% to 7% (Table 15). For Humira® US VS, the mean intra-assay variability ranged from 1% to 3%, the inter-assay variability ranged from 3% to 6%, and the total error ranged from 6% to 17% (Table 16). For Humira® EU VS, the mean intra-assay variability ranged from 1% to 3%, the inter-assay variability ranged from 2% to 6%, and the total error ranged from 4% to 10% (Table 17).

Table 15: Accuracy and Precision of ABP501QC

Validation Samples	Nom Conc. (ng/mL)	Mean Intra-Assay Precision (%CV)	Mean Intra-Assay Accuracy (%RE)	Inter-assay Precision (%CV)	Inter-assay Accuracy (%RE)	Total Error of Method (%)	%CV of individual replicates
VS1-6 (H, M, L)	9600, 1250, 150	1 to 3	-3 to 0	3 to 6	-3 to 0	3 to 8	0 to 5
VS9-10 (LLOQ)	50.0	3	-12	7	-12	19	0 to 8
VS7-8 (ULOQ)	12800	1	0	4	0	4	0 to 4

(source: Table 2 on page 16, validation report MVR115225)

Table 16: Accuracy and Precision of Humira® US QC

Validation Samples	Nom Conc. (ng/mL)	Mean Intra-Assay Precision (%CV)	Mean Intra-Assay Accuracy (%RE)	Inter-assay Precision (%CV)	Inter-assay Accuracy (%RE)	Total Error of Method (%)	%CV of individual replicates
VS11-16 (H, M, L)	9600, 1250, 150	1 to 3	-6 to -3	3 to 6	-6 to -3	6 to 9	0 to 4
VS19-20 (LLOQ)	50.0	3	-11	6	-11	17	0 to 5
VS17-18 (ULOQ)	12800	2	3	4	3	7	1 to 3

(source: Table 3 on page 16, validation report MVR115225)

Table 17: Accuracy and Precision of Humira® EU QC

Validation Samples	Nom Conc. (ng/mL)	Mean Intra-Assay Precision (%CV)	Mean Intra-Assay Accuracy (%RE)	Inter-assay Precision (%CV)	Inter-assay Accuracy (%RE)	Total Error of Method (%)	%CV of individual replicates
VS21-26 (H, M, L)	9600, 1250, 150	1 to 3	-4 to -1	2 to 5	-5 to -1	4 to 10	0 to 7
VS29-30 (LLOQ)	50.0	2	0	6	0	6	0 to 6
VS27-28 (ULOQ)	12800	2	4	3	4	7	1 to 4

(source: Table 4 on page 16, validation report MVR115225)

Limits of quantification

The lower limit of quantitation is defined as the lowest analyte concentration that can be quantitated with acceptable accuracy and precision (± 25.0%). The concentration that met this criterion was determined to be 50 ng/mL.

An upper limit of quantitation is defined as the highest analyte concentration that can be quantitated with acceptable accuracy and precision (± 20.0%). The concentration that met this criterion was determined to be 12,800 ng/mL. A 5,000-fold dilution factor was validated for 1,250,000 ng/mL concentration.

Matrix effect/selectivity

For ABP 501, Humira® US and Humira® EU, selectivity was evaluated in ten individual human serum lots at concentrations of 50.0 ng/mL and 150 ng/mL. A blank of each lot was also analyzed. Eight of the ten lots met the acceptance criteria and all of the un-spiked samples were below the LLOQ for ABP 501. All ten lots met the acceptance criteria and all of the un-spiked samples were below the LLOQ for Humira® US and Humira® EU. In addition, all ten lots accurately quantitated against the positive control for ABP 501 and Humira® US. Nine of ten lots accurately quantitated against the positive control for Humira® EU. Selectivity met the overall acceptance criteria that at least 80% of the spiked lots should have acceptable recovery values and at least 80% of the un-spiked samples should read below the LLOQ.

Dilution Integrity

Dilutional Linearity was demonstrated up to 1:5000. For ABP 501, Humira® US, and Humira® EU, dilutional linearity was evaluated by preparing a dilution QC stock sample at approximate nominal concentration of 1,250,000 ng/mL. The ABP 501 samples diluted 130, 250, 500, 1000, 2500, and 5000-fold had a precision range of 0 to 5% and a %Diff range of -8 to 2. All of the samples diluted within the analytical range met acceptance criteria. The Humira® US samples had a precision range of 1 to 11% and a %Diff range of -3 to 13. All of the Humira® US samples diluted within the range met acceptance criteria. The Humira® EU samples had a precision range of 1 to 5% and %Diff range of 4 to 13%. All of the Humira® EU samples diluted within the range met acceptance criteria.

Specificity
Selectivity and matrix effect experiments provide appropriate evaluation of specificity of the method relative to endogenous antibodies.

Stability
- Solution stability: not assessed.
- Whole blood stability: not assessed.
- Processed sample stability: not assessed.
- Bench top stability was demonstrated when stability samples were subjected to 2° to 8°C for approximately 19 hours and ART for 19 hours.
- Freeze-thaw stability was demonstrated when stability samples were subjected to four freeze (-70°C) and thaw (ART) cycles.
- Long-term stability was demonstrated when stability samples were subjected to -70°C for 18 days.

2.5.2 What bioanalytical methods are used to assess concentrations of the measured moieties?

Details of the bioanalytical method for determination of serum concentrations of ABP501, EU-approved Humira and US-licensed Humira are discussed in section 2.5.1.

2.5.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The standard curve for ABP501, EU-approved Humira and US-licensed Humira serum concentration analysis ranged from 50 to 12800 ng/mL. A 5,000-fold dilution factor was validated for 1,250,000 ng/mL concentration. The range of concentrations cover the concentrations observed in the clinical studies. Most PK samples in the clinical studies can be reliably assessed by this standard curve without dilution.

ABP 501 or adalimumab concentrations are determined using a 4-parameter curve fit with $1/y^2$ weighting.

2.5.4 What is the sample stability under conditions used in the study?

Details of stability conditions are described in section 2.5.1.

2.5.5 What bioanalytical methods are used to assess the immunogenicity?

Samples were evaluated using a two-tiered assay approach that consisted of a screening assay and a specificity assay. This same method was used to detect the presence of binding ADA to ABP 501 or adalimumab. ECLA were used for all ABP501 clinical studies to assess binding ADA.

To detect neutralizing ADA, Phase 1 study (Study 217) used the cell-based bioassay (Method ICDCB 36 and ICDCB 36) utilized an A549 cell line, an adherent, TNFα-responsive

adenocarcinomic human alveolar basal epithelial cell line, that expresses both TNFR1 and TNFR2. ABP 501 inhibited TNFα-induced NFκB phosphorylation in A549 cells. Neutralizing antibody activity attenuated the ABP 501 mediated inhibition of NFκB phosphorylation and caused an increase in signal. An ECL sandwich immunoassay was used to detect the level of NFκB phosphorylation in A549 cell lysates.

The method for the detection of anti-ABP 501 or anti-adalimumab neutralizing antibodies (NAbs) (Method MET-003554) in the Phase 3 studies (Study 262 and 263) was a competitive binding assay that used sTNFα, recombinant human (rHu), Bio to form a complex with ruthenylated drug for the specific drug of interest (i.e., ruthenylated ABP 501 for anti-ABP 501 NAb detection).

Please refer to OBP review for more detailed information regarding ADA assay validation.

3. Detailed Labeling Recommendations

(b) (4)

The clinical pharmacology relevant revisions are summarized as below. Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font. (b) (4) so the relevant information was deleted. Also, (b) (4) is deleted. At the time of this review, cross-discipline labeling review is ongoing and these label revisions may differ from the final label recommendations.

12.2 Pharmacodynamics

After treatment with adalimumab, a decrease in levels of acute phase reactants of inflammation (C- reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL 6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease, and ulcerative colitis (b) (4) *Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after adalimumab administration.*

12.3 Pharmacokinetics

(b) (4)

The maximum serum concentration (Cmax) and the time to reach the maximum concentration (Tmax) with adalimumab treatment were 4.7 ± 1.6 µg/mL and 131 ± 56 hours respectively,

following a single 40 mg subcutaneous administration of adalimumab to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.
The single dose pharmacokinetics of adalimumab in RA patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (Vss) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies.

Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

In RA patients receiving 40 mg adalimumab every other week, adalimumab mean steady-state trough concentrations of approximately 5 µg/mL and 8 to 9 µg/mL, were observed without and with methotrexate (MTX), respectively. MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA. Mean serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40, and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Adalimumab mean steady-state trough concentrations were slightly higher in psoriatic arthritis patients treated with 40 mg adalimumab every other week (6 to 10 µg/mL and 8.5 to 12 µg/mL, without and with MTX, respectively) compared to the concentrations in RA patients treated with the same dose.

The pharmacokinetics of adalimumab in patients with AS were similar to those in patients with RA.

In patients with CD, the loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves mean serum adalimumab trough levels of approximately 12µg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 µg/mL were observed at Week 24 and Week 56 in CD patients after receiving a maintenance dose of 40 mg adalimumab every other week.

In patients with UC, the loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves mean serum adalimumab trough levels of approximately 12µg/mL at Week 2 and Week 4. Mean steady-state trough level of approximately 8 µg/mL was observed at Week 52 in UC patients after receiving a dose of 40 mg adalimumab every other week, and approximately 15 µg/mL at Week 52 in UC patients who increased to a dose of 40 mg adalimumab every week.

In patients with Ps, the mean steady-state trough concentration was approximately 5 to 6 µg/mL during adalimumab 40 mg every other week monotherapy treatment.

(b) (4)

(b) (4)

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to > 75 years.
Minor increases in apparent clearance were also predicted in RA patients receiving doses lower than the recommended dose and in RA patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.
No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

No pharmacokinetic data are available in patients with hepatic or renal impairment. In Study JIA-I for patients with polyarticular JIA who were 4 to 17 years of age, the mean steady-state trough serum adalimumab concentrations for patients weighing < 30 kg receiving 20 mg adalimumab subcutaneously every other week as monotherapy or with concomitant MTX were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥ 30 kg receiving 40 mg adalimumab subcutaneously every other week as monotherapy or with concomitant MTX were 6.6 µg/mL and 8.1 µg/mL, respectively.

4. Appendix

4.1 Appendix – Individual Study Review

INDIVIDUAL STUDY REVIEW

Study 20110217 (3-way PK Bridge/Similarity Study in Healthy Subjects)

Report # 20110217

Study Type: PK similarity study in healthy subjects
Study Dates: 03/Jul/2012– 26/Oct/2012
Drug Product:

- ABP 501 supplied as 40 mg/0.8 mL prefilled syringe.
- US-licensed Humira supplied as 40 mg/0.8 mL prefilled syringe.
- EU-approved Humira supplied as 40 mg/0.8 mL prefilled syringe.

Title: A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel-Group Study to Determine the Pharmacokinetic Equivalence of ABP 501 and Adalimumab (Humira®) in Healthy Adult Subjects

Objectives
Primary: To demonstrate bioequivalence (as assessed principally by area under the serum concentration-time curve [AUC] from time 0 extrapolated to infinity [AUCinf] and the maximum observed serum concentration [Cmax]) of ABP 501 following a 40-mg subcutaneous (SC) injection relative to that from a 40-mg SC injection of US-licensed Humira and EU-approved Humira.

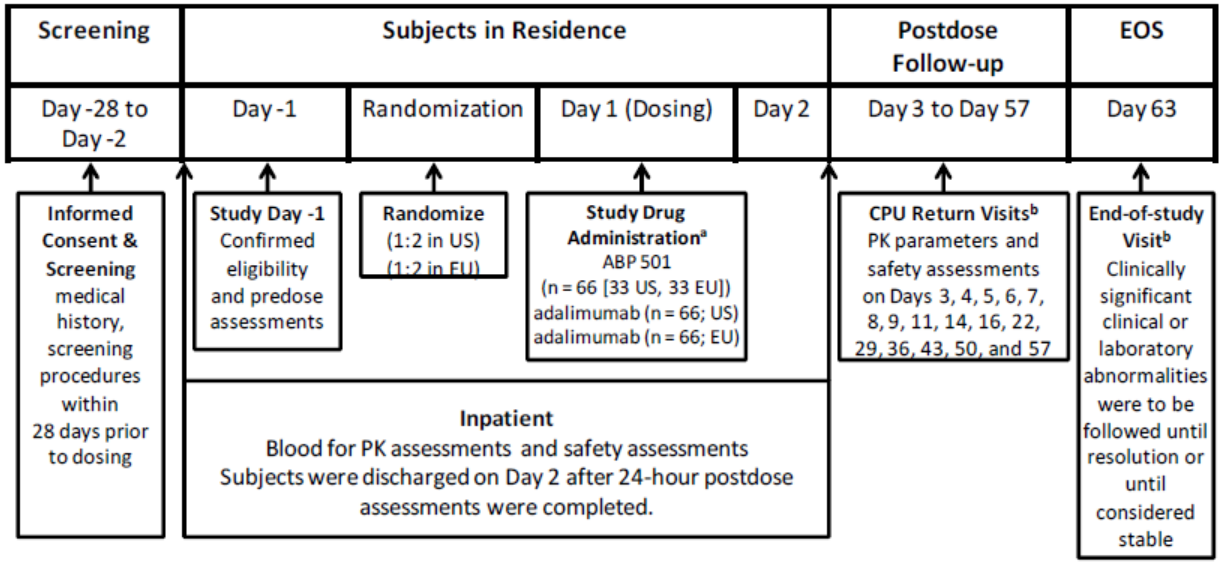
Secondary: To determine the safety, tolerability, and immunogenicity of ABP 501 in healthy adult subjects compared with US-licensed Humira and EU-approved Humira.

Primary endpoints: Cmax, AUC0-t, AUC0-inf

Study Population
Healthy male and female subjects, aged 18-45 years, with BMI 18-30kg/m^2

Study Design

This was a randomized, single-blind, single-dose, 3-arm, parallel group study in healthy adult male and female subjects. The study was conducted at 1 clinical pharmacology unit (CPU) located in the US and 1 CPU located in the EU using regionally approved comparators. A total of 203 healthy subjects were enrolled and randomized to 3 parallel arms with 67 to 69 subjects in each arm. All subjects received a single-dose of 40mg of either ABP501, US-licensed Humira or EU-approved Humira through subcutaneous injection by pre-filled syringe. The PK, safety, tolerability, and immunogenicity of ABP 501, EU-approved Humira and US-licensed Humira were assessed. The primary PK endpoints included Cmax, AUClast and AUC0-inf. The scheme of study design is shown in Figure 7.



Abbreviations: CPU = clinical pharmacology unit; EOS = end-of-study (visit); PK = pharmacokinetic

a. Planned subcutaneous dose: ABP 501 40 mg, adalimumab (US) 40 mg, or adalimumab (EU) 40 mg.

b. Subjects returned to the CPU for collection of blood for PK as close to the nominal time point as possible. Tolerance windows for return visits to the CPU and the EOS visit were consistent with tolerance windows for PK samples on these days (refer to Table 9.3).

Figure 7. The study design
(Source: Figure 9-1, CSR 20110217)

Reviewer's comment: The study design elements and the PK similarity assessments were aligned with the "FDA guidance for industry, clinical pharmacology data to support a demonstration of biosimilarity to a reference product", which was published in May 2014**.**

- **Sampling Schedule**

PK Sampling Schedule

Blood Samples for PK assessment were collected pre-dose on day 1 and day 2, 3, 4, 5, 6, 7, 8, 9, 11, 14, 16, 22, 29, 36, 43, 50, 57, and at the end of study visit (day 63).

Immunogenicity Sampling schedule:

Blood Samples for ADA assessment were collected pre-dose on day 1 and day 16, 29, and at the

end of study visit (day 63).

Results

PK Results and BE assessment

Independent analysis by FDA reviewer:

Method:

Data sets used are summarized in

Table 18 Table 18. The data were assembled in R (Version 2.13.1) for PK analysis. Pharmacokinetic parameters were calculated from the serum concentration-time data using noncompartmental techniques (Phoenix 64/WinNonlin 6.4, Pharsight Corp, St. Louis, MO). Pharmacokinetic parameters were listed by subject and summarized descriptively by treatment for the PK Parameters.

Point estimates and 90% confidence intervals (CIs) for ratios of the geometric means (GMs) for AUClast, AUCinf, and Cmax were estimated using an analysis of covariance (ANCOVA) model for comparisons of ABP 501 and US-licensed Humira, ABP 501 and EU-approved Humira, and US-licensed Humira and EU-approved Humira adjusted for region and weight. The model was in the form:

Log_e (parameter) = region + treatment + weight

The adjusted point estimate and 90% CI were assessed by Phoenix. To establish PK similarity, the 90% CIs for the GM test-to-reference ratios for AUClast, AUCinf, and Cmax were to fall within the protocol-specified similarity criteria of 0.80 and 1.25.

The following subgroup/sensitivity statistical analyses were conducted:

- Antidrug Antibody: A subgroup analysis of subjects who tested negative or positive for binding ADA.
- Region:
    - As "Region" is highly correlated with "Treatment" in the ANCOVA model, with the US site and EU site using regionally approved comparators (US-licensed Humira in US site and EU-approved Humira in EU site), this reviewer considered that region is not an appropriate covariate for the PK similarity assessment. A sensitivity analysis was performed using only Body weight as covariate :

$$Log_e \text{ (parameter)} = \text{treatment} + \text{weight}$$

Table 18: Analysis Data Sets

Study Number	Name	Link to EDR
Study 20110217	adpc.xpt (Concentration, Region) adpp.xpt (Body weight) adsl.xpt (ADA)	**\\cdsesub1\evsprod\bla761024\0001\m5\datasets\20110217\analysis\adam\datasets\adpc.xpt** **\\cdsesub1\evsprod\bla761024\0001\m5\datasets\20110217\analysis\adam\datasets\adpp.xpt** **\\cdsesub1\evsprod\bla761024/0001\m5\datasets\20110217\analysis/adam\datasets\adsl.xpt**

(Source: reviewer summary)

Result:

The adalimumab serum concentration vs time profiles are shown in Figure 8. Both peak and overall exposure were similar across the 3 treatments, as was the Tmax. The terminal t½ was estimated to be 9 to 10 days on average. For the majority of subjects in each treatment arm, AUClast accounted for at least 80% of the total AUC, confirming the adequacy of the duration of PK sampling across the 3 treatments.

Results indicated the adalimumab PK profiles following a single SC dose (40 mg) of ABP501, EU-approved Humira, or US-licensed Humira in healthy subjects are well overlapped. In the pairwise comparisons, the 90% CI of the geometric mean ratio of AUC0-inf, AUC0-last, and Cmax are all within the PK similarity criteria limits of 80-125% (Table 19).

Ancova analysis for PK similarity assessment is acceptable for the parallel group studies, if the covariates in the analysis were baseline patient characteristics, not treatment related, and pre-defined in the protocol. Reviewer's initial analysis used Region and Body weight as covariates in the Ancova analysis, as the sponsor suggested in the study report (Table 19). As Region is highly correlated with treatment, with the US site and EU site using regionally approved comparators (US-licensed Humira in US site and EU-approved Humira in EU site), this reviewer consider that region is not an appropriate covariate for the ANCOVA model. An analysis using only Body weight as covariate confirmed that the 90% CI of the geometric mean ratio of AUC0-inf, AUC0-last, and Cmax are all within the PK similarity criteria limits of 80-125% (Table 20).

Table 19. PK Analysis of the 3-Way PK Bridging/PK Similarity Study 217 (ANCOVA Analysis, Region and Weight as Covariates)

Comparison	Parameter	Adjusted GMR%	90% CI (%)
ABP501 vs US-licensed Humira	**Cmax**	103.23	(94.37, 112.93)
	AUC0-t	102.83	(90.48, 116.87)
	AUC0-inf	107.52	(94.19, 122.74)
ABP501 vs EU-approved Humira	**Cmax**	96.22	(87.80, 105.45)
	AUC0-t	101.60	(89.14, 115.80)
	AUC0-inf	104.95	(91.82, 119.95)
EU-approved Humira vs US-licensed Humira	**Cmax**	107.29	(94.36,121.98)
	AUC0-t	101.21	(84.28, 121.55)
	AUC0-inf	102.45	(84.89, 123.64)

CI: confidence interval; GMR: geometric mean ratio

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

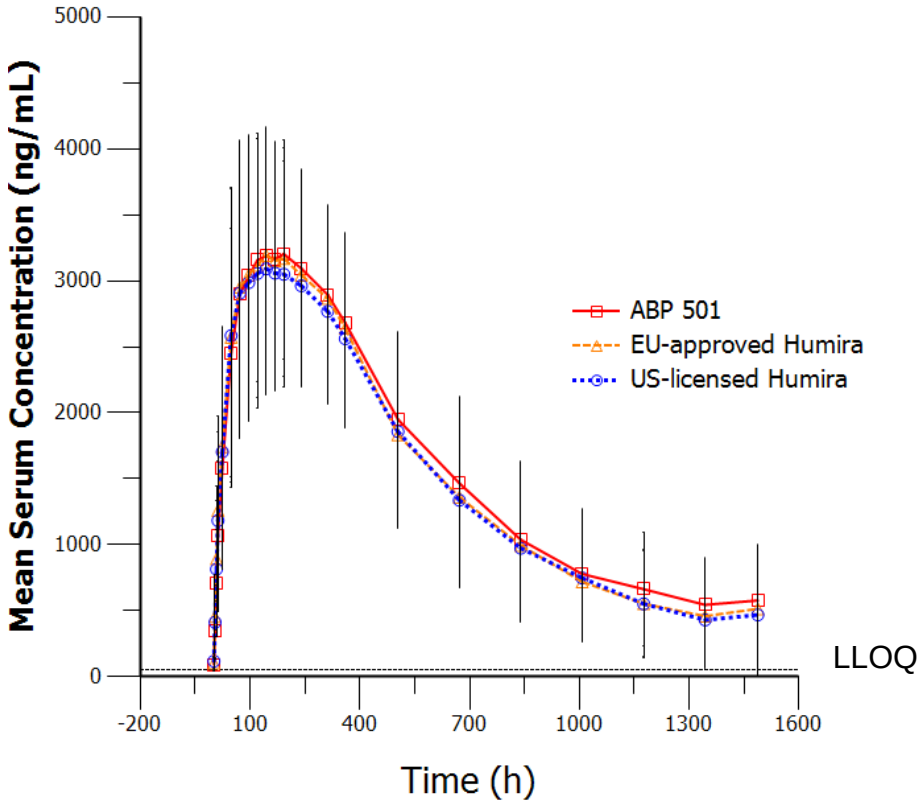
Table 20. PK Analysis of the 3-Way PK Bridging/PK Similarity Study 217 (ANCOVA Analysis, Weight as the only Covariate)

Comparison	Parameter	Adjusted GMR%	90% CI (%)
ABP501 vs US-licensed Humira	**Cmax**	103.73	(96.40, 111.62)
	AUC0-t	105.75	(95.26, 117.41)
	AUC0-inf	110.76	(99.47, 123.32)
ABP501 vs EU-approved Humira	**Cmax**	95.74	(88.89, 103.12)
	AUC0-t	98.70	(88.75, 109.76)
	AUC0-inf	101.87	(91.37, 113.56)
EU-approved Humira vs US-licensed Humira	**Cmax**	108.34	(100.65, 116.62)
	AUC0-t	107.15	(96.43, 119.06)
	AUC0-inf	108.73	(97.68, 121.03)

CI: confidence interval; GMR: geometric mean ratio

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

Figure 8. PK Profiles Following a Single SC 40mg Dose of ABP501, EU-approved Humira, or US-licensed Humira in Healthy Subjects (Study 217)



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

(b) (4)

The agency did not agree with this approach,

(b) (4)

Overall, the 90% CI of the geometric mean ratio of AUC0-inf, AUC0-last, and Cmax are all within the PK similarity criteria limits of 80-125%. These data establish the PK similarity between ABP501 and US-licensed Humira. These data also establish the PK component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of ABP501 to US-licensed Humira.

Immunogenicity Results

No pre-existing ADAs were detected in subject samples at baseline. Table 21 shows the incidence of ADAs throughout the study following a single dose of 40 mg SC of study drug. Importantly, the rate of neutralizing ADA was similar between all three treatments arms at 18%, 22%, and 21%, respectively.

Table 21. Summary of Binding Antidrug Antibody Results, Study 217

	Study 217 in Healthy Subjects		
Timepoint	ABP 501 (N=67) n (%)	US-licensed Humira (N=69) n (%)	EU-approved Humira (N=67) n (%)
Day 1, Predose	0	0	0
Day 16	12 (18%)	12 (17%)	23 (35%)
Day 29	21 (32%)	27 (42%)	27 (42%)
End of Study	29 (43%)	34 (50%)	34 (51%)
Source: FDA analysis of data from Amgen 351(k) BLA submission			

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

To investigate the potential impact of the ADA on PK in healthy subjects, the relationship between ADA and exposure parameters in study 217 was examined. Following the single SC injection, the overall exposure (AUC) was approximately 20% to 30% lower for all 3 treatments in ADA-positive subjects compared to ADA-negative subjects, but the maximum concentration were similar in ADA-positive subjects and ADA-negative subjects for all 3 treatments.

Table 22. Summary of PK Parameters in Study 217 by the binding ADA Status

Parameter	Cmax (ng/ml) GM [n] (GeoCV%)	AUClast (µg.h/mL) GM [n] (GeoCV%)	AUCinf (µg.h/mL) GM [n] (GeoCV%)
ADA positive			
ABP 501	3237 [36] (31.5%)	1726[36] (36.7%)	1831 [33] (27.3%)
US-licensed Humira	3214 [38] (33.0%)	1759 [38] (40.9%)	1782 [36] (41.6%)
EU-approved Humira	3333 [45] (31.8%)	1846 [44] (41.9%)	1874 [42] (42.9%)
ADA negative			
ABP 501	3311 [31] (29.1%)	2488 [31] (31.4%)	2627 [25] (36.9%)
US-licensed Humira	3172 [31] (32.8%)	2157 [31] (44.4%)	2114 [25] (34.8%)
EU-approved Humira	3059 [22] (28.1%)	2360 [22] (26.8%)	2502 [17] (32.6%)

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

Conclusions

- The adalimumab PK profiles following a single SC injection (40 mg) of ABP501, EU-approved Humira, or US-licensed Humira in healthy subjects are similar. In the pairwise comparisons, the 90% CI of the geometric mean ratio of AUC0-inf, AUC0-last, and Cmax are all within the PK similarity criteria limits of 80-125%.

- Overall, the incidence of ADAs by treatment was similar among the 3 treatment groups (ABP501, EU-approved Humira, and US-licensed Humira).

Study 262 (Clinical Comparative Study in RA)

Report # 20120262

Study Type: Clinical comparative study in RA
Study Dates: 24/Oct/2013– 19/Nov/2014
Drug Product:

- ABP 501 supplied as 40 mg/0.8 mL prefilled syringe.

- US-licensed Humira supplied as 40 mg/0.8 mL prefilled syringe.

Title: A Randomized, Double-blind, Phase 3 Study of ABP 501 Efficacy and Safety Compared to Adalimumab in Subjects with Moderate to Severe Rheumatoid Arthritis

Objectives
Primary Objective: The primary objective for this study was to assess the efficacy of ABP 501 compared with US-licensed Humira.

Secondary Objectives: The secondary objectives were to assess the safety and immunogenicity of ABP 501 compared with US-licensed Humira.

Exploratory Objectives: The exploratory objectives were to assess the injection site pain perception based on subject's rankings for ABP 501 compared with US-licensed Humira and to assess the trough serum concentration of ABP 501 compared with US-licensed Humira.

Only results related to PK and immunogenicity are reviewed here. For efficacy and safety results, please refer to clinical review by Dr. Keith Hull.

Study Population
Male or female patients aged 18 to 80 years old, inclusive, with moderate to severe RA

Study Design
This was a randomized, double-blind, active comparator-controlled study of adalimumab-naïve adult subjects with moderate to severe RA who had an inadequate response to methotrexate (MTX). Approximately 500 subjects (250 per treatment group) were to be enrolled. Subjects were randomized 1:1 to receive either ABP 501 or US-licensed Humira at 40 mg subcutaneously (SC) every 2 weeks for 22 weeks. The assessment of the primary endpoint was at week 24, with a safety follow-up period through week 26 (end of study).

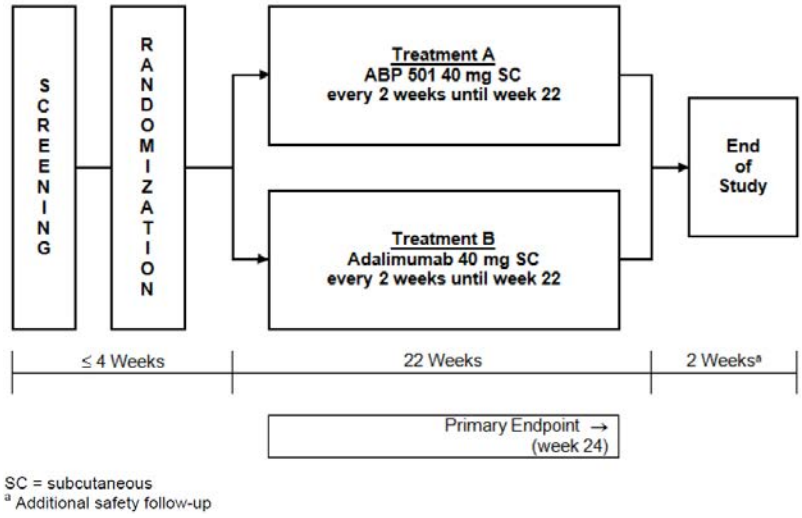


Figure 9. Study Diagram
(Source: Figure 9-1, CSR 20120262)

- **Sampling Schedule**

PK Sampling Schedule

Blood Samples for PK assessment were collected pre-dose on day 1 and at weeks 2, 4, 12, 24, and at the end of study visit (week 26).

Immunogenicity Sampling schedule:

Blood Samples for ADA assessment were collected pre-dose on day 1 and at weeks 4, 12, and at the end of study visit (week 26).

Results

PK Results

All 526 subjects who were randomized in this study had at least 1 evaluable result for serum concentration of ABP 501 or adalimumab at any visit. Pharmacokinetic results revealed that trough serum concentrations, the geometric mean, and the geometric coefficient of variability were similar between the ABP 501and US-licensed Humira groups across all study weeks (Table 23), indicating that exposure was similar between treatment groups in the RA population.

Table 23. Geometric Mean Summary of Trough Serum Pharmacokinetics Concentrations (ng/mL) by Visit and Treatment (Pharmacokinetic Analysis Set)

Time Point	ABP 501 (N = 264)	Adalimumab (N = 262)
Week 2		
n	247	251
Geometric Mean	2062.64	1936.11
Geometric CV (%)	61.79	61.63
Geometric mean ratio	1.07	
90% CI	(1.00, 1.14)	
Week 4		
n	247	252
Geometric Mean	3041.32	2986.43
Geometric CV (%)	106.21	105.61
Geometric mean ratio	1.02	
90% CI	(0.92, 1.13)	
Week 12		
n	231	239
Geometric Mean	4285.82	4084.96
Geometric CV (%)	211.24	210.65
Geometric mean ratio	1.05	
90% CI	(0.90, 1.22)	
Week 24		
n	224	221
Geometric Mean	4844.16	5210.75
Geometric CV (%)	189.92	189.22
Geometric mean ratio	0.93	
90% CI	(0.80, 1.08)	
Week 26		
n	210	212
Geometric Mean	3684.83	3989.68
Geometric CV (%)	182.29	183.99
Geometric mean ratio	0.92	
90% CI	(0.80, 1.07)	

CI = confidence interval
Note: Geometric mean, geometric mean ratio, and 90% CI are estimated based upon analysis of variance model adjusted with stratified factors.
(Source: Table 11-3, CSR 20120262)

Table 24. Mean and Median Trough concentration (ng/mL) by Visit and Treatment

Timepoint	ABP 501 (N = 264)	Adalimumab (N = 262)
Baseline		
n	262	261
Mean (std)	78.1 (578.83)	40.1 (633.70)
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 6121	0, 10237
Week 2		
n	253	253
Mean (std)	2266.3 (998.22)	2185.1 (1030.00)
Median	2147.0	2129.0
Q1, Q3	1628.0, 2741.0	1537.0, 2705.0
Min, Max	0, 7502	0, 9860
Week 4		
n	252	256
Mean (std)	3615.2 (1715.26)	3609.9 (1681.91)
Median	3514.5	3606.0
Q1, Q3	2543.0, 4611.0	2538.0, 4726.0
Min, Max	0, 8003	0, 8678
Week 12		
n	241	248
Mean (std)	5817.0 (3450.06)	5724.6 (3415.47)
Median	5848.0	5707.0
Q1, Q3	3298.0, 8070.0	3136.0, 8107.5
Min, Max	0, 15478	0, 13079
Week 24		
n	239	242
Mean (std)	6480.4 (4221.75)	6265.4 (3930.92)
Median	6790.0	6143.5
Q1, Q3	3254.0, 9249.0	3354.0, 8967.0
Min, Max	0, 22379	0, 17142
Week 26		
n	240	247
Mean (std)	4453.1 (3389.79)	4259.7 (3197.33)
Median	4381.5	3778.0
Q1, Q3	1732.5, 6592.5	1790.0, 6349.0
Min, Max	0, 17894	0, 13849

Note: The PK result of BLQ will be set to 0 in the summary.

(Source: Table 14-9.1, CSR 20120262)

Reviewer's comment: The FDA reviewer's independent analysis is consistent with sponsor's analysis (Figure 10). As the summary of geometric mean (Table 23) did not count in patients with a Ctrough of 0 ng/mL or BLQ, the number of subjects for summary of geometric mean is smaller compared to the subjects for summary of arithmetic mean/median (Table 24). As shown in Figure 10, the trough concentrations are comparable at each time point between ABP501 and US-licensed Humira.

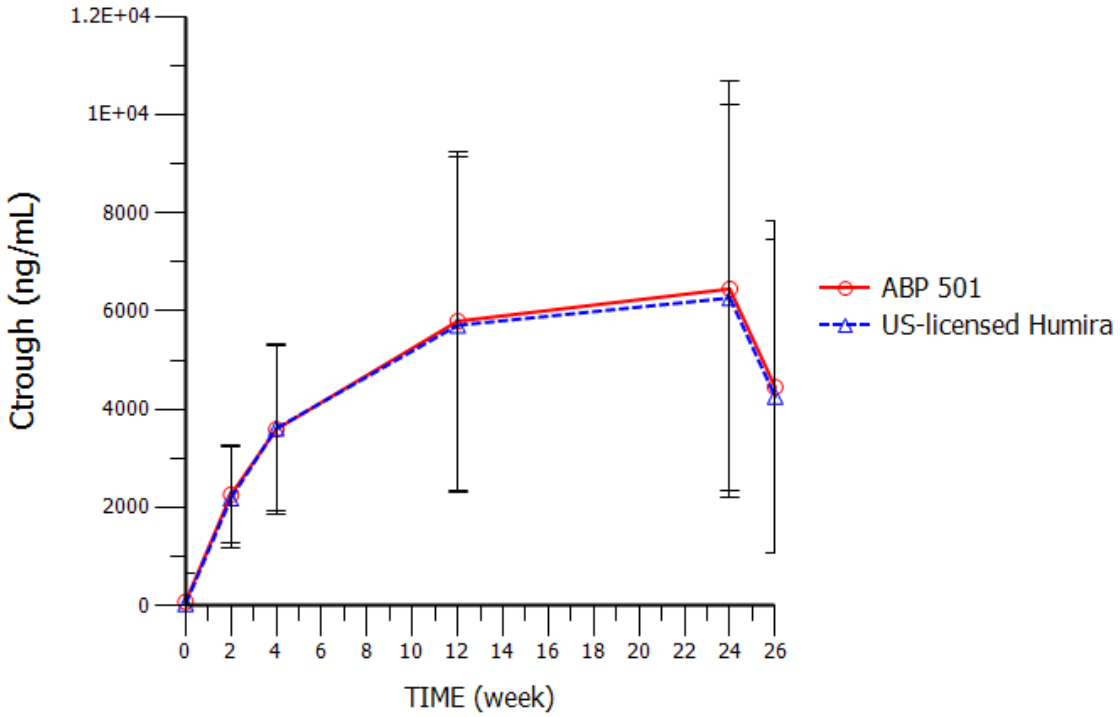


Figure 10. Mean Trough Concentration Following Multiple SC Dosing (40 mg Q2W) of ABP501 or US-Licensed Humira in RA Patients (Study 262)

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

Immunogenicity Results

The ADA incidence increased over time in both arms and was comparable between ABP501 and US-licensed Humira. The number of subjects who had positive ADA results at Week 26 was 84 (31.8%) and 92 (35.1%) subjects in ABP501 and US-licensed Humira arms, respectively. At week 26, 19 (7.2%) and 26 (9.9%) subjects in ABP501 and US-licensed Humira arms tested positive for neutralizing antibodies, respectively (Table 25).

Overall, 38.2% of subjects (201 of 526) tested positive for binding antibodies post-baseline, and this was similar to the proportions in each treatment group: 38.3% of subjects (101 of 264) in the ABP 501 group versus 38.2% of subjects (100 of 262) in the US-licensed Humira group. A total of 10.1% of subjects (53 of 526) tested positive for neutralizing antibodies post-baseline, and this was similar to the proportions in each treatment group: 9.1% of subjects (24 of 264) in the ABP 501 group versus 11.1% of subjects (29 of 262) in the US-licensed Humira group.

For the impact of immunogenicity on PK, efficacy and safety, see QBR section 2.3.1.

Table 25. Anti-Drug Antibodies Results by Visit and Treatment

Visit Binding/Neutralizing	ABP 501 (N = 264) n (%)	Adalimumab (N = 262) n (%)	Total (N = 526) n (%)
Baseline			
Binding			
ABP 501 Assay Positive	5 (1.9)	5 (1.9)	10 (1.9)
Adalimumab Assay Positive	3 (1.1)	5 (1.9)	8 (1.5)
Positive in Either Assay	5 (1.9)	6 (2.3)	11 (2.1)
Neutralizing			
ABP 501 Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)
Adalimumab Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)
Positive in Either Assay	0 (0.0)	0 (0.0)	0 (0.0)
Week 4			
Binding			
ABP 501 Assay Positive	43 (16.3)	43 (16.4)	86 (16.3)
Adalimumab Assay Positive	41 (15.5)	40 (15.3)	81 (15.4)
Positive in Either Assay	50 (18.9)	45 (17.2)	95 (18.1)
Neutralizing			
ABP 501 Assay Positive	4 (1.5)	4 (1.5)	8 (1.5)
Adalimumab Assay Positive	4 (1.5)	3 (1.1)	7 (1.3)
Positive in Either Assay	5 (1.9)	4 (1.5)	9 (1.7)
Week 12			
Binding			
ABP 501 Assay Positive	58 (22.0)	61 (23.3)	119 (22.6)
Adalimumab Assay Positive	51 (19.3)	55 (21.0)	106 (20.2)
Positive in Either Assay	62 (23.5)	62 (23.7)	124 (23.6)
Neutralizing			
ABP 501 Assay Positive	7 (2.7)	10 (3.8)	17 (3.2)
Adalimumab Assay Positive	7 (2.7)	7 (2.7)	14 (2.7)
Positive in Either Assay	8 (3.0)	10 (3.8)	18 (3.4)
Week 26			
Binding			
ABP 501 Assay Positive	75 (28.4)	89 (34.0)	164 (31.2)
Adalimumab Assay Positive	80 (30.3)	80 (30.5)	160 (30.4)
Positive in Either Assay	84 (31.8)	92 (35.1)	176 (33.5)
Neutralizing			
ABP 501 Assay Positive	14 (5.3)	25 (9.5)	39 (7.4)
Adalimumab Assay Positive	18 (6.8)	24 (9.2)	42 (8.0)
Positive in Either Assay	19 (7.2)	26 (9.9)	45 (8.6)

(Source: Table 14-10.2, CSR 20120262)

Conclusions:

- Ctrough values were comparable at each time point between ABP501 and US-licensed Humira.
- The ADA incidence increased over time in both arms and was comparable between ABP501 and US-licensed Humira.

Study 263 (Clinical comparative Study in PsO)

Report # 20120263

Study Type: Clinical comparative study in PsO
Study Dates: 18/Oct/2013– 18/Mar/2015
Drug Product:

- ABP 501 supplied as 40 mg/0.8 mL prefilled syringe.

- EU-approved Humira supplied as 40 mg/0.8 mL prefilled syringe.

Title: A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of ABP 501 Compared with Adalimumab in Subjects with Moderate to Severe Plaque Psoriasis

Objectives
Primary Objective: The primary objective for this study was to evaluate the efficacy of ABP 501 in subjects with moderate to severe plaque psoriasis, as measured by the Psoriasis Area and Severity Index (PASI) percent improvement from baseline, compared with EU-approved Humira.

Secondary Objectives: The secondary objectives of this study were to assess the safety and immunogenicity of ABP 501 compared with EU-approved Humira and to assess efficacy in terms of PASI 75 response (75% or greater improvement from baseline in PASI score), static Physician's Global Assessment (sPGA), and percent body surface area (BSA) affected.

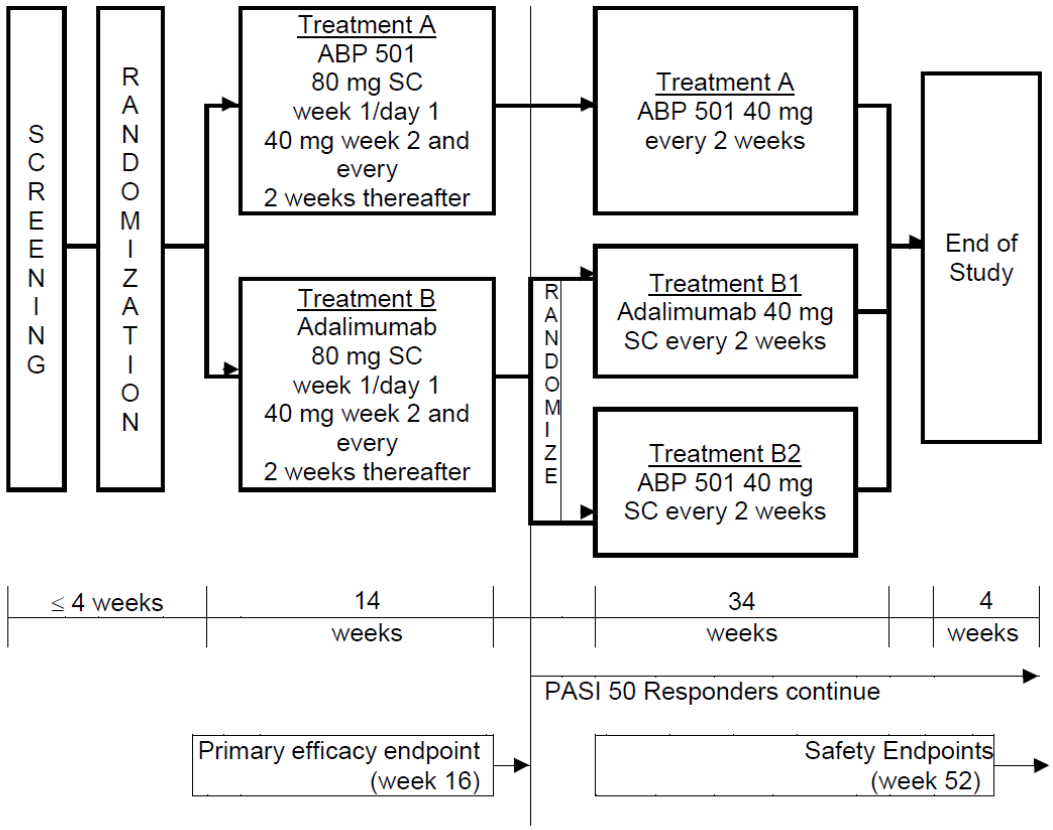
Exploratory Objectives: The exploratory objective was to assess the perception of injection site pain based on subjects' rankings for ABP 501 compared with EU-approved Humira injections.

Only results related to PK and immunogenicity are reviewed here. For efficacy and safety results, please refer to clinical review.

Study Population
Male or female patients aged 18 to 75 years old, inclusive, with moderate to severe plaque psoriasis.

Study Design
This was a randomized, double-blind, active comparator-controlled study in adult subjects with moderate to severe plaque psoriasis. Approximately 340 subjects (170 subjects per treatment group) were to be enrolled. After a 4-week screening period, subjects were randomized (1:1) to Treatment Group A (ABP 501) or Treatment Group B (EU-approved Humira). Randomization was stratified based on prior biologic use for psoriasis and geographic region. Subjects received ABP 501 or EU-approved Humira at an initial loading dose of 80 mg subcutaneous (SC) on week 1/day 1, followed by 40 mg SC every other week starting 1 week after the loading dose (i.e., week 2) and every 2 weeks thereafter.

At week 16, subjects with a PASI 50 response (50% or better improvement) continued on study for up to 52 weeks. Subjects who continued treatment beyond week 16 were re-randomized in a blinded fashion such that all subjects initially randomized to Treatment Group A (ABP 501) continued treatment with ABP 501 and subjects initially randomized to Treatment Group B (EU-approved Humira) were re-randomized (1:1) to either continue treatment with adalimumab (Treatment Group B1 [EU-approved Humira / EU-approved Humira]) or were transitioned to ABP 501 (Treatment Group B2 [EU-approved Humira /ABP 501]). All subjects continued with their assigned treatment until week 48, when the last dose of assigned investigational product was administered. The final efficacy assessments were conducted at week 50 and the end of study visit was at week 52.



PASI = Psoriasis Area and Severity Index; SC = subcutaneous

Figure 11. Study Diagram
(Source: Figure 9-1, CSR 20120263)

- **Sampling Schedule**

PK Sampling Schedule

Blood Samples for PK assessment were collected pre-dose on day 1 and at weeks 4, 16, 20, 32, and at the end of study visit (week 52).

Immunogenicity Sampling schedule:

Blood Samples for ADA assessment were collected pre-dose on day 1 and at weeks 4, 16, 20, 32, and at the end of study visit (week 52).

Results

PK Results

A total of 347 subjects had at least 1 evaluable result for serum concentration of ABP 501 or adalimumab at any visit. Pharmacokinetic results revealed that trough serum concentrations, the geometric mean, and the geometric coefficient of variability were similar between the ABP 501and EU-approved Humira groups across all study weeks (Table 26), indicating that exposure was similar between treatment groups in the PsO population.

Table 26. Geometric Mean Summary of Trough Serum Pharmacokinetics Concentration (ng/mL) by Visit and Treatment – Baseline to Week 16

Timepoint	Treatment Group A (ABP 501) (N = 174)	Treatment Group B (Adalimumab) (N = 173)
Week 4		
n	166	168
Geometric Mean	4728.38	4956.31
Geometric CV (%)	69.89	70.11
GMR	0.95	
90% CI	(0.86, 1.06)	
Week 16		
n	139	131
Geometric Mean	4204.38	4057.78
Geometric CV (%)	229.50	219.62
GMR	1.04	
90% CI	(0.81, 1.32)	

CI = confidence interval; GMR = geometric mean ratio
(Source: Table 11-2, CSR 20120263)

Table 27. Mean and Median Trough concentration (ng/mL) by Visit and Treatment

Timepoint	ABP 501 (N = 174)	Adalimumab (N = 173)
Baseline		
n	164	164
Mean (std)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00
Q1, Q3	0.00, 0.00	0.00, 0.00
Min, Max	0.0, 0.0	0.0, 0.0
Week 4		
n	166	168
Mean (std)	5496.70 (2409.198)	5684.98 (2371.010)
Median	5437.50	5524.50
Q1, Q3	3732.00, 7219.00	4065.00, 7205.00
Min, Max	324.0, 12700.0	486.0, 11848.0
Week 16		
n	160	156
Mean (std)	5330.59 (4005.463)	5296.51 (4227.987)
Median	5145.50	5205.00
Q1, Q3	2072.50, 8392.50	757.50, 8811.00
Min, Max	0.0, 16419.0	0.0, 17798.0

Note: The PK result of BLQ will be set to 0 in the summary.

(Source: Table 14-9.1, CSR 20120263)

From baseline to the end of study, the geometric mean trough serum concentrations were considered to be similar between all re-randomized treatment groups across the various assessed time points (Table 28). These results indicate that adalimumab exposure was similar between treatment groups in this subject population.

Table 28. Mean and Median Trough concentration (ng/mL) by Visit and Treatment

	Non Re-randomized		Re-randomized		
Timepoint	ABP 501 (N = 22)	Adalimumab (N = 17)	ABP 501/ ABP 501 (N = 152)	Adalimumab/ Adalimumab (N = 79)	Adalimumab/ ABP 501 (N = 77)
Baseline					
n	20	17	144	74	73
Mean (std)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)	0.00 (0.000)
Median	0.00	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00
Min, Max	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
Week 4					
n	18	17	148	75	76
Mean (std)	3709.00 (1979.985)	4179.35 (2193.489)	5714.12 (2371.215)	5566.07 (2202.837)	6139.12 (2442.629)
Median	3665.00	3899.00	5667.50	5559.00	5698.00
Q1, Q3	2478.00, 4361.00	2710.00, 5900.00	3976.50, 7351.50	4049.00, 6684.00	4494.00, 8000.00
Min, Max	935.0, 8303.0	834.0, 8048.0	324.0, 12700.0	486.0, 9752.0	766.0, 11848.0
Week 16					
n	12	6	148	77	73
Mean (std)	948.81 (3010.813)	824.83 (1349.738)	5685.87 (3870.486)	5631.82 (4129.079)	5310.37 (4309.646)
Median	0.00	136.50	5415.50	5868.00	5263.00
Q1, Q3	0.00, 94.85	0.00, 1293.00	2597.50, 8507.00	2164.00, 8896.00	376.00, 9085.00
Min, Max	0.0, 10488.0	0.0, 3383.0	0.0, 16419.0	0.0, 13831.0	0.0, 17798.0
Week 20					
n	-	-	149	76	75
Mean (std)			5473.12 (4065.460)	5603.17 (4133.955)	5322.61 (4755.387)
Median			5053.00	5901.00	5242.00
Q1, Q3			1927.00, 8737.00	1804.50, 8253.50	0.00, 8956.00
Min, Max			0.0, 16585.0	0.0, 14439.0	0.0, 19813.0
Week 32					
n	-	-	141	70	69
Mean (std)			5767.16 (4321.107)	5480.84 (4190.694)	5067.22 (4748.202)
Median			5582.00	5770.00	4318.00
Q1, Q3			1866.00, 9449.00	2164.00, 9170.00	0.00, 8220.00
Min, Max			0.0, 16029.0	0.0, 13923.0	0.0, 20258.0
Week 52					
n	-	-	130	66	66
Mean (std)			3835.70 (3474.907)	3839.71 (3337.220)	3584.41 (4240.928)
Median			3187.50	3565.50	2950.00
Q1, Q3			593.00, 6303.00	150.00, 6244.00	0.00, 6519.00
Min, Max			0.0, 12128.0	0.0, 11892.0	0.0, 23732.0

Note: The PK result of BLQ will be set to 0 in the summary.

(Source: Table 14-9.2, CSR 20120263)

Reviewer's comment: FDA reviewer's independent analysis is consistent with sponsor's analysis (Figure 12). As the summary of geometric mean (Table 26) did not count in patients with a Ctrough of 0 ng/mL or BLQ, the number of subjects for summary of geometric mean is smaller compared to the subjects for summary of arithmetic mean/median (Table 27). Figure 12 showed the trough concentrations for ABP501 and EU-approved Humira at week 4 and 16 before the re-randomization. The trough concentrations are comparable at each time point between ABP501 and EU-approved Humira.

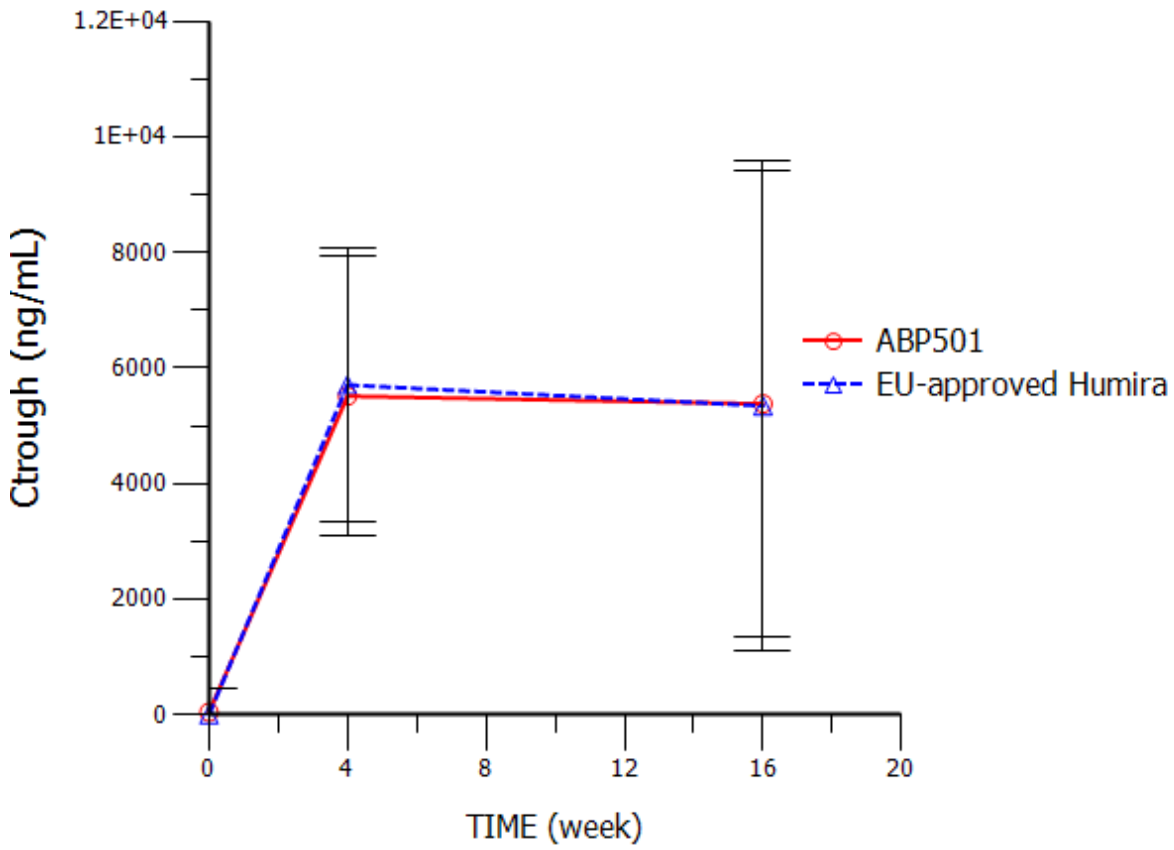


Figure 12. Ctrough at Weeks 4 and 16 Following Multiple SC Doses of ABP501 or EU-approved Humira in PsO Patients (Study 263)

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

Immunogenicity Results

From baseline to week 16, the ADA incidence increased over time in both arms and was comparable between ABP501 and EU-approved Humira. The number of subjects who had positive ADA results on Week 16 was 85/174 (48.9%) and 99/173 (57.2%) in ABP501 and EU-approved Humira arms, respectively. On week 16, 15 (8.6%) and 21 (12.1%) subjects in ABP501 and EU-approved Humira arms tested positive for neutralizing antibodies, respectively (Table 29).

Overall, from baseline to week 16, 206 of 347 subjects (59.4%) tested positive for binding antibodies anytime post-baseline, and this was similar to the proportions in each treatment group: 96 of 174 subjects (55.2%) in the ABP 501 group versus 110 of 173 subjects (63.6%) in the Humira group. A total of 41 of 347 subjects (11.8%) tested positive for neutralizing antibodies anytime post-baseline, and this was similar to the proportions in each treatment group: 17 of 174 subjects (9.8%) in the ABP 501 group versus 24 of 173 subjects (13.9%)in the Humira group.

For subjects who were re-randomized, 72 subjects (47.4%) in Treatment Group A (ABP 501/ABP 501), 43 subjects (54.4%) in Treatment Group B1 (EU-Humira/ EU-Humira), and 48

subjects (62.3%) in Treatment Group B2 (EU-Humira /ABP 501 arms) tested positive for binding antibodies at the time of re-randomization (week 16, Table 29). The number of subjects who had positive binding ADA results on Week 52 was 65 (42.8%), 34 (43%), and 42 (54.5%) subjects in ABP 501/ABP 501, EU-Humira/ EU-Humira and EU-Humira /ABP 501 arms, respectively (Table 29).

For subjects who were re-randomized, the neutralizing ADA incidence increased over time in all arms. 11 subjects (7.2%) in Treatment Group A (ABP 501/ABP 501), 9 subjects (11.4%) in Treatment Group B1 (EU-Humira / EU-Humira), and 8 subjects (10.4%) in Treatment Group B2 (EU-Humira /ABP 501) tested positive for neutralizing antibodies at the time of re-randomization (week 16, Table 29). On week 52, 13 (8.6%), 10 (12.7%) and 16 (20.8%) subjects in ABP 501/ABP 501, EU-Humira/ EU-Humira and EU-Humira /ABP 501 arms tested positive for neutralizing antibodies, respectively (Table 29).

Overall, from baseline to the end of study, among subjects who were re-randomized, 104 of 152 subjects (68.4%) in Treatment Group A (ABP 501/ABP 501), 59 of 79 subjects (74.7%) in Treatment Group B1 (EU-Humira / EU-Humira), and 56 of 77 subjects (72.7%) in Treatment Group B2 (EU-Humira /ABP 501) tested positive for binding antibodies anytime post-baseline. From baseline to the end of study, among subjects who were re-randomized, 21 of 152 subjects (13.8%) in Treatment Group A (ABP 501/ABP 501), 16 of 79 subjects (20.3%) in Treatment Group B1 (EU-Humira / EU-Humira), and 19 of 77 subjects (24.7%) in Treatment Group B2 (EU-Humira /ABP 501) tested positive for neutralizing antibodies anytime post-baseline.

For the impact of immunogenicity on PK, efficacy and safety, see QBR section 2.3.1.

Table 29. Anti-Drug Antibodies Results by Visit and Treatment

Visit Binding/Neutralizing	Non Re-randomized ABP 501 (N = 22) n (%)	Non Re-randomized Adalimumab (N = 17) n (%)	Re-randomized ABP 501/ ABP 501 (N = 152) n (%)	Re-randomized Adalimumab/ Adalimumab (N = 79) n (%)	Re-randomized Adalimumab/ ABP 501 (N = 77) n (%)
Baseline					
Binding					
ABP 501 Assay Positive	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (1.3)
Adalimumab Assay Positive	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	1 (1.3)
Positive in Either Assay	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.3)	1 (1.3)
Neutralizing					
ABP 501 Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adalimumab Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Positive in Either Assay	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Week 4					
Binding					
ABP 501 Assay Positive	10 (45.5)	6 (35.3)	36 (23.7)	19 (24.1)	17 (22.1)
Adalimumab Assay Positive	10 (45.5)	7 (41.2)	36 (23.7)	18 (22.8)	18 (23.4)
Positive in Either Assay	10 (45.5)	7 (41.2)	40 (26.3)	22 (27.8)	19 (24.7)
Neutralizing					
ABP 501 Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adalimumab Assay Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Positive in Either Assay	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Week 16					
Binding					
ABP 501 Assay Positive	13 (59.1)	8 (47.1)	63 (41.4)	40 (50.6)	42 (54.5)
Adalimumab Assay Positive	13 (59.1)	8 (47.1)	66 (43.4)	37 (46.8)	45 (58.4)
Positive in Either Assay	13 (59.1)	8 (47.1)	72 (47.4)	43 (54.4)	48 (62.3)
Neutralizing					
ABP 501 Assay Positive	4 (18.2)	3 (17.6)	9 (5.9)	7 (8.9)	8 (10.4)
Adalimumab Assay Positive	2 (9.1)	4 (23.5)	10 (6.6)	8 (10.1)	7 (9.1)
Positive in Either Assay	4 (18.2)	4 (23.5)	11 (7.2)	9 (11.4)	8 (10.4)
Week 20					
Binding					
ABP 501 Assay Positive			78 (51.3)	43 (54.4)	49 (63.6)
Adalimumab Assay Positive			73 (48.0)	46 (58.2)	46 (59.7)
Positive in Either Assay			83 (54.6)	47 (59.5)	50 (64.9)
Neutralizing					
ABP 501 Assay Positive			10 (6.6)	9 (11.4)	10 (13.0)
Adalimumab Assay Positive			11 (7.2)	9 (11.4)	8 (10.4)
Positive in Either Assay			11 (7.2)	9 (11.4)	10 (13.0)
Week 32					
Binding					
ABP 501 Assay Positive			66 (43.4)	39 (49.4)	46 (59.7)
Adalimumab Assay Positive			72 (47.4)	42 (53.2)	44 (57.1)
Positive in Either Assay			76 (50.0)	45 (57.0)	46 (59.7)
Neutralizing					
ABP 501 Assay Positive			8 (5.3)	7 (8.9)	8 (10.4)
Adalimumab Assay Positive			8 (5.3)	6 (7.6)	7 (9.1)
Positive in Either Assay			8 (5.3)	7 (8.9)	8 (10.4)
Week 52					
Binding					
ABP 501 Assay Positive			59 (38.8)	33 (41.8)	39 (50.6)
Adalimumab Assay Positive			62 (40.8)	32 (40.5)	41 (53.2)
Positive in Either Assay			65 (42.8)	34 (43.0)	42 (54.5)
Neutralizing					
ABP 501 Assay Positive			13 (8.6)	9 (11.4)	16 (20.8)
Adalimumab Assay Positive			13 (8.6)	9 (11.4)	16 (20.8)
Positive in Either Assay			13 (8.6)	10 (12.7)	16 (20.8)

(Source: Table 14-10.3, CSR 20120263)

Reviewer's comment: Among subjects who were re-randomized, more patients with positive binding ADA were randomized to the EU-Humira/ABP501 group compared to the other two groups (62.3% vs 47.4% and 54.4%) at week 16. This imbalance was observed throughout the rest of the study, and may explain the higher incidence of positive binding ADA and neutralizing

ADA observed in the EU-Humira/ABP501 group later at week 52, as subjects with binding antibodies are predisposed to form neutralizing antibodies.

Conclusions:

- Ctrough values were comparable at each time point between ABP501 and EU-approved Humira in PsO patients.
- The ADA incidence increased over time in both arms and was comparable between ABP501 and EU-approved Humira before week 16 and re-randomization. More patients with positive binding ADA were randomized to the EU-Humira/ABP501 group at week 16, and higher incidence of positive binding ADA and neutralizing ADA were observed in the EU-Humira/ABP group at week 52.

4.2 Appendix – Office of Clinical Pharmacology Filing Memo

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	761024	**SDN**	1
Applicant	Amgen	**Submission Date**	11/25/2015
Generic Name	ABP501 (adalimumab-xxxx))	**Brand Name (Proposed)**	(b) (4)
Drug Class	Tumor necrosis factor (TNF) blocker		
Indication	Treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis in patients 4 years of age and older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, plaque psoriasis (PsO)		
Dosage Regimen	Same as reference product HUMIRA		
Dosage Form	Single-use prefilled syringe 40 mg/0.8 mL and 20 mg/0.4 mL; Autoinjector (SureClick): 40 mg/0.8 mL	**Route of Administration**	Subcutaneous injection
OCP Division	II	**OND Division**	Pulmonary, Allergy, and Rheumatology Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Jianmeng Chen	Ping Ji
Pharmacometrics		
Genomics		
Review Classification	☑ Standard ✗ Priority ✗ Expedited	

Filing Date	1/22/2016	**74-Day Letter Date**	2/5/2015
Review Due Date	8/19/2016	**PDUFA Goal Date**	9/23/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

✗ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

✗ Yes

☑ No

Is there a need for clinical trial(s) inspection?

☑ Yes

✗ No

OSI inspection will be requested for study 20110217.

Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☑ Yes ✗ No	Clinical Pharmacology Summary	☑ Yes ✗ No
Bioanalytical and Analytical Methods	☑ Yes ✗ No	Labeling	☑ Yes ✗ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
✗ Metabolism Characterization			
✗ Transporter Characterization			
✗ Distribution			
✗ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
✗ Absolute Bioavailability			
☑ Relative Bioavailability		1	20030121, BE between PFS and AI, with Etanercept
☑ Bioequivalence		1	20110217, PK similarity, ABP 501, HUMIRA-US, HUMIRA-EU
✗ Food Effect			
✗ Other			
Human Pharmacokinetics			
Healthy Subjects	✗ Single Dose		
	✗ Multiple Dose		
Patients	✗ Single Dose		
	☑ Multiple Dose	2	20120262, RA; 20120263, Ps
✗ Mass Balance Study			
✗ Other (e.g. dose proportionality)			
Intrinsic Factors			
✗ Race			
✗ Sex			
✗ Geriatrics			
✗ Pediatrics			
✗ Hepatic Impairment			
✗ Renal Impairment			
✗ Genetics			
Extrinsic Factors			

✗ Effects on Primary Drug		
✗ Effects of Primary Drug		
Pharmacodynamics		
✗ Healthy Subjects		
✗ Patients		
Pharmacokinetics/Pharmacodynamics		
✗ Healthy Subjects		
✗ Patients		
✗ QT		
Pharmacometrics		
✗ Population Pharmacokinetics		
✗ Exposure-Efficacy		
✗ Exposure-Safety		

Total Number of Studies and reports	**In Vitro**		**In Vivo**	4
Total Number of Studies/reports to be Reviewed				4

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ✗No ✗N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	✗Yes ✗No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ✗No ✗N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	✗Yes ✗No ☑N/A	This is a 351(k) biosimilar submission. The reference product is Humira.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ✗No ✗N/A	Method MVR-115225 was used to support pivotal PK study 20110217 (bioanalytical clinical report 178052)
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	✗Yes ✗No ☑N/A	
7. Does the submission contain PK and	☑Yes ✗No ✗N/A	

PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?		
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ✗No ✗N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ✗No ✗N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ✗No ✗N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ✗No ✗N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	✗Yes ✗No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ✗No ✗N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal	✗Yes ✗No ☑N/A	

studies)?		
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	✗ Yes ✗ No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	✗ Yes ✗ No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	✗ Yes ✗ No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ✗ No ✗ N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	✗ Yes ☑No ✗ N/A	

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

/s/

JIANMENG CHEN
08/18/2016

ANSHU MARATHE
08/18/2016