BIOSIMILAR MULTI-DISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	761086
Submit Date	December 14, 2018
Received Date	December 14, 2018
BsUFA Goal Date	December 14, 2019
Division/Office	Division of Pulmonary, Allergy, and Rheumatology Products/ ODE II in collaboration with DDDP and DGIEP
Review Completion Date	August 14, 2019
Product Code Name	ABP 710
Proposed Nonproprietary Name[1]	infliximab-axxq
Proposed Proprietary Name[1]	Avsola
Pharmacologic Class	tumor necrosis factor (TNF) blocker
Applicant	Amgen Inc.
Applicant Proposed Indication(s)	Crohn's disease (CD), pediatric CD, ulcerative colitis (UC), pediatric UC, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and plaque psoriasis (PsO)
Recommendation on Regulatory Action	Approval

[1] The proposed nonproprietary name and proprietary names are conditionally accepted until such time that the application is approved.

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Reviewers of Biosimilar Multi-Disciplinary Evaluation and Review

Regulatory Project Manager	Christine Ford
Nonclinical Reviewer(s)	Steve Leshin
Nonclinical Team Leader(s)	Carol Galvis
Clinical Pharmacology Reviewer(s)	Dipak Pisal
Clinical Pharmacology Team Leader(s)	Ping Ji
Clinical Reviewer(s)	Katherine Clarridge
Clinical Team Leader(s)	Stacy Chin
Clinical Statistics Reviewer(s)	James Travis
Clinical Statistics Team Leader(s)	Rebecca Rothwell
Cross-Discipline Team Leader(s)	Stacy Chin
DGIEP	Sandhya Apparaju, Juli Tomaino, Jessica Lee
DDDP	Gary Chiang, David Kettl

Additional Reviewers of Application

OPQ RBPM	Oumou K. Barry
ATL	Yanming An
CMC - Drug Substance/Analytical Similarity	Yetao Jin
CMC - Drug Product/Immunogenicity	Bruce Huang
OBP Labeling	Scott Dallas
Product Quality Microbiology	Maxwell Van Tassell Maria Candauchacon
OPF/DIA	Ziyang Su, Peter Qiu
CMC Statistics	Chao Wang, Meiyu Shen
OSI	Min Lu
OSIS	Nicola Fenty-Stewart Xikui Chen Xingfang Li
OSE/SRPM	Saharat Patanavanich
OSE/DMEPA	Carlos Mena-Grillasca, Danielle Harris Melina Fanari, Sarah K. Vee
DPMH Pediatrics: Maternal health:	Erica Radden Leyla Sahin, Tamara Johnson
DMPP	Kelly Jackson, Marcia Williams

CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error and Prevention Analysis

DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ACR	American College of Rheumatology
ADA	Anti-drug Antibodies
ACR20	20% improvement in ACR core set measurements
ACR50	50% improvement in ACR core set measurements
ACR70	70% improvement in ACR core set measurements
ADME	Absorption, Distribution, Metabolism, and Excretion
AESI	Adverse Event of Special Interest
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multi-Disciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BRG	Biosimilar Review Guide
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CPU	Clinical Pharmacology Unit
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DAS	Disease Activity Score
DAS28-CRP	Disease Activity Score in 28 joints – C-reactive protein
DEPI	Division of Epidemiology
DMC	Data Monitoring Committee
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
EU-Remicade	E.U.-approved Remicade
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice

GMR	Geometric Mean Ratio
GRP	Good Review Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HDL	High-density Lipoprotein
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LDL	Low-density Lipoprotein
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
NSAID	Nonsteroidal anti-inflammatory drug
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGE	Special Government Employee
SJC	Swollen Joint Count
SOC	System Organ Class
SOP	Standard Operating Procedures
SP	SharePoint
TEAE	Treatment-Emergent Adverse Events
TJC	Tender Joint Count
ULOQ	Upper Limit of Quantitation

US-Remicade	U.S.-licensed Remicade
VAS	Visual Analog Scale

Signatures

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/Approved
Nonclinical Reviewer	Steve Leshin, Ph.D.	OND / ODEII / DPARP	Sections 2.3, 5 and Appendix 12.3
	Signature: Lawrence S. Leshin -S Digitally signed by Lawrence S. Leshin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222013, cn=Lawrence S. Leshin -S Date: 2019.12.04 13:00:53 -05'00'		
Nonclinical Team Leader	Carol Galvis, Ph.D.	OND / ODEII / DPARP	Section 5 and Appendix 12.3
	Signature: Carol Galvis -S Digitally signed by Carol Galvis -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Carol Galvis -S, 0.9.2342.19200300.100.1.1=2000329778 Date: 2019.12.04 12:53:51 -05'00'		
Clinical Pharmacology Reviewer	Dipak Pisal, Ph.D.	OTS / OCP / DIIP	Section 6 and Appendix 12.2
	Signature: Dipak Pisal -S Digitally signed by Dipak Pisal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Dipak Pisal -S, 0.9.2342.19200300.100.1.1=2001808716 Date: 2019.12.04 13:12:07 -05'00'		
Clinical Pharmacology Team Leader	Ping Ji, Ph.D.	OTS/ OCP / DIIP	Section 6 and Appendix 12.2
	Signature: Ping Ji -S Digitally signed by Ping Ji -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ping Ji -S, 0.9.2342.19200300.100.1.1=2000364393 Date: 2019.12.04 13:16:26 -05'00'		
Clinical Reviewer	Katherine Clarridge, M.D.	OND / ODEII / DPARP	Sections 2, 3, 7, 8, 9, 10, 11, and Appendix 12.1
	Signature: Katherine E. Clarridge -S Digitally signed by Katherine E. Clarridge -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001516104, cn=Katherine E. Clarridge -S Date: 2019.12.04 15:50:27 -05'00'		
Clinical Team Leader	Stacy Chin, M.D.	OND / ODEII / DPARP	
	Signature: Stacy Chin -S Digitally signed by Stacy Chin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Chin -S, 0.9.2342.19200300.100.1.1=2001131500 Date: 2019.12.04 13:08:34 -05'00'		

Clinical Reviewer	Gary Chiang, M.D., MPH	OND / ODEIII / DDDP	Appendix 13
	Signature: Gary Chiang -S Digitally signed by Gary Chiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Gary Chiang -S, 0.9.2342.19200300.100.1.1=2000332370 Date: 2019.12.05 06:57:38 -05'00'		
Clinical Team Leader	David Kettl, M.D.	OND / ODEIII / DDDP	Appendix 13
	Signature: David L. Kettl -S Digitally signed by David L. Kettl -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David L. Kettl -S, 0.9.2342.19200300.100.1.1=1300383857 Date: 2019.12.04 22:22:04 -05'00'		
Clinical Reviewer	Sandhya Apparaju, Ph.D.	OND / ODEIII / DGIEP	Appendix 14
	Signature: Sandhya K. Apparaju -S Digitally signed by Sandhya K. Apparaju -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300226558, cn=Sandhya K. Apparaju -S Date: 2019.12.04 16:37:56 -05'00'		
Clinical Team Leader	Juli Tomaino, M.D.	OND / ODEIII / DGIEP	Appendix 14
	Signature: Juli A. Tomaino -S Digitally signed by Juli A. Tomaino -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001149989, cn=Juli A. Tomaino -S Date: 2019.12.04 16:53:37 -05'00'		
Associate Director	Jessica Lee, M.D.	OND / ODEIII / DGIEP	Appendix 14
	Signature: Jessica J. Lee -S Digitally signed by Jessica J. Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica J. Lee -S, 0.9.2342.19200300.100.1.1=2000596373 Date: 2019.12.04 20:22:12 -05'00'		
Clinical Statistics Reviewer	James Travis, Ph.D.	OTS /OB / DBII	Section 7
	Signature: James E. Travis -S Digitally signed by James E. Travis -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001617088, cn=James E. Travis -S Date: 2019.12.04 13:32:13 -05'00'		
Clinical Statistics Team Leader	Rebecca Rothwell, Ph.D.	OTS / OB / DBIII	Section 7
	Signature: Rebecca Rothwell -S Digitally signed by Rebecca Rothwell -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000455521, cn=Rebecca Rothwell -S Date: 2019.12.04 14:56:08 -05'00'		

Cross-Discipline Team Leader	Stacy Chin, M.D.	OND/ ODEII / DPARP	All Sections
	Signature: Stacy Chin -S Digitally signed by Stacy Chin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Chin -S, 0.9.2342.19200300.100.1.1=2001131500 Date: 2019.12.04 13:09:02 -05'00'		
Designated Signatory	Sally Seymour, M.D.	OND/ ODEII / DPARP	All Sections
	Signature: Sally M. Seymour -S Digitally signed by Sally M. Seymour -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222097, cn=Sally M. Seymour -S Date: 2019.12.05 07:44:40 -05'00'		

1. Executive Summary

1.1. Product Introduction

Amgen (hereafter referred to as "Applicant" in this review) submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for ABP 710 as a proposed biosimilar to US-Remicade.

ABP 710 (infliximab-axxq) is a chimeric immunoglobulin G1-kappa (IgG1-κ) monoclonal antibody composed of a murine variable region and human constant region directed against tumor necrosis factor alpha (TNFα).

The Applicant is seeking licensure of ABP 710[2] for the following indications and dosing regimens for which US-licensed Remicade has been previously approved:

Rheumatoid arthritis (RA)

- In combination with methotrexate, reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.
- To be administered in conjunction with methotrexate (MTX) at doses of 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks; for patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks.

Ankylosing spondylitis (AS)

- Reducing signs and symptoms in patients with active ankylosing spondylitis.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

Psoriatic arthritis (PsA)

- Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks with or without MTX.

Plaque psoriasis (PsO)

- Treatment of adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

[2] For purposes of this review, the proposed product is referred to by the applicant's descriptor ABP 710, which was the name used to refer to this product during development

Crohn's disease (CD)

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely Crohn's active disease who have had an inadequate response to conventional therapy.
- Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue.

Pediatric Crohn's disease (CD)

- Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Ulcerative colitis (UC)

- Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to
  severely active ulcerative colitis who have had an inadequate response to conventional therapy.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Pediatric Ulcerative colitis (UC)

- Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Recommended dosing is 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Although the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology and Inborn Errors Products (DGIEP), and the Division of Dermatology and Dental Products (DDDP) during the course of the review.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the PHS Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form and Strength Assessment

ABP 710 neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. ABP 710 does not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNF include induction of proinflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. TNF signaling has been implicated in the pathogenesis of chronic inflammatory conditions, and elevated concentrations of TNF have been found in involved tissues and fluids of patients with Crohn's disease (CD), pediatric CD, ulcerative colitis (UC), pediatric UC, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and plaque psoriasis (PsO).

ABP 710 is a sterile, lyophilized powder for IV infusion, 100 mg/20 mL in a single-dose vial

The strength of ABP 710 in the single-dose vial is the same as that of US-Remicade. ABP 710 also has the same dosage form and route of administration as that of US-Remicade.

1.4. Facilities

FDA's Office of Process and Facilities (OPF) conducted an assessment of the manufacturing facilities for this BLA.

(b) (4) is responsible for drug substance (DS) manufacturing. A pre-license inspection (PLI) was conducted from (b) (4) A 4-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. Refer to the EIR or the Form FDA 483 for a list of the 483 observations. The firm's responses to the observations were reviewed and considered adequate. The inspection was classified as voluntary action indicated (VAI).

(b) (4) is responsible for drug product (DP) manufacturing. A PLI was waived because of the site's compliance status and recent surveillance inspection in (b) (4)

All proposed manufacturing and testing facilities were acceptable based on the current CGMP compliance status of each and recent inspection. OPF recommends approval of BLA 761086 from the standpoint of facilities assessment.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not applicable. See Section 6.1 and 6.2 below.

1.6. Biosimilarity Assessment

Table 1. Summary and Assessment of Biosimilarity

Comparative Analytical Studies	
Summary of Evidence	• ABP 710 is highly similar to US-Remicade notwithstanding minor differences in clinically inactive components • ABP 710 has the same strength, dosage form, and route of administration as US-Remicade
Residual Uncertainties and Outcome	• There are no residual uncertainties from the product quality assessment
Animal Studies	
Summary of Evidence	• The ABP 710 nonclinical development program was considered adequate to support clinical development • A 2-week toxicity study in rats comparing ABP 710 and US-Remicade found no toxicological differences and supports the determination of biosimilarity
Residual Uncertainties and Outcome	• There are no residual uncertainties from the pharmacology/toxicology perspective
Clinical Pharmacology Studies	

Summary of Evidence	• PK similarity between ABP710 and US-Remicade was demonstrated in healthy subjects (Study 20140108) and supports a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade • Comparable incidence of anti-drug antibody and neutralizing antibody formation for ABP 710 and that of US-Remicade in healthy subjects (Study 20140108) and in patients with RA (Study 20140111) supports a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade
Residual Uncertainties and Outcome	• There are no residual uncertainties from the clinical pharmacology perspective
Clinical Studies	
Summary of Evidence	• In Study 20140111, there were no clinically meaningful differences in terms of efficacy and safety between ABP 710 and US-Remicade, and the study thus supports a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade in the studied indication (RA)
Residual Uncertainties and Outcome	• There are no residual uncertainties from the statistical and clinical perspective
Extrapolation of Data to Support Licensure as a Biosimilar	

Summary of Evidence	• DGIEP, DDDP, and DPARP teams have determined that the applicant has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (RA), to support licensure of ABP 710 as a biosimilar under section 351(k) of the PHS Act, for treatment of the following indications for which US-Remicade has been previously approved: o Rheumatoid arthritis in combination with methotrexate o Ankylosing spondylitis o Psoriatic arthritis o Plaque psoriasis o Inflammatory bowel disease (Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis)
Residual Uncertainties and Outcome	• There were no residual uncertainties regarding extrapolation of data and information to support licensure of ABP 710 as a biosimilar to US-Remicade for the above indications

1.7. Conclusions on Licensure

In considering the totality of the evidence, the data submitted by the applicant show that ABP 710 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between ABP 710 and US-licensed Remicade in terms of safety, purity, and potency of the product. The applicant also provided adequate justification for extrapolation of data and information to support licensure of ABP 710 in AS, PsA, UC, pediatric UC, CD, pediatric CD, and PsO. The information submitted by the applicant demonstrates that ABP 710 is biosimilar to US-licensed Remicade for each of following indications for which US-licensed Remicade is currently licensed and for which the applicant is seeking licensure: RA, AS, PsA, UC, pediatric UC, CD, pediatric CD, and PsO.

Author:
Stacy Chin, M.D.
Cross-Disciplinary Team Leader (CDTL)

2. Introduction and Regulatory Background

2.1. Important Safety Issues with Consideration to Reference Product

The program to evaluate the comparative safety between ABP 710 and US-Remicade was designed based on the well-known safety profile of US-Remicade. Potential risks based on class of drug (TNFα inhibitors) and of US-Remicade specifically were considered. Potential risks associated with immunomodulating biologic therapies may include infections, cardiovascular safety, malignancies and autoimmune disorders. Potential risks of a foreign protein may include administration or immune reactions, such as hypersensitivity, infusion reactions and immunogenicity.

The US-Remicade label (USPI) includes a boxed warning as outlined below:

"SERIOUS INFECTIONS
Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death […]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

REMICADE should be discontinued if a patient develops a serious infection or sepsis. Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during therapy. Treatment for latent infection should be initiated prior to REMICADE use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with REMICADE should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with REMICADE, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE […].

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. All reported REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with REMICADE at or prior to diagnosis."

The warning and precautions section (section 5 of the USPI) lists other known safety issues with Remicade and other TNF blockers, including:

- Serious Infections: "Patients treated with REMICADE are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease."
- Malignancies: "Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including REMICADE."
- Hepatitis B Virus Reactivation: "Use of TNF blockers, including REMICADE, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus."
- Hepatotoxicity: "Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving REMICADE."
- Patients with Heart Failure: "REMICADE has been associated with adverse outcomes in patients with heart failure."
- Hematologic Reactions: "Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE.
- Hypersensitivity: "REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases."
- Cardiovascular and Cerebrovascular Reactions During and After Infusion: "Serious cerebrovascular accidents, myocardial ischemia/infacrtion (some fatal), hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of REMICADE infusion. Cases of transient visual loss

have been reported during or within 2 hours of infusion of REMICADE."

- Neurologic Reactions: "REMICADE and other agents that inhibit TNF have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain- Barré syndrome."
- Use with Anakinra: "Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone."
- Use with Abatacept:; "In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF blocking agents alone, without increased clinical benefit."
- Concurrent Administration with other Biological Therapeutics: "There is insufficient information regarding the concomitant use of REMICADE with other biological therapeutics used to treat the same conditions as REMICADE."
- Switching between Biological Disease-Modifying Antirheumatic Drugs (DMARDs): "Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection."
- Autoimmunity: "Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome."
- Live Vaccines/Therapeutic Infectious Agents: "In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines."

2.2. Summary of Presubmission Regulatory Activity Related to Submission

Key interactions with the Applicant under IND 122136 prior to submission:

- July 2014
    - Biosimilar Biological Product Development (BPD) Type 2 meeting to discuss the adequacy of the proposed biosimilar development plan for ABP 710 . The Applicant originally proposed to conduct two separate comparative clinical studies in UC and RA patients; however, the Division noted that a single comparative clinical study in RA, if adequately designed, could be sufficient to support a demonstration of no clinically meaningful differences between ABP710 and the reference product.
- March 2015
    - BPD Type 2 meeting to discuss the revised clinical program for ABP 710 including the comparative clinical study design and endpoints. There was agreement to incorporate a "switch", or single transition, from reference

product to biosimilar, with the primary endpoint of absolute differences in ACR20 at week 22, and to maintain throughout the study duration. While the Division recommended the similarity margin be no greater than ±12%, a relaxed upper bound as part of an asymmetric similarity margin (e.g., -12%, +15%) would be considered if the sponsor provided adequate justification.

- May 2016
  - Submission of original IND 122136
- January 2018
  - iPSP agreement
- February 2018
  - BPD Type 2 meeting scheduled. This meeting was cancelled after the analytical similarity plan on selected assays and statistical analysis plan were agreed upon.
- November 2018
  - BPD Type 4 meeting to discuss the bounds of the upper similarity margin. The division noted that the sponsor's primary analysis showed an estimated difference between the ACR20 response probabilities at week 22 of over 9% with an upper bound of the 90% CI that exceeded the upper similarity margin of +15%. The division indicated that the totality of the evidence would be used to assess biosimilarity of ABP 710 to US-Remicade.

2.3. Studies and Publicly Available Information Submitted by the Applicant

Table 2: Nonclinical Studies Submitted

Study Title	Study Number	Duration/ Dose	Regimen/ Route	Number of Subjects	Population
Nonclinical Studies					
ABP 710: 14-Day Intravenous Toxicology Study in the Sprague Dawley Rat	118849	2 weeks/ 10 and 50 mg/kg	Once weekly, IV	10/sex/ Dose	Rats, males and females
Similarity Assessment of ABP 710 and Infliximab Inhibition of Proliferation in a MLR Assay	R20150173	5 µg/mL	Mixed Lymphocyte Reaction assay in vitro	Cells from 2 healthy human donor	Ex vitro, human peripheral blood white cells (mononuclear cells)
Assessment of ABP 710 and Infliximab in an ADCC Assay	TA-009389	0.0214 – 6000 ng/mL, and one	ADCC in vitro assay	Cells from 5 healthy subject,	Ex vitro, human peripheral blood white cells

Study Title	Study Number	Duration/ Dose	Regimen/ Route	Number of Subjects	Population
Using PBMC From Healthy Subjects and Crohn's Disease Donors		healthy donor 0.1286 – 36000 ng/mL		form 3 subjects with Crohn's Disease	(mononuclear cells)
Method Validation Report for the Quantification of ABP 710 and Infliximab in Sprague-Dawley Rat Serum by Electrochemiluminescence Assay	119411	NA	NA	NA	ABP 710 and US-Remicade Assay validation from rat serum

Table 3. Listing of all Relevant Submitted Clinical Studies

Study Identity	NCT no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
Study 20140108	ACTRN12614000903684	Comparative pharmacokinetics and safety of ABP 710, U.S.-Remicade, and EU-Remicade	Randomized, single-blind, single-dose, 3-arm, parallel group study	Healthy subjects	5 mg/kg IV ABP 710: 50 US-Remicade: 50 EU-Remicade: 50
Comparative Clinical Study(ies)					
Study 20140111	NCT02937701	Efficacy of ABP 710 compared with U.S.-Remicade	Randomized, double-blind, active-controlled, multiple-dose, clinical similarity study	RA patients	3 mg/kg IV day 1 (week 0), at weeks 2 and 6, and every 8 weeks thereafter ABP 710: 279 U.S.-Remicade: 279

Authors:
L. Steven Leshin DVM, PhD
Pharmacology-Toxicology Reviewer

Katherine Clarridge, MD
Clinical Reviewer

3. Clinical Studies: Ethics and Good Clinical Practice

3.1. Submission Quality and Integrity

The data quality and integrity of the studies were acceptable; the amount of missing data was minimal and did not impact overall conclusions. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

3.2. Statistical Analysis of Clinical Data

The applicant conducted a comparative clinical study, 20140111, which was designed to evaluate the efficacy and safety of ABP 710 in comparison to US-Remicade in patients with rheumatoid arthritis. The submitted datasets for this study were of sufficient quality to allow thorough statistical review and reproduction of the Applicant's analyses.

The original and amended protocols and statistical analysis plans for Study 2014011 were provided for this application prior to study unblinding; the original protocols were reviewed by the Agency and no statistical deficiencies were noted.

3.3. Compliance with Good Clinical Practices

All studies were conducted by Good Clinical Practice as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation.

Written informed consent was obtained prior to the subject entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

3.4. Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry *Financial Disclosure by Clinical Investigators*. The applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54. No potentially conflicting financial interests were identified.

Authors:
Katherine Clarridge, MD
Clinical Reviewer

Stacy Chin, MD
CDTL

4. Summary of Conclusions of Other Review Disciplines

4.1. Chemistry, Manufacturing and Controls (CMC)

The Office of Pharmaceutical Products (OPQ) in CDER recommends approval of BLA 761086 for ABP 710 manufactured by Amgen. The OPQ team determined that the data submitted in this application are adequate to support the following conclusions:

- The manufacture of ABP 710 is well-controlled and leads to a product that is pure, potent, and safe
- ABP 710 is highly similar to US-Remicade notwithstanding minor differences in clinically inactive components
- ABP 710 (100 mg lyophilized solid in a 20 mL vial) has the same dosage form, route of administration, and strength as US-Remicade (100 mg)

4.2. Microbiology

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective.

4.3. Devices

Not applicable.

4.3.1. Center for Devices and Radiological Health (CDRH)

Not applicable.

4.3.2. Division of Medication Error Prevention and Analysis (DMEPA)

Not applicable.

4.4. Office of Study Integrity and Surveillance (OSIS)

The biopharmaceutical inspection was requested for both clinical and bioananalytical

sites in Study 20140108. OSIS conducted an inspection for one of the requested clinical sites, (b) (4) No objectionable conditions were observed during the inspection and Form FDA 483 was not issued. The final inspection classification was NAI. The inspection review concluded that the data are reliable to support a regulatory decision, after excluding data from subjects (b) (6) (see Section 6.3).

Based on the recent inspection history, OSIS declined to conduct inspection of the bioanalytic site and the second clinical site and recommended accepting data for Agency review.

For more detailed information, refer to the review memos by Dr. Nicola Fenty-Stewart dated April 12, 2019 and Dr. Xingfang Li dated October 11, 2019.

4.5. Office of Scientific Investigations (OSI)

Two clinical sites were selected for inspections for study protocol 20140111. The study data derived from the clinical sites, based on inspections, were considered reliable, and the studies in support of this application appear to have been conducted adequately. At the time of this review, the final classification for both sites is No Action Indicated (NAI). For further details, please see Dr. Min Lu's clinical inspection summary dated October 2, 2019.

Author:
Stacy Chin, M.D.
CDTL

5. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

5.1. Nonclinical Executive Summary and Recommendation

ABP 710 was developed as a biosimilar to US-Remicade. Binding of infliximab products to TNFα inhibits the interaction of TNFα with its receptors and the subsequent signal transduction, thus resulting in suppression of inflammation.

A 2-week toxicological study in rats was conducted to compare US-Remicade with ABP 710. Once weekly injections of vehicle control, US-Remicade (10 or 50 mg/kg, IV), or ABP 710 (10 or 50 mg/kg, IV) with sacrifice on day 15, resulted in no toxicological differences between US-Remicade and ABP 710 treatment groups and minimal toxicity effects.

Since the rat is not a pharmacologically relevant species for infliximab products (chimpanzee TNFα was the only non-human species able to bind ABP 710 or US-Remicade), this study was limited to off-target effects. The results from this study support a demonstration of biosimilarity between ABP 710 and US-Remicade.

5.1.1. Nonclinical Residual Uncertainties Assessment

There are no residual uncertainties identified in the nonclinical studies.

For legal and ethical reasons, toxicity studies cannot be conducted in chimpanzees. The Applicant instead conducted a toxicity study in rats, which evaluated off-target toxicity. Off-target toxicity was minimal and at an exposure much greater than the therapeutic clinical exposure.

At the July 2014 BPD Type 2 meeting under IND 122136 with the current Applicant (Minutes dated August 14, 2014), the Division recommended a study in transgenic rats that were engineered to produce human TNFα. The Applicant indicated they had already conducted their toxicity study as an off-target study in normal rats based on comments made in Module 2 Pharmacology summary section that "the rat was selected as the lowest phylogenetic species for the conduct of a toxicology study, per request from the Japanese Pharmaceutical and Medical Devices Agency, to evaluate unanticipated toxicities associated with ABP 710 administration." The acceptance of the rat study was considered a review issue as it was not the recommended study. Both types of study have their limitations. A study in rats that lack pharmacodynamic activity for the drug would only address off-target effects, while a study in a transgenic rat model that produces human TNFα could yield difficult to interpret data since the types of cells producing human TNFα could be more prevalent than normal and unphysiologically expressed. The Agency determined that, based on its experience and expertise, notwithstanding the interpretive challenges, the submitted "off-target" study was acceptable and supported the conclusion of biosimilarity between ABP 710 and US-Remicade.

5.2. Product Information

Product Formulation

ABP 710 and US-Remicade are chimeric IgG1κ monoclonal antibodies against TNFα, composed of human constant and murine variable regions. ABP 710 drug product is supplied as a sterile, lyophilized powder for reconstitution, containing 100 mg of ABP 710

in a glass vial with an [redacted] stopper, covered by an aluminum seal with a plastic flip-off cap. The excipients and quantities in the APB 710 drug product are listed in the table below.

ABP 710 is intended for reconstitution with 10 mL of sterile water for injection. Upon reconstitution, the product is intended for dilution in normal saline (0.9% sodium chloride) for intravenous administration through an in-line filter.

Table 4. Quantitative and Qualitative Composition of ABP 710 Drug Product

Component	Reference to Standard	Function	Concentration[a]	Quantity per 100 mg Vial
ABP 710	In house[b]	Active ingredient	10 mg/mL	100 mg
Sucrose	NF, PhEur	[redacted]	50 mg/mL	500 mg
Dibasic sodium phosphate, anhydrous	USP, PhEur		0.5 mg/mL	4.9 mg
Monobasic sodium phosphate, monohydrate	USP		0.2 mg/mL	2.2 mg
Polysorbate 80	NF, PhEur		0.05 mg/mL	0.5 mg

NF = United States National Formulary; PhEur = European Pharmacopeia; USP = United States Pharmacopeia

[a] Target concentration upon reconstitution

[b] Tested to internal specifications (3.2.S.4.1, Specification).

Source: BLA 761086, Module 2.3.P, Table 1

US-Remicade is manufactured in a SP2/0 (mouse myeloma) cell line, whereas ABP 710 is manufactured using Chinese hamster ovary (CHO) cells. ABP 710 does not contain detectable levels of non-human glycans, such as N-glycolylneuraminic acid and alpha-galactosylation which US-Remicade does contain. ABP 710 contains N-acetylneuraminic acid sialylation, at minor levels, which is absent in US-Remicade. These differences do not preclude a finding that ABP 710 is highly similar to US-Remicade (see OBP Integrated Quality Assessment).

Comments on Novel Excipients

There are no novel excipients.

Comments on Impurities/Degradants of Concern

Impurities and degradants are within appropriate specifications (refer to the Integrated Quality Assessment review). There are no impurities or degradants of concern.

Authors:
L. Steven Leshin DVM, PhD
Pharmacology-Toxicology Reviewer Leader

Carol Galvis, PhD
Pharmacology-Toxicology Team

6. Clinical Pharmacology Evaluation and Recommendations

6.1. Clinical Pharmacology Executive Summary and Recommendation

Table 5. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics Similarity	• PK similarity between ABP710 and US-Remicade was demonstrated in healthy subjects (Study 20140108) and supports a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade.
Pharmacodynamics Similarity	• Not applicable
Immunogenicity	• The incidence of ADA and NAb formation for ABP 710 was comparable to that of US-Remicade in healthy subjects (Study 20140108) and in patients with RA (20140111). The comparable incidence of immunogenicity for ABP 710 and US-Remicade in both studies support a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade.

The clinical development for ABP 710 included 2 clinical studies: (1) Study 20140108, one 3-arm, single-dose, pharmacokinetic (PK) similarity study in healthy subjects comparing ABP 710, US-Remicade and EU-Remicade; (2) Study 20140111, randomized, double-blind, active-controlled comparative clinical study comparing efficacy, safety, PK, and immunogenicity of ABP 710 to US-Remicade in patients with moderate to severe RA who have an inadequate response to methotrexate.

The results of the PK similarity study (Study 20140108) demonstrated PK similarity between ABP 710, US-Remicade and EU-Remicade. For this submission, there was no need to establish an adequate scientific bridge to US-Remicade. Therefore, while the clinical pharmacology study 20130108 included the use of a non-US-licensed comparator product, EU-Remicade, the data generated using EU-Remicade was not used to support

the demonstration of biosimilarity.

In the 3 way-PK similarity study (Study 20140108), the 90% CI for the geometric mean ratios (GMRs) for area under the serum drug concentration-time curve (AUC) from time 0 to infinity (AUC_{inf}), maximum observed drug concentration (C_{max}), and AUC from time 0 to the last quantifiable concentration (AUC_{last}) were contained within the prespecified criteria of 80 to 125% (Table 6**Error! Reference source not found.**).

Table 6. PK Similarity Assessment-Statistical Analysis for PK Parameters (Study 20140108)

Parameter	Comparison	GMR (%)	90% CI of Ratio
Primary			
AUC_{inf}	ABP710 vs. US-Remicade	89.70	(81.43, 98.81)
	EU-Remicade vs. US-Remicade	89.16	(80.90, 98.26)
	ABP710 vs. EU-Remicade	100.61	(91.29, 110.88)
Secondary			
C_{max}	ABP710 vs. US-Remicade	96.97	(91.31, 102.99)
	EU-Remicade vs. US-Remicade	94.96	(89.39, 100.88)
	ABP710 vs. EU-Remicade	102.12	(96.12 108.48)
AUC_{last}	ABP710 vs. US-Remicade	91.16	(83.78, 99.19)
	EU-Remicade vs. US-Remicade	90.51	(83.15, 98.53)
	ABP710 vs. EU-Remicade	100.71	(92.51, 109.63)

Source: FDA Analysis.

The immunogenicity of ABP 710 was comparable to that of US-Remicade, and EU-Remicade.

The overall incidence of anti-drug antibody (ADA) formation over the course of the study in healthy subjects was 39.6%, 32.0%, and 27.1% for ABP710, US-Remicade, and EU-Remicade, respectively (Study 20140108). After multiple doses of IV infusion of ABP 710 or US-Remicade, the incidence of ADA formation was also similar (57.1% and 60.6%, respectively) between ABP710, US-Remicade in patients with RA (Study 20140111).

The overall incidence of Neutralizing Antibodies (NAb) formation over the course of the study in healthy subjects was 12.5%, 10%, and 18.8 % for ABP710, US-Remicade, and EU-Remicade, respectively (Study 20140108). After multiple doses of IV infusion of ABP

710 or US-Remicade, the incidence of NAb formation was also similar (18% and 20.8%, respectively) between ABP710, US-Remicade in patients with RA (Study 20140111).

6.1.1. Clinical Pharmacology Residual Uncertainties Assessment

PK similarity was demonstrated between ABP7 10 and US-Remicade in the 3-way PK similarity study (Study 20140108). Comparable incidence of immunogencity for ABP 710 and US-Remicade was observed in Studies 2014018 and 20140111. There were no clinical pharmacology residual uncertainties regarding the PK or immunogenicity assessments intended to support a demonstration of biosimilarity.

6.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not applicable. Data generated from studies using a non-U.S.-licensed comparator product [EU-Remicade] were not used to support the demonstration of biosimilarity.

6.3. Human Pharmacokinetics and Pharmacodynamics

Clinical Pharmacology Study Design Features

Study 20140108 was a randomized, single-blind, single-dose, 3-arm, parallel group study to determine the pharmacokinetic similarity of ABP 710 to US-Remicade and EU-Remicade in healthy adult subjects. The study was conducted at 2 clinical pharmacology unit (CPUs) located in Australia. Approximately 150 healthy subjects were planned for dosing as described in the schematic below.

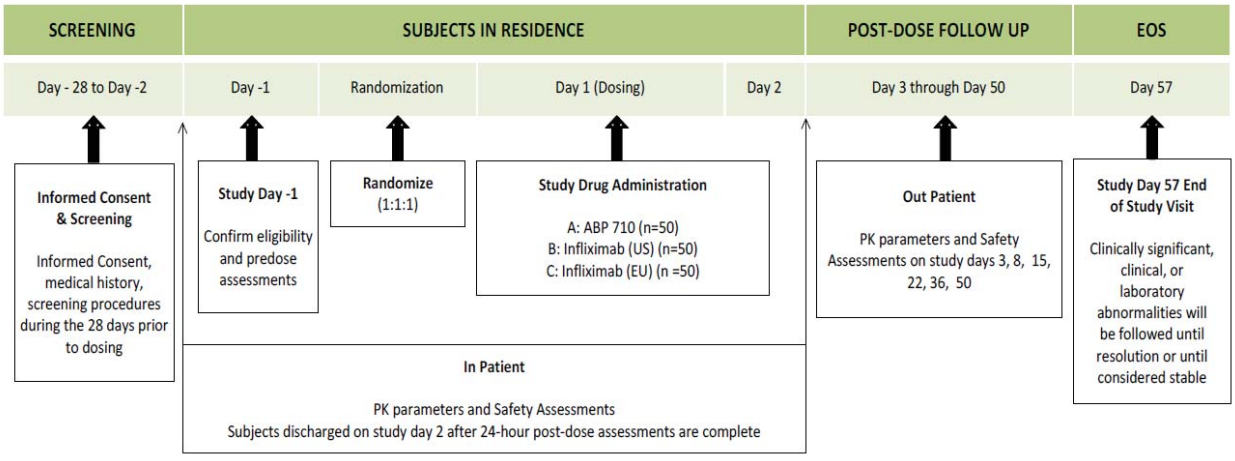

Figure 1. Study 20140108 Design Schematics

(source: Figure 9.1, CSR for study 20140108, page 22)

Blood sampling for PK analysis during each return visit to the CPU, including the EOS visit, occurred per the scheduled time point.

Clinical Pharmacology Study Endpoints

In study 20140108, the primary end point was AUC_{inf}, where as other secondary parameters were C_{max}, and AUC_{last} to evaluate and compare the PK profiles of ABP710, US-Remicade, and EU-Remicade in healthy subjects. Safety, tolerability and immunogenicity were also other secondary endpoints.

Study 20140111 was the comparative clinical study in RA patients. The primary efficacy endpoint was the response difference (RD) of 20% improvement in ACR score set measurements (ACR20) at week 22, whereas PK (C_{trough}), safety, immunogenicity and other efficacy endpoints (ACR50, and ACR70, Disease Activity Score 28 (DAS28), were secondary
endpoints. For the choice of efficacy and safety endpoints in Study 20140111, see details in Section 7.

Bioanalytical PK Method and Performance

The methodologies used in the analysis of biological samples were sensitive, robust, and fully validated.

The serum concentrations of ABP 710, US-Remicade and EU-Remicade were appropriately quantified using a validated electrochemiluminescence (ECL) assay in Study 20140108 and ABP 710 and US-Remicade in Study 20140111 (validation report 119704 and 119704 addendum 1).
During the method validation, ABP 710, US-Remicade and EU-Remicade were used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ)) was evaluated using ABP 710, US-Remicade and EU-Remicade as QC samples. See detailed information about the assay validation in Appendix 12.2.1.

PK Similarity Assessment

PK similarity has been demonstrated between ABP 710, US-Remicade and EU-Remicade in the 3-way PK similarity Study 20140108. In the 3-way PK similarity comparisons (ABP 710 vs. US-Remicade, ABP 710 vs. EU-Remicade and EU-Remicade vs. US-Remicade), the 90% CIs for the geometric mean ratios of C_{max}, $AUC_{0\text{-}inf}$ and AUC_{last} were all within the pre-defined criteria of 80% –125% (Table 7). The mean serum concentration-time profiles were similar between the ABP 710, US-Remicade and EU-Remicade treatment groups (Figure 2). The geometric means of PK parameters were similar following a single 5 mg/kg IV infusion of ABP 710, US-Remicade and EU-Remicade (Table 7

Treatment	C_{max} (µg/mL) Geometric Mean, [n] (Geo CV%)	AUC_{last} (µg.h/mL) Geometric Mean, [n] (Geo CV%)	AUC_{inf} (µg.h/mL) Geometric Mean, [n] (Geo CV%)
ABP710	128.14 [49] (18)	33716.07 [49] (25)	35995.38 [49] (28)
U.S.-Remicade	131.90 [50] (19)	36661.96 [50] (28)	39762.95 [50] (33)
EU-Remicade	125.48 [48] (17)	33409.15 [48] (24)	35722.56 [48] (28)
Geo CV% = CV% geometric mean			

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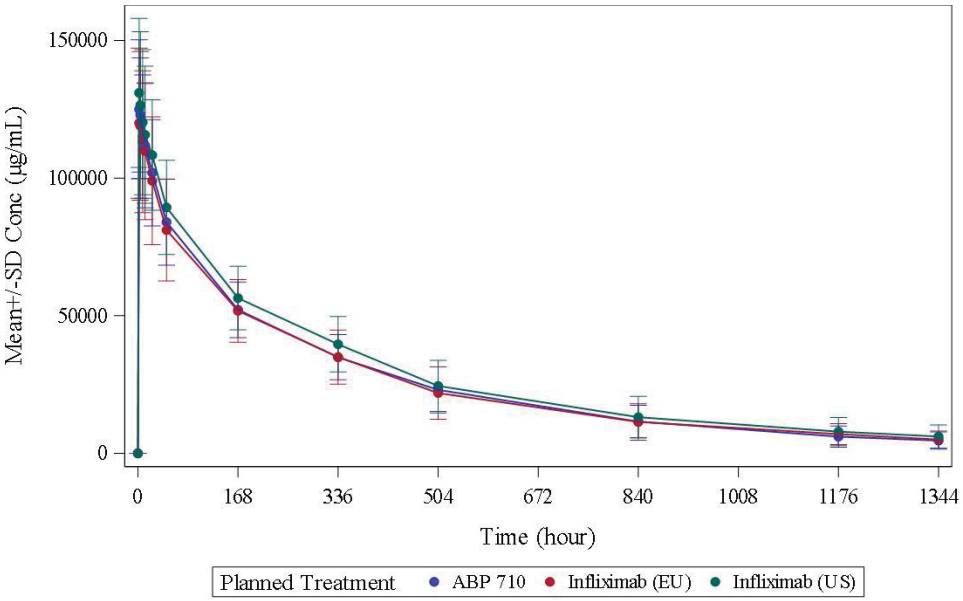


Figure 2. Mean (±SD) Serum ABP 710, US-Remicade, and EU-Remicade Concentration-time Profiles (Study 20140108)

Source: FDA Analysis.

Table 7. Summary of ABP 710, US-Remicade, and EU-Remicade Pharmacokinetic Parameters

Treatment	C_{max} (µg/mL) Geometric Mean, [n] (Geo CV%)	AUC_{last} (µg.h/mL) Geometric Mean, [n] (Geo CV%)	AUC_{inf} (µg.h/mL) Geometric Mean, [n] (Geo CV%)
ABP710	128.14 [49] (18)	33716.07 [49] (25)	35995.38 [49] (28)

U.S.-Remicade	131.90 [50] (19)	36661.96 [50] (28)	39762.95 [50] (33)
EU-Remicade	125.48 [48] (17)	33409.15 [48] (24)	35722.56 [48] (28)
Geo CV% = CV% geometric mean			

Source: FDA Analysis.

OSIS review reported that "Investigator Deyampert discussed the documentation of infusion

volume for subjects (b) (6) **The documentation stated that each of these subjects received 260 mL of study product. Subjects were supposed to have received 250 mL of study product. " As per the OSIS evaluation "The EIR and exhibits had no records to confirm the infused volume or an error in recording". Hence it was not certain that there was a documentation error or dosing error in these two subjects (Subject IDs,** (b) (6) **. We performed sensitivity analysis with and without study data from these two subjects, and the results demonstrated that the PK similarity criteria was met in both cases.**

PD Similarity Assessment

Not applicable.

6.4. Clinical Immunogenicity Studies

Design features of the clinical immunogenicity assessment

Immunogenicity upon single dosing has been assessed in healthy subjects in PK similarity Study 20140108, and upon repeated dosing in the comparative clinical Study 20140111. See Table 3 for more details regarding the study designs.

Immunogenicity in Study 20140108:
Subjects in PK similarity Study 20140108 were monitored for the development of ADAs. Samples for ADA analysis were collected prior to dosing on day 1 and on days 15, 36, and 57 or upon early study discontinuation (EOS visit). All samples were screened for binding ADA activity, and samples confirmed positive for binding ADAs were also tested for neutralizing activity.

Immunogenicity in Study 20140111:
This randomized, double-blind, active-controlled, multiple-dose, comparative clinical study was designed to evaluate the efficacy, safety, and immunogenicity of ABP 710 compared with US-Remicade in adult patients with moderate to severe rheumatoid arthritis (RA) who have an inadequate response to methotrexate (MTX) (**Error! Reference source not found.**). A total of 550 subjects were initially randomized in a 1:1

ratio to receive a 3-mg/kg IV infusion of either ABP 710 (N=275) or US-Remicade (N=275) on day 1 (week 0), at weeks 2 and 6, and every 8 weeks thereafter until week 22. At week 22, subjects initially randomized to US-Remicade were re-randomized in a 1:1 ratio to either continue receiving US-Remicade every 8 weeks (referred to as US-Remicade/US-Remicade treatment group) or transition to receive ABP 710 every 8 weeks (referred to as US-Remicade/ABP 710 treatment group) through week 46. Subjects initially randomized to ABP 710 continued receiving the same treatment every 8 weeks through week 46 (referred to as ABP 710/ABP 710 treatment group). Re-randomization was managed to ensure that the blind to the initial study treatment group was maintained. Subjects unable to complete the week 22 visit within the allowed visit window were not re-randomized and were discontinued from the study. Study completion was defined as completion of the week 50 visit. The primary analysis was performed after all subjects completed the week 34 visit (or were terminated early from the study) using a data cutoff date of 16 April 2018.

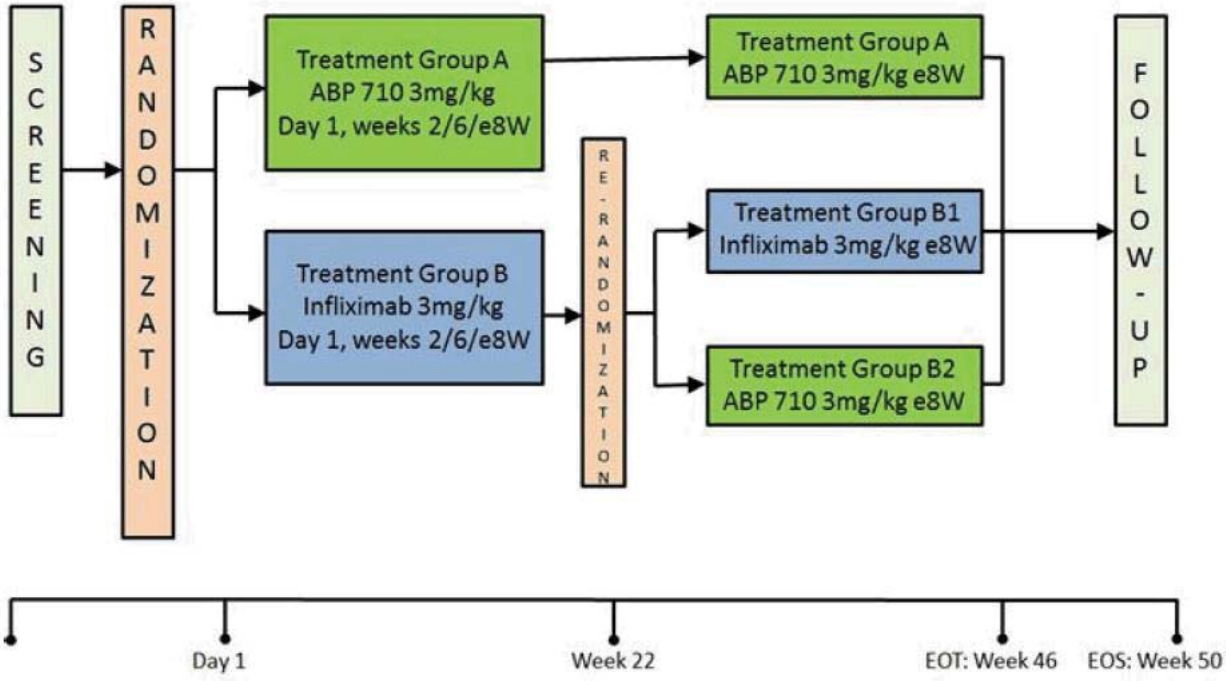


Figure 3. Study 20140111 Design Schematics

e8W = every 8 weeks; EOS = end-of-study (Week 50); EOT = end-of-treatment (week 46); PA = primary analysis; Infliximab = US-Remicade
(Source: Clinical Study Report 20140111, Figure 8-1. Page 37)

Immunogenicity endpoints

The formation of ADA and the neutralizing activity of ADA was evaluated for immunogenicity
assessment.

Immunogenicity assay's capability of detecting the antidrug antibodies (ADA) and Neutralizing antibodies (NAb) in the presence of proposed product, reference product, and comparator product (as applicable) in the study samples

The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of concentrations of ABP 710, US-Remicade and US-Remicade expected following administration. Refer to OBP's review of the immunogenicity assays for more details.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

The sampling plan is adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation.

1. **Study 20140108:** Samples for ADA analysis were collected prior to dosing on day 1 and on days 15, 36, and 57 or upon early study discontinuation (EOS visit). All samples were screened for binding ADA activity, and samples confirmed positive for binding ADAs were also tested for neutralizing activity.

2. **Study 20140111:** Blood samples for ADA analysis were collected at day 1 (baseline) and at weeks 2, 6, 14, 22, 30, 34, 38, and 50/EOS. Samples were collected prior to dosing with the exception of week 34 and week 50/EOS visits where doses were not administered. All samples were screened for binding ADA activity, and samples confirmed positive for binding ADAs were also tested for neutralizing activity.

Incidence of ADA and NAb (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA and NAb throughout the study.)

The immunogenicity of ABP 710 was comparable to that of US-Remicade and EU-Remicade in healthy subjects (Study 20140108). The immunogenicity data from study 20140111 indicates that there is no increase in immunogenicity risk for ABP 710 compared to US-Remicade, which supports a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade.

In study 20140108, overall following a single 5-mg/kg IV dose of study drug 19 (39.6%), 16 (32.0%), and 13 (27.1%) subjects in the ABP 710, US-Remicade, and EU-Remicade treatment groups developed treatment-emergent ADA by Day 57 (Table 8). Overall, the ADA incidence was similar between all three treatment groups.

The overall incidence of Neutralizing Antibodies (NAb) formation over the course of the study in healthy subjects was 12.5%, 10%, and 18.8 % for ABP710, US-Remicade, and EU-Remicade, respectively (Study 20140108) (Table 9**Error! Reference source not found.**). Overall, the NAb incidence was comparable between all three treatment groups.

Table 8. Summary of Binding and Neutralizing Antidrug Antibody Results (Study 20140108)

	ABP 710 (N = 49)	Infliximab (US) (N = 50)	Infliximab (EU) (N = 49)	Overall (N = 148)
Visit	Number and Percentage of Subjects with Binding Antibody Assay Positive Results			
Day 1, predose	0/49 (0.0%)	0/50 (0.0%)	0/49 (0.0%)	0/148 (0.0%)
Day 15	3/47 (6.4%)	2/48 (4.2%)	4/48 (8.3%)	9/143 (6.3%)
Day 36	16/47 (34.0%)	11/49 (22.4%)	13/48 (27.1%)	40/144 (27.8%)
Day 57 (EOS)	19/48 (39.6%)	16/50 (32.0%)	13/48 (27.1%)	48/146 (32.9%)
Positive at any time during the study	21/49 (42.9%)	18/50 (36.0%)	16/49 (32.7%)	55/148 (37.2%)
	Number and Percentage of Subjects with Neutralizing Antibody Assay Positive Results			
Day 1, predose	0/49 (0.0%)	0/50 (0.0%)	0/49 (0.0%)	0/148 (0.0%)
Day 15	0/47 (0.0%)	0/48 (0.0%)	0/48 (0.0%)	0/143 (0.0%)
Day 36	3/47 (6.4%)	0/49 (0.0%)	1/48 (2.1%)	4/144 (2.8%)
Day 57 (EOS)	6/48 (12.5%)	5/50 (10.0%)	9/48 (18.8%)	20/146 (13.7%)
Positive at any time during the study	6/49 (12.2%)	5/50 (10.0%)	9/49 (18.4%)	20/148 (13.5%)

CSR = clinical study report; EOS = end of study/early termination; EU = European Union; US = United States.

(Source: Summary of Clinical Pharmacology Studies Table 2, page 15)

Study 20140111:

In Study 20140111, following multiple 3 mg/kg IV infusion doses of study drug, by Week 22, 149/278 (57.1%) and 160/278 (60.6%) subjects developed ADA in ABP 710 and US-Remicade treatment groups, respectively. Post week 22, 23/96 (24%), 13/45 (28.9%), and 16/45 (35.6%) subjects developed ADA in ABP 710/ ABP 710, US-Remicade / US-Remicade, and US-Remicade /ABP710 treatment group, respectively.

After multiple doses of IV infusion of ABP 710 or US-Remicade, the incidence of NAb formation was also similar (18% and 20.8%, respectively) between ABP710, US-Remicade in patients with RA (Study 20140111).

Overall, the incidence of ADA and NAb is comparable between ABP 710 and US-Remicade throughout the study, including the transition-extension period (Table 9 and Table 10**Error! Reference source not found.**).

Table 9. Summary of Binding and Neutralizing Antidrug Antibody Results (Study 20140111)

Variable	ABP 710 (N = 278)	Infliximab (N = 278)
Subjects with an on-study result[a]	278	278
Total antibody incidence, n (%)		
Binding antibody positive anytime	165 (59.4)	171 (61.5)
Neutralizing antibody positive anytime	52 (18.7)	58 (20.9)
Subjects with a result at baseline	278	277
Pre-existing antibody incidence, n(%)		
Binding antibody positive at baseline	16 (5.8)	11 (4.0)
Neutralizing antibody positive at baseline	0 (0.0)	0 (0.0)
Subjects with a binding negative or no result at baseline and a postbaseline result by week 2	260	261
Developing antibody incidence, n(%)		
Binding antibody positive postbaseline	17 (6.5)	15 (5.7)
Neutralizing antibody positive postbaseline	0 (0.0)	0 (0.0)
Subjects with a binding negative or no result at baseline and a postbaseline result by week 6	261	263
Developing antibody incidence, n(%)		
Binding antibody positive postbaseline	56 (21.5)	52 (19.8)
Neutralizing antibody positive postbaseline	0 (0.0)	2 (0.8)
Subjects with a binding negative or no result at baseline and a postbaseline result by week 14	261	264
Developing antibody incidence, n(%)		
Binding antibody positive postbaseline	107 (41.0)	108 (40.9)
Neutralizing antibody positive postbaseline	21 (8.0)	30 (11.4)
Subjects with a binding negative or no result at baseline and a postbaseline result by week 22	261	264
Developing antibody incidence, n(%)		
Binding antibody positive postbaseline	149 (57.1)	160 (60.6)
Transient[b]	18 (6.9)	12 (4.5)
Neutralizing antibody positive postbaseline	47 (18.0)	55 (20.8)
Transient[b]	5 (1.9)	3 (1.1)

IP = investigational product.
Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of study IP.
Percentages are calculated using the corresponding category count as the denominator.
a Subjects considered on-study after signing informed consent.
b Negative result at the subject's last time point tested within the study period.
Infliximab = US-Remicade

(Source: Clinical Study Report, Table 11.4, page 127)

Table 10. Summary of Binding and Neutralizing Antidrug Antibody Results-Post Week 22 (Study 20140111)

Variable	ABP 710/ ABP 710 (N = 240)	Infliximab/ Infliximab (N = 121)	Infliximab/ ABP 710 (N = 119)
Subjects with a binding negative at week 22 and negative or no result before week 22 and a post week 22 result	96	45	45
Developing antibody incidence [n (%)]			
Binding antibody positive post week 22	23 (24.0)	13 (28.9)	16 (35.6)
Transient[a]	4 (4.2)	5 (11.1)	8 (17.8)
Neutralizing antibody positive post week 22	1 (1.0)	0 (0.0)	1 (2.2)
Transient[a]	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages were calculated using the corresponding category count as the denominator.
CSR = clinical study report.
[a] Negative result at the subject's last time point tested within the study period.

(Source: Summary of Clinical Pharmacology Studies Table 5, page 26)
Note: Infliximab = US-Remicade

Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed biosimilar product

Impact of ADA and NAb on PK

While the development of ADAs influenced the PK profiles in study 20140111, the magnitude of impact was comparable between ABP 710 and US-Remicade (Figure 4). Of note, the geometric mean values for trough concentrations (Ctroughs) of ABP 710 and US-Remicade were comparable between the 2 treatment groups at all time points tested through week 22, with GMR values ranging from 0.91 to 1.05.

Similarly, in the PK comparison by NAb status, Ctroughs of ABP 710 and US-Remicade in NAb-positive were generally lower than NAb negative, but remained comparable between ABP 710 and US-Remicade treatments in each of the subgroups (Figure 5).

Overall, the systemic exposure was lower in patients who were ADA-positive and in patients
who were NAb-positive over the treatment duration of 22 weeks.

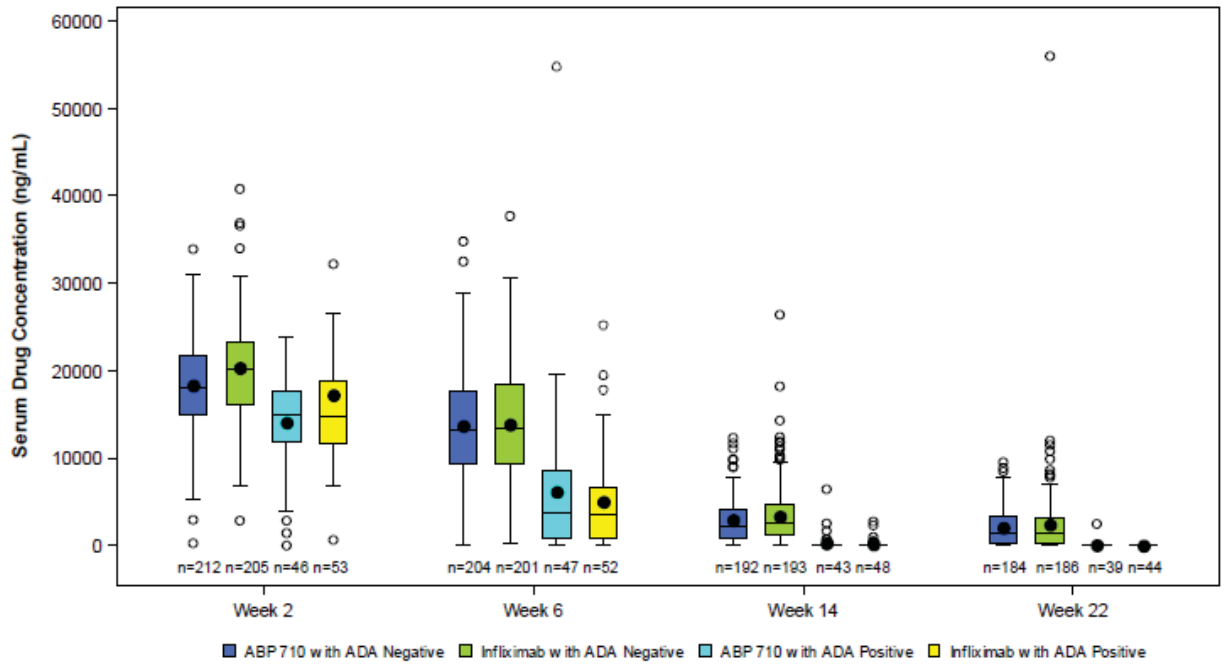


Figure 4. Pre-Infusion Pharmacokinetics by Binding Antibody Status and Visit – Though Week 22 (Study 20140111 Safety Analysis Set)

ADA = antidrug antibody. Note: Boxes show mean (dot), median (line), and 25th (bottom) and 75th (top) percentiles.
Infliximab = US-Remicade
(Source: Summary of Clinical Pharmacology, Figure:4, page 23)

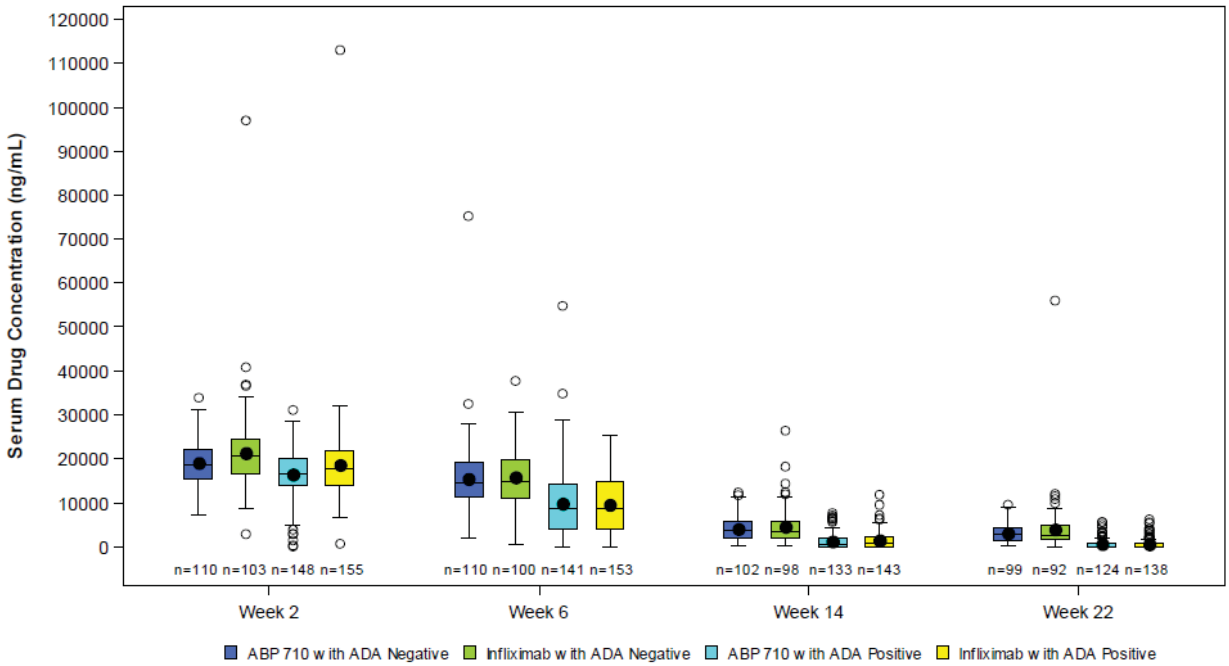


Figure 5. Pre-infusion Pharmacokinetics by Neutralizing Antibody Status and Visit - Through Week 22 (Study 20140111)

ADA = antidrug antibody. Note: Boxes show mean (dot), median (line), and 25th (bottom) and 75th (top) percentiles.
Infliximab = US-Remicade
(Source: Summary of Clinical Pharmacology, Figure:5, page 24)

Impact of ADA and NAb on Efficacy

Overall, no evidence of differences in efficacy between ABP 710 and US-Remicade was observed in RA patients in Study 20140111 who were ADA-positive and who were NAb-positive. While, NAb-positive subjects demonstrated lower efficacy as compared to NAb-negative subjects, the impact on efficacy was comparable between treatment groups (Figure 6).

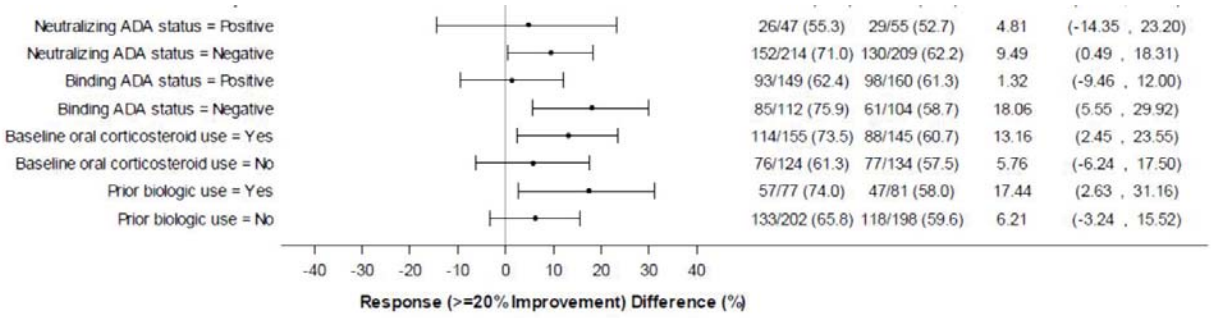


Figure 6. Forest Plot of Response Difference of ACR20 by Subgroup at Week 22 with 95% CIs (ITT Analysis Set With NRI)

(Source: Clinical Study Report 20140111, modified from Figure 10.2, page 81.)

Impact of ADA and NAb on safety

In study 20140108, the safety and immunogenicity profiles for ABP 710, US-Remicade, and EU-Remicade were comparable-.

In study 20140111, the incidence of any treatment-emergent adverse events (TEAEs) was comparable between ABP 710 and US-Remicade treatment groups in both ADA-positive and ADA-negative subgroups and NAb-positive and NAb-negative subgroups (Table 11). Overall, no evidence of altered safety between ABP 710 and US-Remicade was observed in RA patients in Study 20140111 who were ADA-positive.

Table 11. Overall Summary of Adverse Events by ADA and NAb Group - Through Week 22 (Study 20140111)

Adverse Event Category [% (n/N)]	**ABP 710**	US-Remicade
Binding ADA Status: Positive		
Any Treatment-related	26.8% (40/149)	24.4% 39/160

Adverse Events		
Binding ADA Status: Negative		
Any Treatment-related Adverse Events	11.6% (13/112)	16.3 (17/104)
NAb Status: Positive		
Any Treatment-related Adverse Events	38.3% (18/47)	27.3% (15/55)
NAb Status: Negative		
Any Treatment-related Adverse Events	16.4% (35/214	19.6% (41/209)

Note: Only treatment-emergent adverse events are summarized. For each category, subjects are included only once, even if they experienced multiple events in that category.
Infliximab = US-Remicade
(Source: Clinical Study Report, Modified from Table 14-6.1.1.7 to Table 14-6.1.1.8, page 680 to 683)

Authors:

Dipak S. Pisal, MS, PhD
Clinical Pharmacology Reviewer

Ping Ji, PhD
Clinical Pharmacology Team Leader

7 Statistical and Clinical Evaluation and Recommendations

7.1. Statistical and Clinical Executive Summary and Recommendation

Brief Overview of the Clinical Program
The following two controlled studies provided the primary evidence to support the determination of no clinically meaningful differences between ABP 710 and US-Remicade:

- Study 20140108, a single-dose, 3-way, pharmacokinetics (PK) study, assessed the similarity in PK between ABP 710 and US-Remicade.

- Study 20140111, the comparative clinical study, provided comparative efficacy, safety, and immunogenicity data between ABP 710 and US-Remicade in patients with RA. The comparative clinical study was a randomized, double-blind, parallel-group study in which patients were randomized to receive a 3 mg/kg intravenous infusion of either ABP 710 or US-Remicade on day 1 (week 0), at weeks 2 and 6, and every 8 weeks thereafter until week 22. At week 22, subjects initially randomized to US-Remicade were re-randomized to either continue US-Remicade or transition to receive ABP 710 through week 46. Those initially randomized to ABP 710 continued receiving the same treatment through week

46. The applicant chose the indication of RA in this comparative clinical study as RA has been well-studied among the indications treated with anti-TNF monoclonal antibodies. Further, use of US-Remicade in the RA population has been well characterized with regard to PK profile, safety and efficacy. The Agency agrees with the applicant's rationale that the study population is an appropriate population to use in the assessment of no clinically meaningful differences in this context.

Clinical Efficacy Overview and Conclusions

The determination of no clinically meaningful differences between ABP 710 and US-Remicade in terms of efficacy was based on a totality-of-evidence that included results comparing ABP 710 and US-Remicade from Study 20140108, the 3-way PK study, and Study 20140111, the comparative clinical study in patients with RA. In Study 20140111, the proportion of patients achieving ACR20 response at week 22 in ABP 710 and the US-Remicade treatment groups were 68.1% and 59.1%, respectively. The lower bound of the 90% confidence interval for the estimate of treatment difference for ACR20 response was within the lower bound of the agreed similarity margin of -12%, but the upper bound of the confidence interval exceeded the margin of 15%. The results from the primary analysis were reviewed and are discussed in detail in Section 7.3.2. While the estimated difference between the ACR20 response probabilities at week 22 exceeded the upper margin, the additional analyses and evaluations, including analyses of the individual components of the ACR20 response and analysis of key secondary efficacy endpoints, support the demonstration of no clinically meaningful difference (see section 7.1.1 for more detail).

Clinical Safety Overview and Conclusions

Comparative safety was assessed based on the safety database containing a total of 704 subjects who received at least 1 dose of ABP 710 or US-Remicade, including 148 healthy subjects from Study 20140108 and 566 RA patients from Study 20140111. A total of 446 subjects were exposed to ABP 710. The safety review concludes that ABP 710 was similar to US-Remicade with respect to the overall adverse event profile, adverse events of special interest and immunogenicity, supporting the demonstration of no clinically meaningful differences.

Clinical Immunogenicity Overview and Conclusions

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from a single dose PK study) and in RA patients (multiple dose up to 46 weeks). ABP 710 was similar to US-Remicade in regard to the formation of ADA and NAb and their impact on PK, efficacy, and safety. Therefore, the immunogenicity evaluation supports the demonstration of no clinically meaningful differences. Refer to Section 6.4**Error!**

Reference source not found. Error! Reference source not found. for more details and discussion of the results.

Overall Summary and Recommendation

While Study 20140111 in RA patients did not meet its primary objective, because the upper bound of the 90% CI for the estimated difference in ACR20 response between ABP 710 and US-Remicade exceeded the pre-specified upper margin for the 90% confidence interval, this observed difference does not preclude a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade when considered with other information and data provided by the Applicant, including:

1) PK similarity between ABP-710 and US-Remicade as demonstrated in Study 20140108 and described in Section 6
2) No clinically meaningful differences observed regarding safety or immunogenicity in Studies 20140111 and 20140108
3) Additional efficacy analyses of individual ACR components and DAS28, as well as additional supportive post-hoc analyses by the applicant, supported a demonstration of no clinically meaningful differences as described in Section 7.3.2.

7.1.1. Statistical and Clinical Residual Uncertainties Assessment

After discussion with the Agency, the comparative efficacy of ABP 710 and US-Remicade was evaluated based on assessing the 90% confidence interval for the difference between ACR20 response in patients treated with ABP 710 or US-Remicade. The margins for the 90% confidence interval were -12% and +15%. Results from the primary analysis of the comparative clinical study 20140111 met the lower bound of the prespecified margin. The ACR20 90% confidence interval upper bound was 15.96%, slightly exceeding the 15% upper margin. In this section, in consultation with the clinical team, we summarize and discuss this, and other uncertainties. We discuss this finding in the context of the totality of evidence to investigate if this precludes a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade.

The applicant noted that there were several imbalances in the baseline disease severity characteristics between the two treatment groups. To investigate the effect of these differences, the applicant conducted additional post-hoc analyses adjusting for imbalances in the baseline severity between the two treatment groups. Specifically, in addition to the covariates used in the primary analysis, the applicant included all seven baseline values for the ACR components, as well as age, NSAID use, and steroid use. Under this analysis, the estimated difference in ACR20 response rate decreased, and the upper limit of the 90% confidence bound fell within the prespecified margin for three ITT-based analyses. These results help to resolve the concerns raised in the primary

analysis and that the results may be due to chance imbalances in the baseline covariates.

The ACR20 evaluation is a composite measure, consisting of seven components: swollen and tender joint counts, subject and investigator global health assessment, subject pain assessment, a disability questionnaire (HAQ-DI), and serum CRP. Therefore, in interpreting the results from Study 20140111, it is important to assess the components individually and in the context of the overall findings. We assessed the individual components in two ways: first, for each component, we evaluated the difference in the proportion of subjects who had at least a 20% improvement in that component (that is, met the response criteria for that component); and, second, we examined the difference in the average change between the two treatment groups for those components.

In evaluating the difference between treatment arms in the proportion of patients that had at least a 20% improvement, the individual components with the largest observed differences were: subject's assessment of pain (70% ABP 710 vs 61% US-Remicade) followed by the HAQ-DI (62% ABP 710 vs 55% US-Remicade) and tender joint counts (85% ABP 710 vs 81% US-Remicade).

In examining the difference between treatment arms in the average change for these individual components (after adjusting for stratification variables), the differences between the treatment groups were relatively small, with the exception of the change in CRP. For example, for the subject's assessment of pain, there was a mean reduction of 25 and 31 points in the average reported pain for US-Remicade and ABP 710, respectively. After adjustment for stratification variables, there was an estimated treatment difference of only 4 points, which is relatively small compared to the 25 point change from baseline on the 0 to 100 mm VAS seen within the US-Remicade arm. As noted above, the difference in CRP was relatively larger than the difference seen for the other components. However, given the high variability in subject baseline and post-treatment CRP, this difference in absolute change in CRP between the ABP 710 and US-Remicade groups is not considered clinically meaningful.

The applicant also included data for ACR20, ACR50 and ACR70 response rates at several pre-specified weeks in the study (Weeks 2, 6, 14, and 22) and change from baseline in the Disease Activity Score – C-reactive Protein (DAS-28 CRP) endpoint over the same weeks. There were no pre-specified margins for these secondary endpoints. For the ACR20 response rates at timepoints other than Week 22, the 90% CI for the differences between ACR20 response in ABP 710 and US-Remicade were smaller than for Week 22 and contained within the (-12%, +15%) margin defined for the primary endpoint. For both the ACR50 and ACR70 response rates, consistent with the results of the ACR20 analyses, patients receiving ABP 710 responded at higher rates at the majority of the timepoints up to Week 22. For DAS-28, there were minimal differences in the change in scores between treatment groups. While a similarity margin for DAS-28 has not been

predetermined for US-Remicade, a margin of (-0.5, +0.5) has been used by the Agency to support approval of other biosimilar products,[3] and, here, the most extreme DAS score values for the confidence intervals fell between -0.22 and 0.17. Thus, the DAS28 provides further support for a conclusion of no clinically meaningful differences.

Given the PK similarity of ABP 710 and US-Remicade, along with the absence of safety or immunogenicity differences, the higher ACR response rates and improvements in ACR components observed with ABP 710 in comparison to US-Remicade in Study 20140111 likely occurred due to chance, as opposed to reflecting a notable increase in potency of the proposed biosimilar product. Additionally, the comparative analytical assessment is also consistent with this conclusion. Furthermore, the inconsistency in the differences observed in ACR versus DAS-28 responses, despite the fact that similar concepts are captured by these outcome measures, suggests that any observed differences are likely due to the construction of the different outcome measures used in the study and are not considered a clinically meaningful difference. In summary, slightly exceeding the upper bound for ACR20 prespecified margin does not preclude a finding of no clinically meaningful differences, and Study 20140111, in combination with the totality of data, supports the overall conclusion of no clinically meaningful differences between ABP 710 and US-Remicade.

7.2. Review Strategy

The focus of this review is the two comparative controlled clinical studies, 20140108 and 20140111, conducted to support the determination that there are no clinically meaningful differences between ABP 710 and US-Remicade. Comparative efficacy of ABP 710 and US-Remicade was assessed in Study 20140111, the comparative clinical study, comparing ABP 710 with U.S.-Remicade in patients with RA. Comparative efficacy was not assessed in Study 20140108, a 3-way PK similarity study between ABP 710, US-Remicade, and EU-Remicade. An analysis of the comparative PK data can be found in the clinical pharmacology Section 6 by Dr. Dipak Pisal, PhD.

7.3. Review of Comparative Clinical Studies with Statistical Endpoints

7.3.1. 20140108 – ACTRN12614000903684

Study 20140108 was conducted to determine the PK similarity of ABP 710 to US-Remicade in healthy adult subjects. The first subject was enrolled on November 6, 2014 and concluded on February 14, 2015. The study was conducted in Australia at two clinical sites: (b) (4) . The final study report was submitted July 29, 2015.

[3] See, e.g., page 14
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761088Orig1s000ODMemo.pdf

Study Design and Endpoints

Study 20140108 was a randomized (1:1:1), single-blind, single-dose, 3-arm, parallel-group comparative PK study of ABP 710, US-Remicade, and EU-Remicade administered IV to healthy volunteers. The study design is depicted in Figure 1 in Section 6.

Key inclusion criteria for healthy male and female subjects were:

- Age between 18 to 45 years, inclusive
- Body mass index (BMI) between 18.0 and 30.0 kg/m2, for non-Japanese subjects
- Body mass index (BMI) between 18.0 and 25.0 kg/m2, for Japanese subjects
- Clinically normal physical examination, laboratory test results, vital signs, electrocardiograms (ECGs) at screening, urinalysis, urine drug screen, alcohol screen
- Negative pregnancy test
- Up-to-date immunizations per local standards
- To be enrolled as a Japanese subject, subjects were either first- or second-generation Japanese:
    - First-generation Japanese were subjects who were living outside of Japan but were born in Japan to parents of Japanese descent
    - Second-generation Japanese were subjects who were born outside of Japan to first-generation Japanese parents

Key exclusion criteria were:

- Women of childbearing potential or men of reproductive potential who were unwilling to practice a highly effective method of birth control for the duration of the study and for 6 months following treatment
- Breastfeeding
- Positive pregnancy test or planning to become pregnant during the study
- Men who were unwilling to refrain from donating sperm during the study
- Men with pregnant partners

- History or evidence of a clinically-significant disorder (including psychiatric), condition, or disease that, in the opinion of the investigator and Amgen medical monitor or designee, posed a risk to subject safety or interfered with the study evaluation, procedures, or completion

- History or presence of conditions known to interfere with the distribution, metabolism, or excretion of drugs

- Evidence of any bacterial, viral, parasitic, or systemic fungal infections within the past 30 days prior to investigational product administration (e.g., upper respiratory tract infection, viral syndrome, flu-like symptoms)

- Evidence of recent (within 6 months) infection requiring in-patient hospitalization or IV antibiotics

- History of known positive tuberculin skin test or exposure to an individual with tuberculosis or positive QuantiFERON test (or equivalent) consistent with previous exposure to tuberculosis prior to or during the screening period (if not treated with appropriate chemoprophylaxis)

- Tuberculosis or fungal infection seen on chest x-ray taken within 6 months of screening or during the screening period

- History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study

- History of malignancy of any type other than surgically excised non-melanomatous skin cancers, within 5 years prior to randomization

- Any investigational drug within the 30 days or 5 half-lives (whichever was longer), prior to receiving investigational product

- Use of any over-the-counter (OTC) or prescription medications within the 14 days or 5 half-lives (whichever was longer) prior to receiving investigational product

- All herbal medicines (e.g., St. John's wort) and supplements consumed by the subject within the 30 days prior to receiving investigational product, and continuing use if applicable, were reviewed by the investigator and the ICON Medical Monitor

- Received live vaccines ≤ 1 month prior to investigational product administration or were planning to receive a vaccine during the study

- Prior exposure to infliximab or related compounds

- Known or suspected sensitivity to products derived from mammalian cell lines
- Known or suspected sensitivity to premedication
- Donated blood (including blood products) or experienced loss of blood ≥ 500 mL within 2 months of screening
- Positive screen for alcohol and/or potential drugs of abuse (urine drug screen) at screening or prior to randomization
- Positive screen for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV)
- History of alcohol and/or substance abuse within the last 12 months prior to screening
- Subjects who used > 10 cigarettes per day within the last 3 months or were not able to abide by the smoking policy of the site
- Inability or unwillingness to reside at the CPU for 3 consecutive days (2 nights) or inability to be available for follow-up assessments or protocol-required procedures

The primary endpoint of study 20140108 was to determine the PK similarity as assessed by AUC from time 0 extrapolated to infinity (AUC_{inf}) of ABP 710 following a 5 mg/kg intravenous (IV) infusion relative to that of a 5 mg/kg IV infusion of US-Remicade or a 5 mg/kg IV infusion of EU-Remicade.

The secondary endpoints of study 20140108 were:

- to determine PK similarity as assessed by AUC_{inf} of a 5 mg/kg infusion of US-Remicade relative to a 5 mg/kg IV infusion of EU-Remicade
- to determine safety, tolerability, and immunogenicity of ABP 710 in healthy adult subjects compared with US-Remicadeand EU-Remicade.

Subjects were admitted to the CPU on the day prior to infusion. The schedule of assessments is shown in **Table 12**.

Table 12. Schedule of Assessments and Procedures for Study 20140108

Study Day[a]	Screening -28 to -2	-1[b]	1						2	3	8	15	22	36	50	EOS[c] 57
Nominal Times (h)			predose	0	1	2	4	8	12	24	48	168	336	504	840	1176	1344
Residency		→	→	→	→	→	→	→	→	→							
Medical History	X																
Physical Examination	X	X								X							X
Vital Signs	X	X	X		X	X	X			X	X	X	X	X	X	X	X
Body Weight, BMI	X	X[d]															X
Body Height	X																
Electrocardiogram	X		X[e]			X											X
Hematology	X	X								X		X	X		X		X
Chemistry	X	X								X		X	X		X		X
Pregnancy Test	X	X															X
Urinalysis	X	X															X
Serology[f]	X																
TB Test[g]	X																
Chest X-ray[h]	X																
Alcohol Screen	X	X															
Urine Drug Screen	X	X															
Premedications[i]			X														
Investigational Product/Comparator Administration				X													
Antidrug Antibodies			X[j]									X		X		X	
Pharmacokinetic Sampling			X			X[k]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events				→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious Adverse Events	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant Medications	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

Statistical Methodologies

The statistical methodologies are described in detail in Section 6.3 in the clinical pharmacology evaluation.

Subject Disposition

A total of 150 subjects were randomized (1:1:1) to receive 1 dose (IV infusion) at a dose of 5 mg/kg of:

- ABP 710
- EU-Remicade
- US-Remicade

Demographics and Baseline Characteristics

Healthy male and female subjects of normal body mass index (BMI). Baseline demographics are outlined in Table 13. The baseline demographics were fairly balanced across treatment groups. The mean age ranged from 26-27 years, with a majority white (68-71%) female (50-65%).

Table 13. Demographic and Baseline Physical Characteristics in Study 20140108

Characteristic	ABP 710 (N=49)	EU-Remicade (N=49)	US-Remicade (N=50)
Sex [n (%)]			

Female	25 (51.0)	32 (65.3)	25 (50.0)
Male	24 (49.0)	17 (34.7)	25 (50.0)
Race [n (%)]			
White	35 (71.4)	34 (69.4)	34 (68.0)
Black or African American	0 (0.0)	1 (2.0)	0 (0.0)
Asian	12 (24.5)	13 (26.5)	13 (26.0)
Hawaiian or other Pacific Islander	1 (2.0)	0 (0.0)	0 (0.0)
Ethnicity [n (%)]			
Hispanic or Latino	4 (8.2)	2 (4.1)	1 (2.0)
Not Hispanic or Latino	45 (91.8)	47 (95.9)	49 (98.0)
Age (years)			
Mean (SD)	27.4 (6.0)	26.3 (5.7)	25.8 (5.8)
Median	28.0	25.0	24.0
Min, Max	18, 44	18, 43	18, 45
Age group [n (%)]			
< 65 years	49 (100)	49 (100)	50 (100)
≥ 65 years	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)			
Mean (SD)	69.0 (13.8)	64.6 (12.4)	71.2 (12.3)
Median	68.5	62.5	69.6
Min, Max	44.9, 154.0	44.8, 139.0	44.8, 139.0
Height (cm)			
Mean (SD)	171.8 (9.3)	167.3 (11.0)	171.7 (8.3)
Median	172.0	166.0	171.0
Min, Max	150.0, 192.0	150.0, 192.0	151.0, 190.0
BMI (kg/m^2)			
Mean (SD)	23.2 (2.98)	22.9 (2.48)	24.0 (2.98)
Median	22.7	22.4	23.4
Min, Max	18.8, 29.6	18.6, 29.0	18.3, 29.4

Source: Study 20140108 CSR, Table 10.4; clinical reviewer verified using JMP and ADSL dataset by TRT01A.

Analysis of Clinical Endpoint(s)

The clinical endpoints and corresponding analyses are discussed in detail in section 6 in the clinical pharmacology evaluation.

7.3.2. 20140111 – NCT02937701

Study 20140111 was a randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of ABP 710 5mg/kg compared to US-Remicade.

Study Design and Endpoints

Study Design

This study was a randomized, double-blind, active-controlled comparative efficacy study in adult patients with moderate to severe RA who have an inadequate response to methotrexate (MTX). Patients were randomized in a 1:1 ratio to receive either ABP 710 3mg/kg infusion or US-Remicade 3 mg/kg. Infusions were on days 1, weeks 2 and 6, and every 8 weeks thereafter until week 22.

At week 22, patients who remained in the study and were initially randomized to the US-Remicade treatment group were re-randomized in a 1:1 ratio to either continue receiving US-Remicade every 8 weeks or switch to ABP 710 every 8 weeks. Patients continued to receive infusions every 8 weeks until Week 46 when they received their final infusion. Patients then completed a 4-week efficacy, safety, and immunogenicity follow-up period. The study design is depicted in Figure 3 in Section 6.3.

Reviewer Comment: The study design, duration, dose, and study population are acceptable.

Study Location

The study was conducted at a total of 82 sites with 75 sites that randomized patients into the study. The enrollment by country is summarized in Table 14.

Table 14: Enrollment by Country

Country	ABP 710 (N=279)	US-Remicade (N=279)	Total (N=558)
Australia	5 (1.8%)	4 (1.4%)	9 (1.6%)
Bulgaria	14 (5.0%)	11 (3.9%)	25 (4.5%)
Canada	2 (0.7%)	1 (0.4%)	3 (0.5%)
Czech Republic	52 (18.6%)	49 (17.6%)	101 (18.1%)
Germany	15 (5.4%)	11 (3.9%)	26 (4.7%)
Hungary	7 (2.5%)	14 (5.0%)	21 (3.8%)
Poland	125 (44.8%)	133 (47.7%)	258 (46.2%)
Spain	7 (2.5%)	4 (1.4%)	11 (2.0%)
United States	52 (18.6%)	52 (18.6%)	104 (18.6%)

Source: Study 20140111 CSR, Table 14-1.2.1; clinical reviewer verified using JMP and ADSL dataset by TRT01A.

Study Population

Subjects aged 18 to 80 years of age with moderate to severe RA disease and refractory response to methotrexate were defined by the following criteria:

- RA as determined by meeting the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria for RA
- RA duration of at least 3 months
- ≥ 6 swollen joints and ≥ 6 tender joints at screening and baseline AND
    - Erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr OR
    - C-reactive protein (CRP) > 1.0 mg/dL
- Positive rheumatoid factor (RF) OR anti-cyclic citrullinated peptide (CCP) at screening
- Methotrexate use for ≥ 12 consecutive weeks and stable dose of oral or subcutaneous methotrexate 7.5 to 25 mg/week for ≥ 8 weeks before receiving study drug and duration of the study
- Stable dose of concomitant NSAIDs and low-potency analgesics (e.g., tramadol, Soma Compounds, Fioricet, or Fiorinal) for ≥ 2 weeks before screening , if applicable
- Stable dose of concomitant oral corticosteroids (≤ 10 mg prednisone or equivalent) for ≥ 4 weeks before screening, if applicable
- No known history of active tuberculosis

Subjects were excluded for RA related disease such as Class IV RA, Felty's syndrome, or history of prosthetic or native joint infection. Other key exclusion criteria included medical conditions, including infectious diseases and malignancies, and certain laboratory abnormalities. Furthermore, washouts and/or nonpermitted drugs are outlined as follows:

- Use of any of the following within 28 days before the first dose of study drug:
    - intra-articular (IA) hyaluronic acid injections
    - intramuscular (IM), IA, or IV corticosteroids, including adrenocorticotropic hormone
- Use of any nonbiologic DMARDs other than MTX within 28 days prior to first dose except:
    - leflunomide (unless an active washout with cholestyramine has been performed), cyclosporine, azathioprine, tacrolimus within 3 months
    - intramuscular or oral gold within 6 months
    - cytotoxic agents such as cyclophosphamide, D-penicillamine within 6 months
    - intravenous gamma-globulin or Prosorba column therapy within 3 months
    - Janus kinase inhibitor within 28 days
- Prior use of 2 or more distinct biologic therapies for RA
- Prior use of commercially available or investigational biologic therapies for RA as follows:
    - anakinra, etanercept within 1 month
    - abatacept, tocilizumab, adalimumab, golimumab, certolizumab within 3 months

    - other experimental or commercially available biologic therapies for RA within 3 months or 5 half-lives
    - rituximab within 9 months
- Received live vaccines within 28 days
- Chronic use of high potency narcotic analgesics
- Previous use of infliximab or biosimilar to infliximab

Study Treatments

- ABP 710 (biosimilar candidate to US-Remicade) 3 mg/kg infusion given on day 1, weeks 2 and 6, and every 8 weeks thereafter
- US-Remicade 3 mg/kg infusion given on day 1, weeks 2 and 6, and every 8 weeks thereafter

Eligible subjects were randomized in a 1:1 ratio to receive either ABP 710 or US-Remicade. Randomization was stratified based on prior biologic use (yes vs. no) and geographic region (Asia Pacific, Europe, North America).

Administrative structure

Subjects were randomly assigned at baseline (day 1) to receive ABP 710 or US-Remicade. In both treatment groups, doses were administered by study staff per the study design schedule described above. Premedications were required and were selected according to local practice and/or the approved product label for US-Remicade. In general, the premedications included acetaminophen and an antihistamine as well as methylprednisone 100 mg IV or equivalent approximately 30 minutes before each infusion. The definition of rescue medication was any medication other than the prohibited medication that is used to treat RA. The use of rescue medication was allowed during the study under the following conditions:

- Oral corticosteroids, up to a maximum dose of 10 mg prednisone (or equivalent), per the investigator's clinical judgment
- Acetaminophen, hydrocodone, codeine, tramadol, and/or propoxyphene were allowed as rescue analgesics, but not within 12 hours before clinical efficacy assessments
- NSAIDS and cyclooxygenase-2 (COX-2) inhibitors were allowed if the subject entered the study taking these medications. In case of flare, the subjects were allowed to temporarily increase the dose as needed given they returned to maintenance dose after resolution of the flare
- Topical anesthetic creams were permitted granted the agents were not applied within 12 hours prior to clinical efficacy assessment.

The schedule of assessments and procedures performed at each study visit is outlined in Table 15.

Table 15. Schedule of Assessments and Procedures

	Screening (≤ 28 days)	Baseline Day 1	Week 2	6	14	22	30	34	38	46	50/EOS[a]
Windows (day[s])			±2	±3	±3	±3	±5	±5	±5	±5	±5
Clinical Assessments/Procedures											
Informed consent	X										
Medical/treatment history	X										
Physical examination	X					X					X
Height	X										
Weight[b]	X	X	X	X	X	X	X		X	X	
Vital signs pre and post infusion (BP, pulse, RR, and temp)[c]	X	X	X	X	X	X	X		X	X	X
12-lead ECG	X										
Chest radiography	X[d]										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X[e]	X	X	X	X	X	X	X	X	X	X
Treatment											
Randomization		X				X					
ABP 710/infliximab		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		X[f]	X[f]	
Disease Assessment											
Joint assessments	X	X	X	X	X	X	X	X	X	X	X
Subject's assessment of pain	X	X	X	X	X	X	X	X	X	X	X
Subject's Global Health Assessment		X	X	X	X	X	X	X	X	X	X
Investigator's Global Health Assessment		X	X	X	X	X	X	X	X	X	X
HAQ-DI		X	X	X	X	X	X	X	X	X	X
Laboratory Assessments											
Tuberculosis testing[g]	X										
Serology (HBsAg, hepatitis B core antibody, HCV)	X										
Serum chemistry	X[h]	X	X	X	X	X		X			X
Hematology	X	X	X	X	X	X	X	X	X	X	X
CRP[i]	X	X	X	X	X	X	X	X	X	X	X

	Screening (≤ 28 days)	Baseline Day 1	Week 2	6	14	22	30	34	38	46	50/EOS[a]
Pharmacokinetic samples[j]		X	X	X	X	X	X	X	X		X
Antidrug antibodies[k]		X	X	X	X	X	X	X	X		X
Urinalysis	X					X		X			X
Pregnancy[l]	X	X		X		X		X		X	X

Source: Modified from applicant's clinical study report: 20140111; p41-42 of 90.

Efficacy Endpoints

The primary endpoint is the response difference of 20% improvement in ACR core set measurements (ACR20) at week 22. To achieve ACR20 response, subjects need to report at least 20% improvement in both swollen joint count with 66 joints (SJC66) and tender joint count with 68 joints (TJC68), as well as 20% improvement in at least 3 out of the following 5 additional parameters:

- Subject's Global Health Assessment on a 100-mm visual analogue scale (VAS)
- Investigator's Global Health Assessment on a 100-mm VAS
- Subject's assessment of pain (on a 100-mm VAS)
- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- Serum C-Reactive Protein (CRP)

The secondary endpoints are:

- Response difference of ACR20 at weeks 2, 6, 14, 30, 34, 38, 46, and 50
- Response differences of at least 50% improvement (ACR50) and at least 70% improvement (ACR70) in ACR core set measurements at weeks 2, 6, 14, 22, 30, 34, 38, 46, and 50.
- Disease activity score in 28 joints – C-reactive protein (DAS28-CRP) change from baseline at weeks 2, 6, 14, 22, 30, 34, 46, and 50.

ACR50 and ACR70 are defined in a similar fashion to ACR20, with at least 50% or 70% improvement in SJC66 and TJC68 required, along with 50% or 70% improvement in at least 3 out of the 5 parameters listed above (i.e., HAQ-DI, CRP, Global Health Assessments, pain).

DAS28 is a composite measure of disease activity that is commonly evaluated in RA. It is a continuous measure based on 28 selected joints from the ACR, the subject's Global Health Assessment score and either CRP or erythrocyte sedimentation rate (ESR). The applicant used the CRP version which is given by the following formula:

$$\text{DAS28-CRP} = 0.56 * (\text{TJC28})^{0.5} + 0.28 * (\text{SJC28})^{0.5} + 0.36 * \ln(\text{CRP} + 1) * 0.014 * \text{GH} + 0.96,$$

where TJC28 is the tender joint count of the 28 joints in the DAS, SJC28 is the swollen joint count of the 28 joints in the DAS, CRP is in mg/L, and GH is the Subject's Global Health Assessment on a 0 to 100 scale.

In a post-hoc analysis the applicant evaluated a continuous version of the usual ACR criteria, entitled the Hybrid-ACR score using the algorithm described by Felson et. al. in 2007[4]. This endpoint is not typically used. As this endpoint has not been evaluated in the previous studies, the contextual information needed to assess the clinical meaningfulness of those results is unavailable. As sufficient data is available from the primary and secondary endpoints, we do not consider this exploratory endpoint to be informative nor necessary to draw a conclusion, and therefore, will not be discussed further.

Subject completion, discontinuation, withdrawal

Subjects were considered study completers for the initial randomization phase if they completed the Week 22 assessments. The statistical methods for handling missing data are described in detail in the Statistical Methodologies section below.

Statistical Methodologies

This study was designed to test if the 90% confidence interval of the difference in the ACR20 response rate for ABP710 compared with US-Remicade falls within a pre-specified similarity margin. The comparison to the similarity margin consists of two parts, (1) the lower bound of the confidence interval for the difference between products and (2) the upper bound of the confidence interval for the difference between products.

[4] Felson, D., & American College of Rheumatology Committee to Reevaluate Improvement Criteria. (2007). A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. Arthritis Care & Research, 57(2), 193-202. doi:10.1002/art.22552

In March 2015, the Agency recommended a similarity margin of (-12%, +12%) with a 90% confidence interval for the risk difference, which was based on meta-analyses of historical effects of adalimumab[5] and discussions with clinicians weighing the clinical importance of different losses in effect against the feasibility of different study sizes. The studies and the meta-analyses that the Agency based their recommendation on are shown below in Table 16. The +/- 12% margin was originally recommended to preserve at least half of the effect of US-Remicade. The Agency also stated that a relaxed upper bound of +15% could be used if an adequate justification was provided.

Table 16. Historical Effect of Infliximab on ACR20 Response in Randomized Clinical Trials of Patients with Active RA Despite Treatment with Methotrexate (MTX)

Study	Week	MTX + Placebo		MTX + Infliximab		Difference in % Response
		N	% Response	N	% Response	
Maini et al.[6]	30	88	20%	86	50%	30%
Westhovens et al.[7]	22	361	24%	360	55%	31%
Schiff et al.[8]	28	110	42%	165	59%	18%
Zhang et al.[9]	18	86	49%	87	76%	27%
Abe et al.[10]	14	47	23%	49	61%	38%
Meta-Analysis (fixed effects[11]): Difference (95% CI)						28.4% (23.6%, 33.3%)
Meta-Analysis (random effects[12]): Difference (95% CI)						28.3% (22.6%, 34.1%)
Heterogeneity p-value						0.3

Source: Meeting Minutes from March 2, 2015 BPD Type 2 Meeting.

[5] References to unknown sources of infliximab (e.g., based on historical studies) will use infliximab.
[6] Maini, R., St Clair, E. W., Breedveld, F., Furst, D., Kalden, J., Weisman, M., ... & ATTRACT Study Group. (1999). US-Remicade (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. The Lancet, 354(9194), 1932-1939.
[7] Westhovens, R., Yocum, D., Han, J., Berman, A., Strusberg, I., Geusens, P., & Rahman, M. U. (2006). The safety of US-Remicade, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis & Rheumatism, 54(4), 1075-1086.
[8] Schiff, M., Keiserman, M., Codding, C., Songcharoen, S., Berman, A., Nayiager, S., ... & Dougados, M. (2008). Efficacy and safety of abatacept or US-Remicade vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Annals of the rheumatic diseases, 67(8), 1096-1103.
[9] ZHANG, F. C., Hou, Y., Huang, F., WU, D. H., BAO, C. D., NI, L. Q., & YAO, C. (2006). US-Remicade versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. APLAR Journal of Rheumatology, 9(2), 127-130.
[10] Abe, T., Takeuchi, T., Miyasaka, N., Hashimoto, H., Kondo, H., Ichikawa, Y., & Nagaya, I. (2006). A multicenter, double-blind, randomized, placebo controlled trial of US-Remicade combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. The Journal of rheumatology, 33(1), 37-44.
[11] Based on Mantel-Haenszel weights.
[12] Based on DerSimonian-Laird approach.

In May 2016 the applicant provided their justification for the asymmetric margin. They stated that a margin of 15% would preserve approximately 2/3 of the lower 95% confidence bound of the treatment effect ($2/3 * 23.6\% \approx 15.7\%$) instead of 1/2 which was used for the lower bound. FDA agreed that this asymmetric margin was reasonable.

In the first randomization, subjects were randomized in a 1:1 ratio to receive either ABP 710 and US-Remicade. This randomization was stratified on geographic region (Asia Pacific, Europe and North America) and prior biologic use (yes/no). Subjects receiving US-Remicade at Week 22 and who were willing to continue in the study were randomized in a 1:1 ratio to either continue receiving US-Remicade or switch to ABP 710.

The applicant analyzed the primary endpoint, ACR20 at Week 22, using the Mantel-Haenszel method to obtain the point estimate of the difference in the ACR20 response rate and the stratified Newcombe method to obtain the related confidence intervals. Both of these methods adjusted for the stratification factors, i.e., geographic region and prior biologic use. For the primary analysis, subjects with missing visits were imputed as non-responders (abbreviated as NRI). The primary analysis population for this study was the intention-to-treat (ITT) analysis set, which was defined as all subjects randomized into the study and was analyzed based on the randomized treatment assignment.

The applicant conducted several additional analyses to examine the reliability of the conclusion under different missing data analysis assumptions, analysis methods, and population definitions. These analyses were:

- ITT analysis set, using only available observed outcomes
- ITT analysis set with last-observation carried forward (LOCF) imputation
- ITT analysis set with non-responder imputation (NRI) using a generalized linear model
- ITT analysis set, as observed using a repeated measures analysis.
- Per Protocol (PP) analysis set, as observed.
  The PP analysis set was defined as all subjects randomized in the study who have completed the specified treatment period and did not experience a protocol deviation that affected their evaluation for the primary objective of the study and was based on the actual treatment.

In addition, a tipping point analysis was performed where the missing data were imputed using varying assumed response rates to try to identify if and where the conclusion of the study changes. The analysis was based on the primary analysis model.

After unblinding the study, the applicant noted that there were several imbalances in the baseline disease status. To examine the effects of these imbalances the applicant conducted a post-hoc analysis which adjusted for the baseline values of the covariates.

The applicant used a non-parametric analysis of covariance method[13] which included the variables used in the original analysis (treatment, stratification variables) and added the baseline tender joint count, swollen joint count, subject's global health assessment, investigator's global health assessment, subject's global assessment of disease related pain, HAQ-DI, CRP, age, use of oral corticosteroid (yes/no), and use of NSAID (yes/no). The statistical reviewer performed similar parametric analyses using a logistic regression model which included the same set of variables.

The applicant analyzed the DAS28-CRP using the analysis of covariance (ANCOVA) method. The dependent variable was the change from baseline and the independent variables were treatment, baseline DAS28-CRP and the stratification variables, geographic region and prior biologic use.

Protocol Amendments

The protocol was amended once after initiation of the study, in March 2017. The changes to the protocol are summarized below:

- Clarify the premedication requirement.
- Specify that subjects who are unable to make the week 22 visit within the allowed window are discontinued from the study. These subjects should return for an end of study visit to complete the end-of-study assessments within 28 days, if possible.
- Specify that restrictions on pre-assessment analgesics apply to the baseline visit, in addition to subsequent on-treatment visits, and to clarify the restrictions.
- Specify that joint assessments at the baseline visit be performed before randomization.
- Require that subjects who cannot complete the screening procedures within 28 days before baseline will be considered screen failures. These subjects can be rescreened, and they may be rescreened under the same informed consent form if rescreening occurs within 30 days.
- Remove "adverse events" from the list of examples of "Reasons for removal of a subject from the study." Subjects who discontinue treatment because of adverse events are encouraged to stay on study for continued assessment.
- Emphasize that post-treatment PK samples are required to be collected within 10 minutes after the end of infusion.
- Specify that 95% confidence intervals (CIs), in addition to 90% CIs, will be presented for efficacy endpoints.
- Clarify the inclusion and exclusion criteria.

[13] Koch GG and Tangen CM. Nonparametric analysis of covariance and its role in noninferiority clinical trials. Drug Inf J. 1999;33:1145-1159
Koch GG, Tangen CM, Jung JW, Amara IA. Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and nonparametric strategies for addressing them. Stat Med. 1998;17(15-16):1863-1892.
Dmitrienko A, Koch GG. Analysis of Clinical Trials Using SAS®, A Practical Guide. 2nd ed. Cary, NC: SAS Institute Inc; 2017.

- Minor editorial corrections and clarifications were made. These changes are not included in the summary below.

Reviewer comment: The modifications are reasonable.

Subject Disposition

The first period disposition in the study is shown in Table 17. There do not appear to be any notable imbalances between the two treatment arms.

Table 17. Investigational Product Disposition Initial Randomization

Variable	ABP 710 n (%)	US-Remicade n (%)
Randomized	279	279
Treated	278 (99.6)	278 (99.6)
Discontinued study prior to Week 22	15 (5.4)	20 (7.2)
Reason for study discontinuation prior to Week 22		
Adverse event	5 (1.8)	10 (3.6)
Consent withdrawn	5 (1.8)	4 (1.4)
Patient dissatisfied with treatment efficacy	2 (0.7)	4 (1.4)
Protocol violation	1 (0.4)	1 (0.4)
Death	1 (0.4)	1 (0.4)
Other	1 (0.4)	0
Discontinued IP prior to Week 14†	21 (7.5)	18 (6.5)
Reason for discontinuation of IP prior to Week 14		
Adverse event	7 (2.5)	9 (3.2)
Consent withdrawn for treatment	5 (1.8)	4 (1.4)
Patient dissatisfied with treatment efficacy	3 (1.1)	3 (1.1)
Protocol violation	2 (0.7)	1 (0.4)
Death	1 (0.4)	1 (0.4)
Physician decision	1 (0.4)	0
Lost to follow-up	1 (0.5)	0
Other	1 (0.4)	0

Source: Clinical Study Report, Table 9-2 and FDA Statistical Reviewer
IP: investigational product
† Week 14 = final scheduled treatment in Phase 1 of the study.

Demographics and Baseline Characteristics

The baseline demographic and physical characteristics are shown in Table 18. There do not appear to be any major differences between the two treatment arms.

Table 18. Demographic and Baseline Physical Characteristics by Initial Treatment

Characteristic	ABP 710 (N=279)	US-Remicade (N=279)
Sex [n (%)]		
Female	214 (76.7)	223 (79.9)
Male	65 (23.3)	56 (20.1)
Race [n (%)]		
White	265 (95.0)	267 (95.7)
Black or African American	12 (4.3)	12 (4.3)
Asian	2 (0.7)	0 (0.0)
Ethnicity [n (%)]		
Hispanic or Latino	18 (6.5)	13 (4.7)
Not Hispanic or Latino	261 (93.5)	266 (95.3)
Age (years)		
Mean (SD)	55.0 (11.7)	54.8 (11.4)
Median	57.0	57.0
Min, Max	23, 77	19, 77
Age group [n (%)]		
< 65 years	217 (77.8)	217 (77.8)
≥ 65 years	62 (22.2)	62 (22.2)
Weight (kg)		
Mean (SD)	76.9 (18.7)	77.9 (18.4)
Median	74.0	74.0
Min, Max	44.9, 154.0	44.8, 139.0
Height (cm)		
Mean (SD)	166.0 (9.4)	166.0 (8.6)
Median	165.0	164.0
Min, Max	135.0, 191.0	142.0, 188.0
BMI (kg/m^2)		
Mean (SD)	27.8 (6.14)	28.4 (6.35)
Median	26.9	27.4
Min, Max	17.1, 56.7	16.7, 52.1

Source: Clinical Study Report, Table 9-3
SD: Standard Deviation

The baseline disease characteristics are shown in Table 19. As noted by the Applicant, there appear to be some differences between the two treatment arms in the duration of RA, the median swollen joint counts, median c-reactive protein and median methotrexate use at baseline. The average duration of RA was roughly four months longer for ABP 710 than for the US-Remicade group, and the median swollen joint counts, baseline CRP, and baseline methotrexate dose were all larger for ABP 710 than for the US-Remicade group. The applicant performed several post-hoc analyses which

considered the impact of baseline imbalances by adjusting for the baseline values of the ACR20 components. The results of these analyses are shown in Table 21 and discussed in subsequent sections.

In addition, there were discrepancies between the actual prior biologic use data (reported in Table 19) and the biologic use data used for the stratified randomization. These discrepancies affected 18 subjects total (9 per treatment arm). Given the relatively small number of patients affected, these discrepancies were not considered to be an issue.

Table 19. Baseline Disease Characteristics by Initial Treatment (ITT Analysis Set)

Characteristic	ABP 710 (N=279)	US-Remicade (N=279)
Prior biologic use for RA [n (%)]‡		
Yes	77 (27.6)	81 (29.0)
No	202 (72.4)	198 (71.0)
Duration of RA (years)		
Mean (SD)	8.7 (7.9)	8.3 (7.6)
Median	7.0	6.0
Min, Max	0.35, 45.0	0.29, 39.0
Duration for RA category [n (%)]		
< 5 years	104 (37.3)	123 (44.1)
≥ 5 years	175 (62.7)	156 (55.9)
DAS28-CRP		
N	268	267
Mean (SD)	5.59 (0.90)	5.60 (0.89)
Median	5.56	5.54
Min, Max	1.77, 7.78	3.46, 8.18
Swollen joint counts (66)		
Mean (SD)	14.6 (8.1)	14.7 (8.8)
Median	13.0	11.2
Min, Max†	0, 50	6, 57
Tender joint count (68)		
Mean (SD)	23.1 (12.2)	23.8 (13.4)
Median	21	21
Min, Max†	4, 64	6, 68
Subject Global Health Assessment		
Mean (SD)	65.4 (18.1)	64.1 (20.0)
Median	67.0	67.0
Min, Max	18.1, 100.0	20.0, 99.0
Investigator Global Health Assessment		
Mean (SD)	64.5 (15.9)	64.1 (15.8)

Characteristic	ABP 710 (N=279)	US-Remicade (N=279)
Median	65	66
Min, Max	13, 98	21, 98
Subject's Assessment of Disease-related Pain		
Mean (SD)	63.5 (20.3)	61.5 (21.7)
Median	67	65
Min, Max	9, 100	2, 100
HAQ-DI		
Mean (SD)	1.44 (0.58)	1.42 (0.62)
Median	1.5	1.5
Min, Max	0, 2.75	0, 3.0
CRP (mg/L)*		
Mean (SD)	14.3 (20.2)	14.6 (23.1)
Median	7.5	6.6
Min, Max	1, 150	1, 184
Use of oral corticosteroid at baseline [n (%)]		
Yes	155 (55.6)	145 (52.0)
No	124 (44.4)	134 (48.0)
Use of NSAID at baseline [n (%)]		
Yes	154 (55.2)	164 (58.8)
No	125 (44.8)	115 (41.2)
Baseline methotrexate dose (mg/week)		
Mean (SD)	17.6 (4.84)	17.2 (4.94)
Median	17.5	15.0
Min, Max	7.5, 25.0	7.5, 25.0
RF status at screening [n (%)]		
Positive	244 (87.5)	251 (90.0)
Negative	35 (12.5)	28 (10.0)
Anti-CCP status at screening [n (%)]		
Positive	253 (90.7)	253 (90.7)
Negative	25 (9.0)	25 (9.0)
Missing	1 (0.4)	1 (0.4)
RF and anti-CCP status at screening [n (%)]		
RF positive and anti-CCP positive	219 (89.8)	227 (90.4)
RF positive and anti-CCP negative	24 (9.8)	23 (9.2)
RF negative and anti-CCP positive	34 (97.1)	26 (92.9)
RF negative and anti-CCP negative	1 (2.9)	2 (7.1)
Missing	1 (0.4)	1 (0.4)

Source: Clinical Study Report, Table 9-4

† One patient who had zero swollen joints (minimum six required) was randomized into the study. This patient had 4 tender joints at baseline.

‡ There were discrepancies between the prior biologic use recorded at baseline used in the stratified randomization and the actual prior biologic use. The numbers presented in this table correspond to the actual prior biologic use. Eighteen subjects (9 per treatment arm) were effected.
* Baseline was defined as Day 1 in the protocol. Twenty-two (22) patients were missing Day 1 CRP results. For the purposes of this table, screening CRP results were used.
SD: Standard Deviation

Analysis of Primary Clinical Endpoint

The results of the applicant's primary analysis are shown in Table 20. While the lower bound of the 90% confidence interval was contained within the lower margin of -12%, the upper bound of the 90% confidence interval exceeded the agreed upper margin of 15% and so the prespecified criteria were not met. These results were highlighted by the applicant and discussed in the BPD Type 4 meeting held on October 31, 2018. The Agency requested that the applicant justify that their data support that there are no clinically meaningful differences despite the primary analysis findings.

Table 20. Applicant's Primary Analysis of ACR20 at Week 22 by Treatment (ITT Analysis set with NRI)

Statistic	ABP 710 (N=279)	US-Remicade (N=279)
ACR 20 response rate n/N1 (%)	190/279 (68.1)	165/279 (59.1)
95% CI for ACR20 response rate	(62.6, 73.6)	(53.4, 64.9)
Response Difference of ACR20 (%)	9.37	
90% CI	(2.67, 15.96)	
95% CI	(1.39, 17.19)	

Source: Clinical Study Report, Table 10-1
N= number randomized, n = number of patients meeting the response criteria at the visit; N1 = number of patients who were randomized and had an assessment at the visit; NRI = non-responder imputation, CI: Confidence interval.
Note: Estimates were computed using the Cochran-Mantel-Haenszel method and confidence intervals were computed using the statified Newcombe method, adjusting for the statification factors: geographic region (Asia Pacific, Europe or North America) and prior biologic usage (yes/no).

The applicant noted that there were some imbalances in the baseline disease severity between the two treatment groups and so the applicant conducted an additional post-hoc analysis that adjusted for these imbalances. In addition to the covariates used in the primary analysis (region and prior biologic use) the applicant included all seven baseline values for the ACR components, as well as age, NSAID use, and steroid use. Compared to the primary analysis (shown in Table 20), the estimated difference in ACR20 response rate decreased slightly and the upper limit of the 90% confidence bound fell within the similarity margin for the three ITT-based analyses, but not for the PP set-based analysis (Table 21). In particular the post-hoc analysis based on the ITT population with NRI (first row of Table 21), which is based on the primary analysis, the confidence interval fell

within the pre-specified margin. This lends support to the applicant's assertion that the primary analysis results, with regards to slightly missing the upper bound of the CI, may be due to chance imbalances in the baseline covariates.

Table 21: Summary of Post-Hoc Analyses of ACR20 at Week 22 Adjusting for Additional Baseline Covariates

Statistic	Non-Parametric (Applicant) Estimate (90% CI)	Parametric (FDA Reviewer) Estimate (90% CI)
ITT with NRI	7.9 (1.4, 14.3)	8.0 (1.5, 14.5)
ITT with LOCF	6.8 (0.4, 13.2)	6.9 (0.5, 13.3)
ITT as observed	7.2 (0.7, 13.7)	7.3 (0.8, 13.8)
PP set as observed	9.3 (2.6, 16.0)	9.4 (2.7, 16.2)

Source: Clinical Study Report, Table 10-4 and FDA Statistical Reviewer
CI: Confidence interval; NRI: Non-responder imputation; LOCF: Last observation carried forward; PP: Per Protocol.
Note: The non-parametric estimates and confidence intervals were calculated using non-parametric analysis of covariance (NPANCOVA) method adjusting for stratification factors geographic region (Asia Pacific, Europe or North America), prior biologic use (yes/no) as above and by baseline disease severity covariates (tender joint count, swollen joint count, subject's global health assessment, investigator's global health assessment, Subject's Assessment of Disease-related pain, HAQ-DI, CRP, age, use of oral corticosteroid [yes/no], and use of NSAIDs[yes/no]). Parametric estimates and confidence intervals were computed using logistic regression with the same variables as the non-parametric analysis.

The ACR20 is a composite endpoint and it is therefore important to examine the individual components of the composite to examine whether there are any notable differences in the response rate between the components. Table 22 shows the difference in response rates for the seven components of the ACR response criteria. The largest differences in response rates are for the subject's assessment of pain, HAQ-DI and the tender joint count. The differences in the response rates for the other components were relatively small.

Table 22. Response (>= 20% Improvement) Difference at Week 22 in 7 Components in ACR (ITT Analysis Set, Non-responder Imputation)

ACR Component	ABP 710 n/N (%)	US-Remicade n/N (%)	RD [%] (90% CI [%])
Swollen Joint Counts (66)	238/279 (85.3)	233/279 (83.5)	1.86 (-3.22, 6.95)
Tender Joint Counts (68)	237/279 (84.9)	225/279 (80.6)	4.44 (-0.83, 9.75)
Subject's Global Health Assessment	183/279 (65.6)	174/279 (62.4)	3.52 (-3.16, 10.16)

Investigator's Global Health Assessment	229/279 (82.1)	223/279 (79.9)	2.58 (-2.89, 8.04)
Subject's Assessment of Pain	196/279 (70.3)	169/279 (60.6)	10.10 (3.47, 16.60)
HAQ-DI	172/279 (61.6)	154/279 (55.2)	6.67 (-0.19, 13.45)
C-reactive Protein	146/279 (52.3)	148/279 (53.0)	-0.40 (-7.33, 6.53)

Source: Table 1, Information request response, March 1, 2019
CI: Confidence interval; n = number of patients who met the response criteria; N = number of randomized patients in the treatment arm
Note: Estimates and confidence intervals were computed using the Cochran-Mantel-Haenszel method and confidence intervals were computed using the statified Newcombe method, adjusting for the statification factors: geographic region (Asia Pacific, Europe or North America) and prior biologic usage (yes/no).

When the changes from baseline in the components are analyzed using ANCOVA models (Table 23), the differences between the two treatment arms are small. For six out of seven of the components, the relative magnitude of the differences for these components is less than 20% of the magnitude of change seen within either treatment arm. The relatively small size of these changes is supportive of a conclusion of no clinically meaningful differences. While the relative size of the difference is bigger for the CRP measure, there is a high level of variability among patients. Therefore, this result does not preclude a demonstration of no clinically meaningful differences.

Table 23. Change from Baseline at Week 22 in 7 Components of ACR by Treatment (ITT Analysis Set, As Observed)

ACR Component	ABP 710 Mean (SD) (N=279)	US-Remicade Mean (SD) (N=279)	Difference Between Means	90% Confidence Interval
Swollen Joint Counts (66)	-10.8 (7.57)	-10.4 (8.09)	-0.35	(-1.11, 0.40)
Tender Joint Counts (68)	-14.8 (10.02)	-15.0 (12.19)	-0.11	(-1.39, 1.17)
Subject's Global Health Assessment	-29.5 (30.77)	-27.1 (28.54)	-0.85	(-4.57, 2.87)
Investigator's Global Health Assessment	-42.1 (23.68)	-39.2 (23.38)	-2.58	(-5.44, 0.27)
Subject's Assessment of Pain	-30.8 (28.75)	-25.1 (29.33)	-3.77	(-7.38, -0.16)
HAQ-DI	-0.5 (0.59)	-0.4 (0.56)	-0.07	(-0.15, 0.01)
C-reactive Protein	-4.2 (20.74)	-3.3 (18.28)	-1.26	(-3.54, 1.02)

Source: Table 2, Information request response, March 1, 2019
SD: Standard Deviation
Note: Estimates and confidence intervals were computed using an analysis of covariance model adjusting for the stratification factors: geographic region (Asia Pacific, Europe or North America) and prior biologic usage (yes/no).

Potential Effects of Missing Data

In this section we present analyses that evaluate the extent of the effect of missing data on the study conclusion for the primary endpoint, ACR20 at Week 22. Overall, the rates of study completion were high, with 5.4% and 7.2% of patients in the ABP 710 and US-Remicade groups respectively discontinuing from the study before Week 22 visit. There were 18 subjects on ABP 710 and 23 subjects on the US-Remicade arm missing an observation for the primary endpoint. As summarized in Table 17, there were similar reasons for study drug discontinuation and study dropout between the two groups.

The applicant's primary analysis used a non-responder imputation approach, where patients who did not have a Week 22 visit were classified as non-responders. As noted above, the discontinuation rates were similar between arms so the difference in effect from this approach is likely small. Although not specified by the applicant, this approach implicitly targets the following estimand using the framework described in the draft ICH E9 (R1) guidance:

a) Population: Patients with moderate to severe RA, refractory to methotrexate as described by the inclusion/exclusion criteria.
b) Variable: ACR20 response.
c) Intercurrent events: regardless of treatment adherence; patients who did not complete the week 22 visit are imputed as non-responders.
d) Population level summary: The percentage of patients who met the response criteria.

The applicant performed several pre-specified supplemental analyses to evaluate the sensitivity of the findings to assumptions about the missing data and handling of intercurrent events. These analyses either focused on single imputation approaches which are known to underestimate the uncertainity arising from missing data[14], or restricted the analysis set to only subjects with completely observed data. The outcomes of each of these supplemental analyses were similar to the primary analysis using the non-responder imputation approach.

The other planned sensitivity analysis was a tipping point analysis, where subjects with missing data are imputed with varying response rates. The results of the FDA statistical reviewer's version of this analysis are in Table 24. In this analysis, responses for subjects with missing data were imputed at rates shifted from the response rate for subjects with observed Week 22 data (first analysis in Table 24). The magnitude of the shift by treatment arm is shown in the header row and first column of the table. Typically, these analyses are used to identify the "tipping point", i.e., the shift in underlying assumptions that results in a loss of concluding similarity. Given that the primary analysis results already have an upper bound that goes beyond the pre-specified similarity margin, the

[14] National Research Council. The prevention and treatment of missing data in clinical trials. National Academies Press, 2010.

utility and interpretability of these results is difficult. However, for completeness, and to provide a broader picture of the impact on the missing data assumptions, we've included these results here. As would be expected, when the results are shifted in favor of US-Remicade (top-right corner) the confidence intervals move in favor of US-Remicade, resulting in a change of conclusion. The cells where the pre-specified criteria are not met are highlighted in gray.

A zero shift or equal worsening shift (decreasing likelihood of ACR20 response) for both treatments arms is represented by the cells with a bold outline. We expect that improvement in ACR outcomes after study drug discontinuation is unlikely. In all three highlighted cases, the upper bound of the confidence interval exceeds 15% which was the same conclusion reached in the primary analysis.

Table 24. ACR20 Tipping Point Analyses

Shift for ABP 710 [RD, (90% CI)]	Shift for US-Remicade				
	-25.0	**-12.5**	**0**	**12.5**	**25.0**
-25.0	9.5 (2.7, 16.3)	8.5 (1.7, 15.3)	7.5 (0.7, 14.2)	6.5 (-0.2, 13.2)	5.5 (-1.2, 12.1)
-12.5	10.4 (3.7, 17.2)	9.4 (2.7, 16.1)	8.3 (1.7, 15.0)	7.4 (0.8, 14.0)	6.3 (-0.2, 12.9)
0	11.1 (4.4, 17.8)	10.1 (3.4, 16.7)	9.0 (2.4, 15.6)	8.0 (1.4, 14.7)	7.0 (0.4, 13.6)
12.5	11.8 (5.1, 18.5)	10.8 (4.1, 17.5)	9.7 (3.1, 16.3)	8.8 (2.2, 15.3)	7.7 (1.2, 14.2)
25	12.6 (6.0, 19.2)	11.6 (5.0, 18.1)	10.5 (4.0, 17.0)	9.5 (3.1, 16.0)	8.5 (2.1, 14.9)

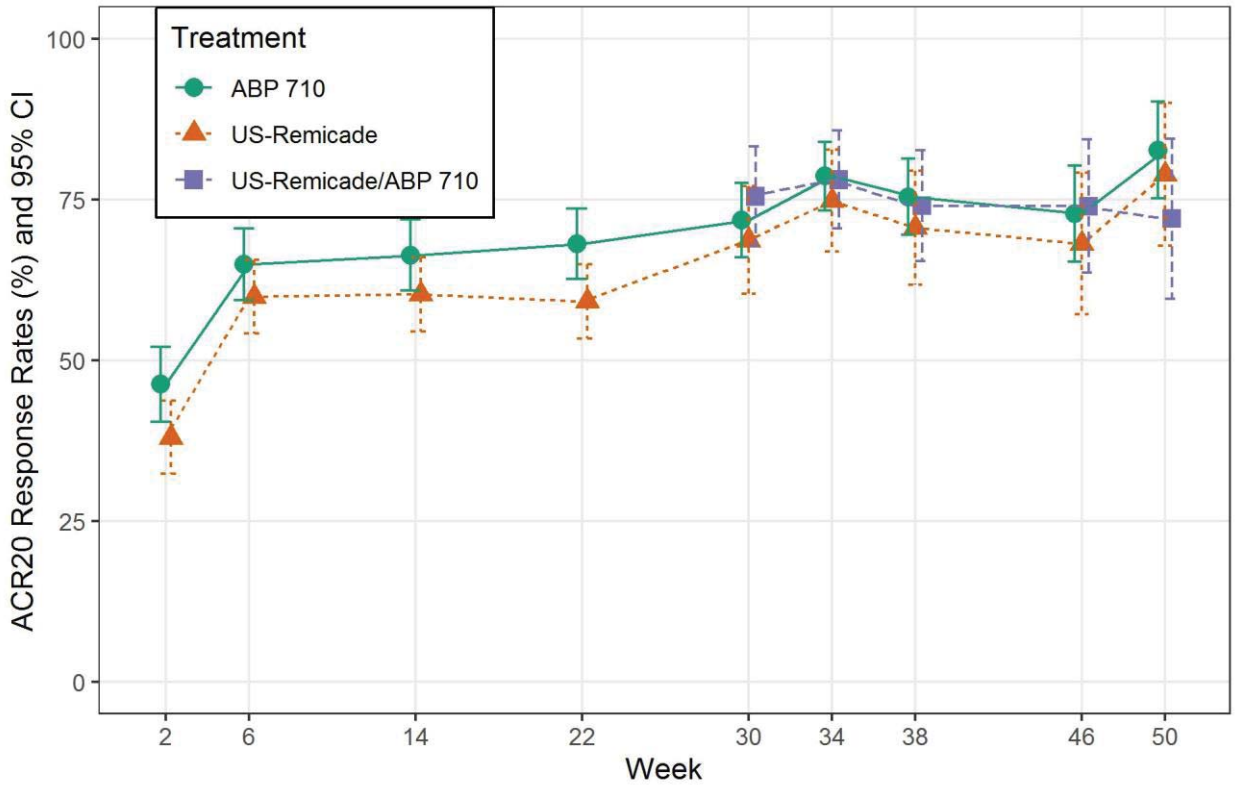
Source: FDA Statistical Reviewers reproduction of Clinical Study Report, Table 10-3
Cells highlighted in gray correspond to confidence intervals that fall outside the pre-specified margin (-12%, +15%). Bold outline indicates the scenarios that the statistical reviewer believes are most plausible.
CI: Confidence interval
RD: Response difference
Note: Missing outcomes were imputed using a missing not at random model where the response rate for missing data is shifted from the overall response rate in that treatment arm by the amount shown in the corresponding row and column with estimates and confidence intervals calculated using the Cochran-Mantel-Haenszel method.

Analysis of Secondary Clinical Endpoint(s)

In this section we will discuss the results of the pre-specified secondary clinical endpoints, which were analyzed descriptively. These include, analyses of three typical ACR response criteria (ACR20, ACR50, and ACR70) over the course of the entire study, and the DAS28 scores.

The results of the ACR20, ACR50, and ACR70 over the study are shown in Figure 7, Figure 8, and Figure 9, respectively, and the corresponding analyses are shown in Table 25, Table 26, and Table 27, respectively. For all three endpoints, as is typical, the response rates increase over time and begin to peak towards the end of the double-blind period. For each of the three endpoints, subjects in the ABP 710 treatment group responded at higher rates for ABP 710 in comparison to US-Remicade in the later stages of the study (Weeks 14 and 22). For ACR20 at Week 2, 6, and 14, the 90% confidence intervals of the differences are all contained within the margin used for the primary endpoint (-12%, +15%) providing additional support for a conclusion of no clinically meaningful differences. For the ACR50 and ACR70 endpoints, margins were not pre-specified and such margins have not been established previously. However, overall the results were similar to the ACR20 results with patients in the ABP 710 treatment arm responding at higher rates than the US-remicade patients at the majority of the timepoints up to Week 22 (prior to re-randomization).

Figure 7. ACR20 by Treatment and Visit – Through Entire Study (ITT Analysis Set)



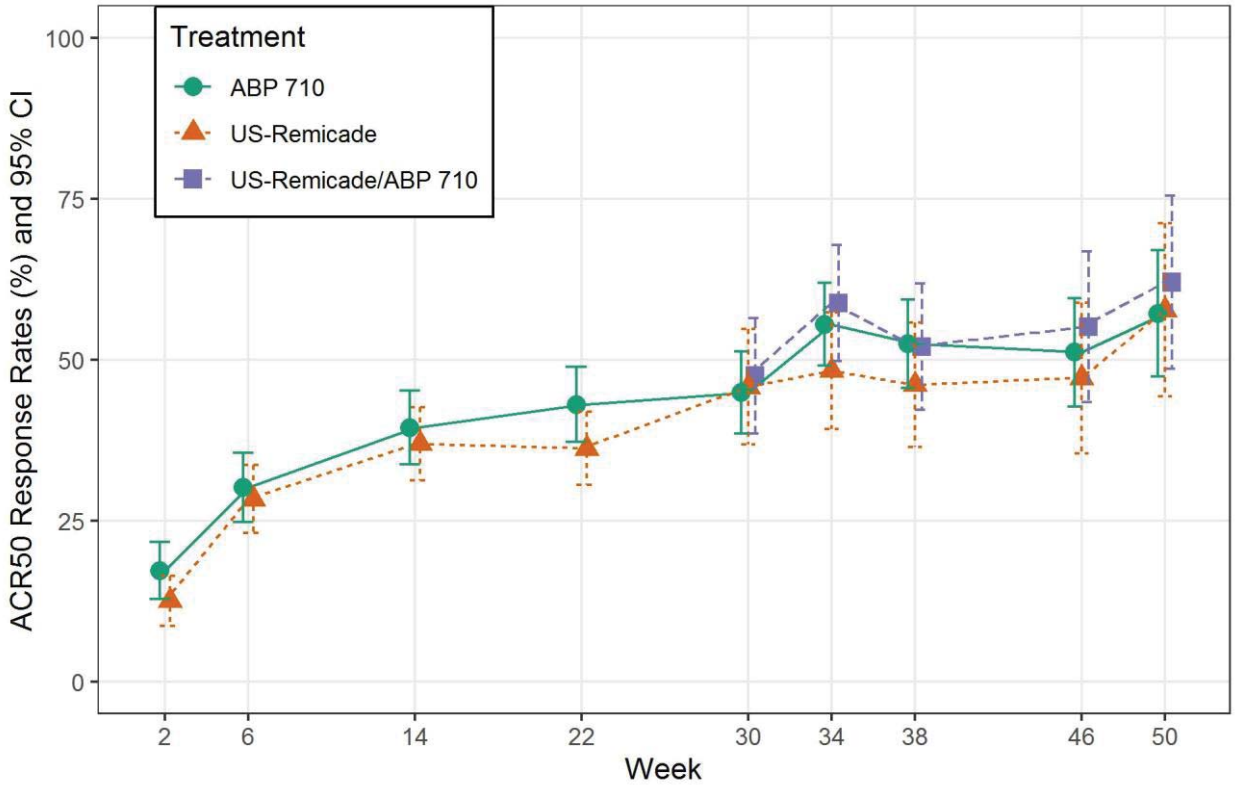
Source: FDA Statistical Reviewer
CI: Confidence interval
Note: Missing data through Week 22 was imputed as non-response. Only subjects with observed data were included beyond Week 22. Unadjusted means and 95% Wald confidence intervals are shown.

Table 25: ACR20 Response Rates by Treatment and Visit - Through Week 22

Week	ABP 710 (N=279) [n/N (%)]	US-Remicade (N=279) [n/N (%)]	Response Difference (90% CI)
Week 2	129/279 (46.2)	106/279 (38.0)	8.0 (1.2, 14.8)
Week 6	181/279 (64.9)	167/279 (59.9)	5.0 (-1.8, 11.6)
Week 14	185/279 (66.3)	168/279 (60.2)	6.2 (-0.5, 12.9)
Week 22	190/279 (68.1)	165/279 (59.1)	9.4 (2.7, 16.0)

Source: Adapted from Clinical Study Report, Table 10-7
CI: Confidence interval
Note: Estimates and confidence intervals were computed using the Cochran-Mantel-Haenszel method and confidence intervals were computed using the statified Newcombe method, adjusting for the statification factors: geographic region (Asia Pacific, Europe or North America) and prior biologic usage (yes/no). Missing data was imputed as non-response.

Figure 8. ACR50 by Treatment and Visit – Through Entire Study (ITT Analysis Set)



Source: FDA Statistical Reviewer
CI: Confidence interval
Note: Missing data through Week 22 was imputed as non-response. Only subjects with observed data were included beyond Week 22.

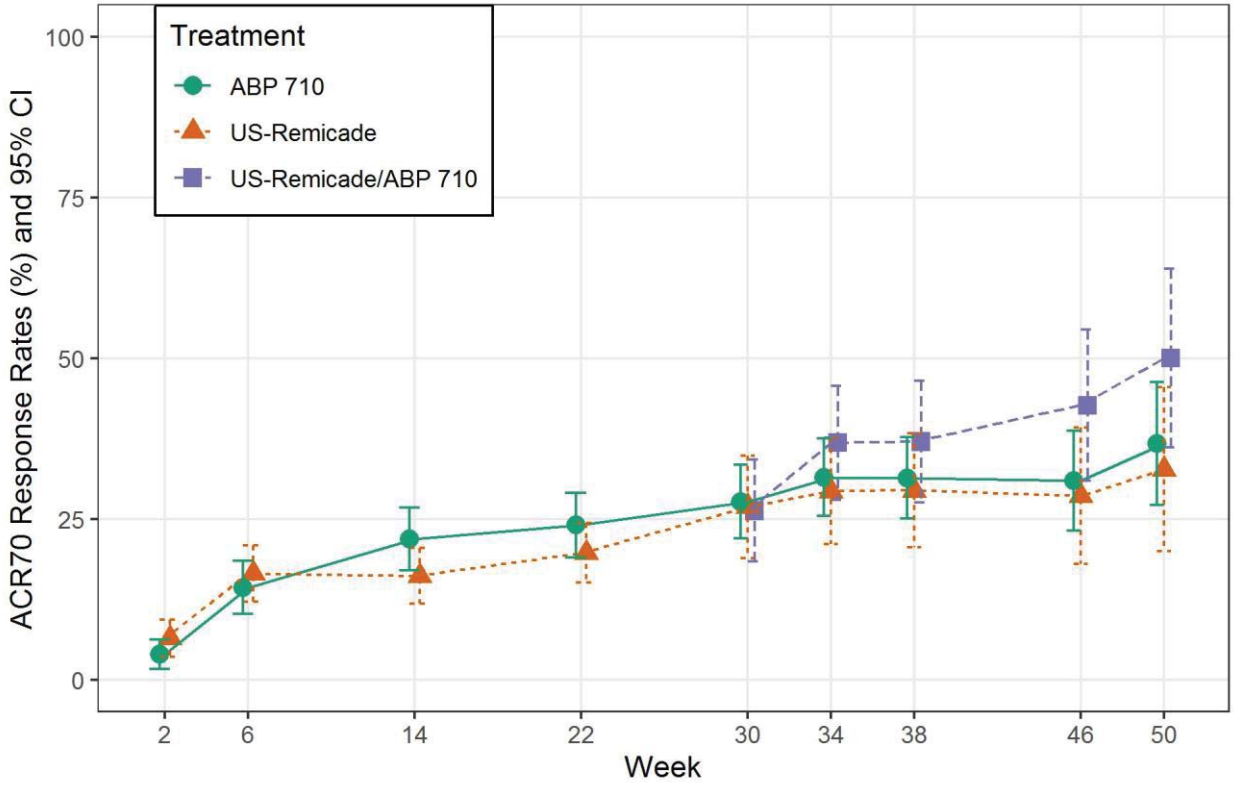
Table 26: ACR50 Response Rates by Treatment and Visit – Through Week 22

Week	ABP 710 (N=279) [n/N (%)]	US-Remicade (N=279) [n/N (%)]	Response Difference (90% CI)
Week 2	48/279 (17.2%)	35/279 (12.5%)	4.4 (-0.6, 9.4)
Week 6	84/279 (30.1%)	79/279 (28.3%)	1.6 (-4.7, 7.9)
Week 14	110/279 (39.4%)	103/279 (36.9%)	2.3 (-4.5, 9.0)
Week 22	120/279 (43.0%)	101/279 (36.2%)	7.1 (0.3, 13.8)

Source: Adapted from Clinical Study Report, Table 10-11
CI: Confidence interval
Note: Estimates and confidence intervals were computed using the Cochran-Mantel-Haenszel method and confidence intervals were computed using the statified Newcombe method, adjusting for the statification factors: geographic region (Asia

Pacific, Europe or North America) and prior biologic usage (yes/no). Missing data was imputed as non-response.

Figure 9. ACR70 by Treatment and Visit – Through Entire Study (ITT Analysis Set)



Source: FDA Statistical Reviewer
CI: Confidence interval
Note: Missing data through Week 22 was imputed as non-response. Only subjects with observed data were included beyond Week 22.

Table 27: ACR70 Response Rates by Treatment and Visit – Through Week 22

Week	ABP 710 (N=279) [n/N (%)]	US-Remicade (N=279) [n/N (%)]	Response Difference (90% CI)
Week 2	11/279 (3.9)	18/279 (6.5)	-2.5 (-5.8, 0.8)
Week 6	40/279 (14.3)	46/279 (16.5)	-2.4 (-7.5, 2.6))
Week 14	61/279 (21.9)	45/279 (16.1)	5.5 (-0.0, 10.9)
Week 22	67/279 (24.0)	55/279 (19.7)	4.6 (-1.2. 10.3)

Source: Adapted from Clinical Study Report, Table 10-13
CI: Confidence interval
Note: Estimates and confidence intervals were computed using the Cochran-Mantel-Haenszel method and confidence intervals were computed using the statified Newcombe method, adjusting for the statification factors: geographic region (Asia

Pacific, Europe or North America) and prior biologic usage (yes/no). Missing data was imputed as non-response.

The results of the applicant's analysis of the DAS28 scores through Week 22 are shown in Table 28 and the results of the statistical reviewer's version of this analysis are shown in Table 29 and Figure 10. The applicant used only the observed scores, excluding subjects from the analysis with missing observations, while the statistical reviewer's analysis imputed the missing scores using a multiple imputation method. Both analyses found similar, relatively small differences (<6% of the overall change from baseline) between ABP 710 and US-Remicade. The confidence intervals are also relatively small compared to the overall change observed to Week 22 (approximately 10% of the observed effect at Week 22) for both methods.

Table 28. Change from Baseline in DAS28 Score – Through Week 22 (Applicant)

Visit	ABP 710 Mean (SD)	US-Remicade Mean (SD)	RD (90% CI)
Week 2	-1.36 (0.99)	-1.26 (1.01)	-0.07 (-0.20, 0.07)
Week 6	-1.82 (1.22)	-1.82 (1.20)	0.00 (-0.17, 0.16)
Week 14	-1.95 (1.22)	-1.91 (1.29)	-0.04 (-0.21, 0.14)
Week 22	-2.06 (1.29)	-2.06 (1.30)	-0.01 (-0.20, 0.17)

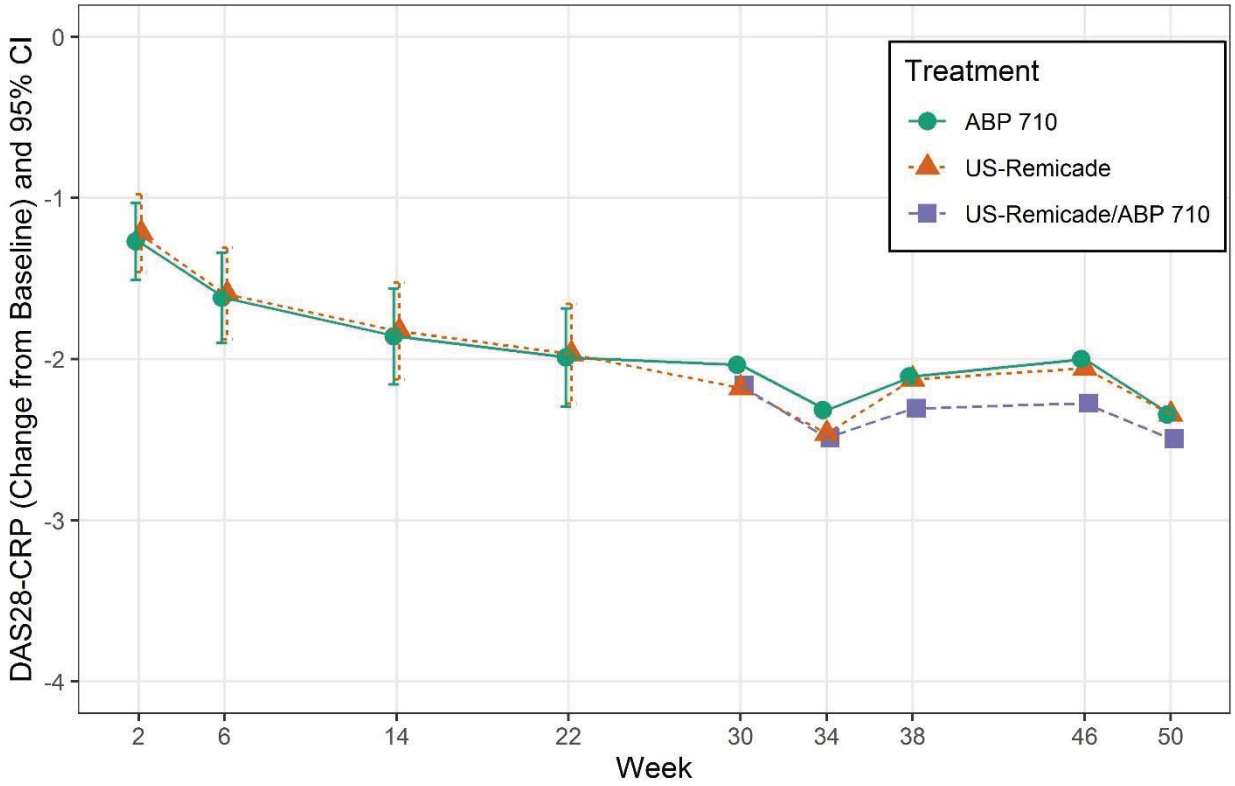
Source: Clinical Study Report, Table 14-4.4.1
SD: Standard Deviation; CI: Confidence interval
Note: Estimated differences and 90% CI obtained using an analysis of covariance model which included treatment, prior biologic use, geographic region, and baseline DAS28 score.

Table 29. Change from Baseline in DAS28 Score – Through Week 22 (FDA Reviewer)

Visit	ABP 710 Mean (SD)	US-Remicade Mean (SD)	RD (90% CI)
Week 2	-1.34 (1.00)	-1.30 (1.03)	-0.06 (-0.20, 0.09)
Week 6	-1.82 (1.22)	-1.81 (1.21)	-0.02 (-0.18, 0.14)
Week 14	-1.96 (1.22)	-1.93 (1.29)	-0.04 (-0.22, 0.14)
Week 22	-2.08 (1.28)	-2.06 (1.29)	-0.03 (-0.21, 0.14)

Source: FDA Statistical Reviewer
SD: Standard Deviation; CI: Confidence interval
Note: Patients with missing DAS28 scores were imputed using a Missing at Random model which included Baseline DAS28 score and all baseline DAS28 components, treatment, visit, prior biologic use (yes/no) and geographic region (Asia Pacific, Europe or North America). The resulting data was analyzed using an analysis of covariance model which included treatment, prior biologic use, geographic region, and baseline DAS28 score.

Figure 10. DAS28-CRP Change from Baseline by Treatment and Visit – Through Entire Study (ITT Analysis Set)



Source: FDA Statistical Reviewer
CI: Confidence interval
Note: Model-adjusted marginal estimates shown. The model adjusted for prior biologic usage (yes/no), geographic region (Asia Pacific, Europe or North America) and baseline DAS28 score shown. Missing data was imputed using the model described in the footnote to Table 29.

In order to examine the sensitivity of the DAS28 outcome to the missing data, the statistical reviewer also conducted a tipping point sensitivity analysis, where the missing observations in both treatment arms are shifted by a varying degree from the observed response rates for the relevant treatment arm. The objective is to identify where, if at all, the conclusion of the study tips. The results of the FDA statistical reviewer's tipping point analysis of the DAS28 endpoint are shown in Table 30. The most extreme tips will be seen in the top right and bottom left and correspond to a large positive shift for one arm and a large negative shift for the other arm. The shaded cells in this table correspond to the 90% confidence excluding zero. This occurs only with relative shifts of approximately 2 points between the two treatment arms.

While no similarity margin has been agreed for the DAS28 endpoint for US-Remicade, a similarity margin of (-0.5, 0.5) has been used by the Agency to support approval of other

biosimilar products [15]. This margin is exceeded only when there is a greater than 3-point relative shift between the two treatment arms. In conclusion, the DAS28 data provides support for a conclusion of no clinically meaningful differences between ABP 710 and US-Remicade.

Table 30. Tipping Point Analysis Results for DAS28 at Week 22

Shift for ABP 710/ Mean (90% CI)	Shift for US-Remicade				
	-2	-1	0	1	2
-2	0.02 (-0.18, 0.21)	0.10 (-0.08, 0.29)	0.19 (0.01, 0.38)	0.28 (0.09, 0.47)	0.37 (0.18, 0.57)
-1	-0.07 (-0.26, 0.11)	0.02 (-0.17, 0.20)	0.10 (-0.07, 0.28)	0.19 (0.01, 0.38)	0.28 (0.10, 0.47)
0	-0.16 (-0.35, 0.02)	-0.07 (-0.25, 0.11)	0.02 (-0.16, 0.19)	0.10 (-0.07, 0.28)	0.19 (0.01, 0.38)
1	-0.25 (-0.44, -0.06)	-0.16 (-0.34, 0.02)	-0.07 (-0.25, 0.11)	0.02 (-0.17, 0.20)	0.10 (-0.08, 0.29)
2	-0.34 (-0.54, -0.15)	-0.25 (-0.44, -0.06)	-0.16 (-0.35, 0.02)	-0.07 (-0.26, 0.11)	0.02 (-0.18, 0.21)

Source: FDA Statistical Reviewer
Note: Gray shading indicates 90% confidence intervals that exclude zero. Patients with missing data were imputed first using the missing-at-random imputation model described in the note for Table 29. The imputed values were shifted by the corresponding value for the selected row and column. The resulting DAS28 outcomes were analyzed using an analysis of covariance model with treatment, prior biologic usage, region, and baseline DAS28 score as covariates.

Additional Analyses

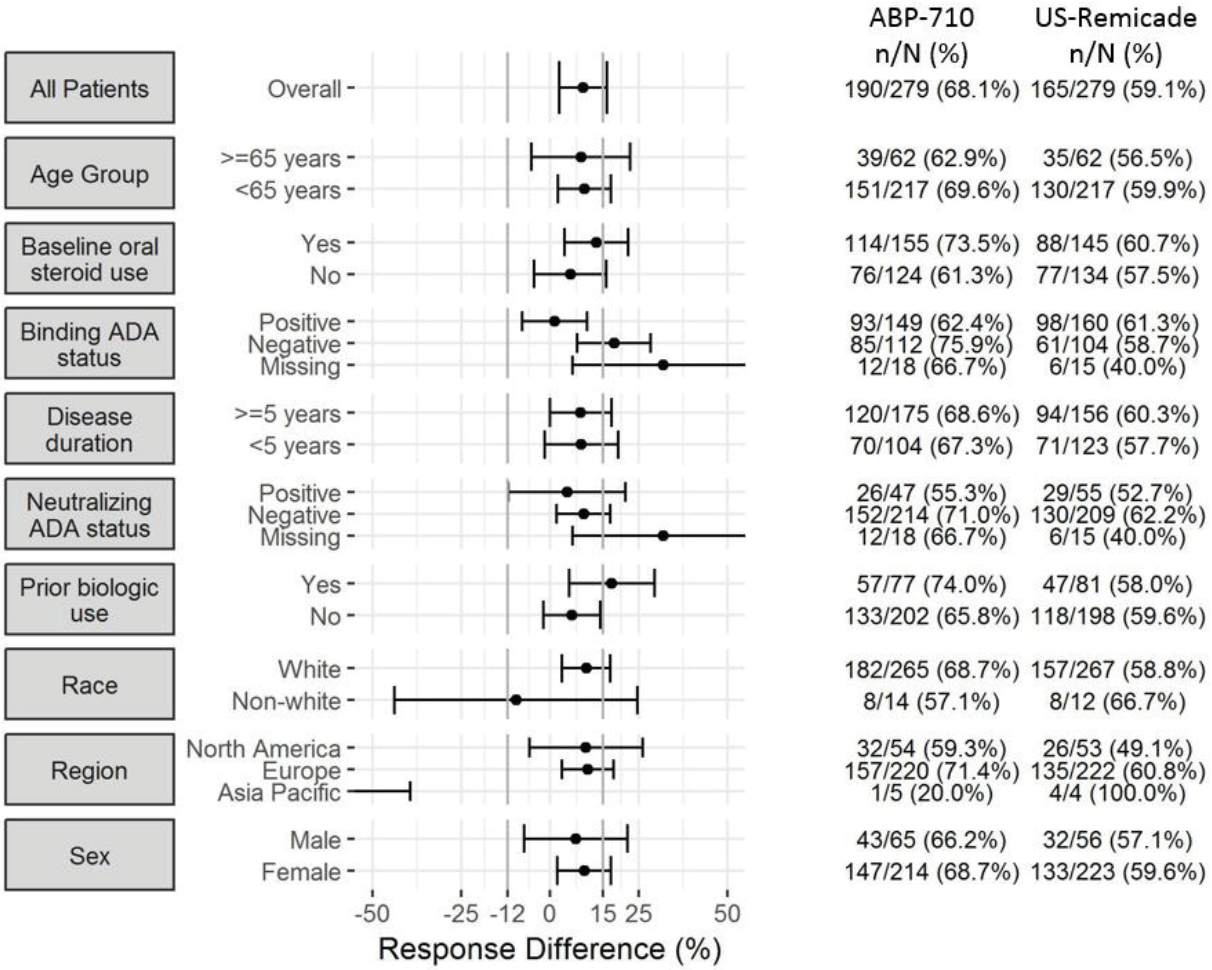
Subgroup Analyses

The results of analyses by demographic and key disease status variables are shown below in Figure 11. The results for the larger subgroups appear consistent with the lower bound of the 90% confidence interval consistently within the 12% lower margin in the majority of cases (non-white and patients enrolled in Asia being the only two exceptions). There do not appear to be any notable differences between the treatment groups' ACR20 response rates for the various demographic subgroup categories (age, sex, race, region). There do appear to be slightly larger differences between the treatment groups for several of the disease status subgroups, most notably positive vs negative binding ADA status (a post-randomization variable), baseline oral steroid use status, and prior biologic use status. Heterogeneity in the estimated differences in

[15] See page 14
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761088Orig1s000ODMemo.pdf

response probabilities across many subgroups (some very small in size) is expected and this does not preclude a demonstration of no clinically meaningful differences.

Figure 11: Subgroup Analyses by Demographic and Disease Status Variables for ACR20 at Week 22



Source: FDA Statistical Reviewer
N=number of patients in the subgroup per treatment arm, n = the number of patients who met the ACR20 response criteria

Assay Sensitivity

In determining whether the proposed similarity margins are relevant to the evaluation of clinically meaningful differences, we must assess and compare the similarity of the conduct and patient population of the submitted study to the historical studies with infliximab used to determine the similarity margin (also known as assessing the constancy assumption). If there are significant changes to either the population or the conduct, then the agreed margins might not be relevant. This can also be used to assess if this study was adequately designed to provide sensitivity to detect differences

between the proposed biosimilar and US-Remicade, if such differences exist, i.e., assay sensitivity.

The key characteristics of the historical studies and the current study, 20140111, are summarized in Table 31. Overall, the inclusion/exclusion criteria appear consistent except for the allowance of prior anti-TNF medications. If we look solely at the biologic-naïve patients seen in the historical studies, then, as seen in the subgroup analyses above (Figure 11), the ACR20 response rates fall within the historical range seen for both treatment arms and the confidence interval falls entirely within the similarity margin. Though higher than the observed rate for US-Remicade, the ACR20 response rate for the biologic-experienced patients in the ABP 710 arm is in line with response rate seen in Zhang et al, which also included biologic experienced patients.

Both the current and historical study allowed stable doses of methotrexate, and the regions where the studies were conducted were similar. The observed baseline disease severity characteristics appear similar, with the tender joint counts, swollen joint counts, disease duration and HAQ-DI/HAQ scores for the study 20140111 all being close to the reported historical averages. The selected time frame for the primary ACR20 assessment was within the range used for the historical studies and the observed US-Remicade ACR20 response rates fell within the historical range. The withdrawal rates were also similar to the historical studies. Overall, there do not appear to be any significant changes to the conduct or population that would impact the appropriateness of the selected margin and overall also support a conclusion of assay sensitivity in the current study.

Table 31. Comparison of Key Characteristics of Historical Randomized, Placebo-Controlled Clinical Trials[1] of infliximab in RA and Study 20140111

	Maini (1999)	**Westhovens (2006)**	**Schiff (2008)**	**Zhang (2006)**	**Abe (2006)**	**Study 20140111**
Selected inclusion/ exclusion criteria	≥ 6 SJ, ≥6 TJ, 2 of: Morning stiffness ≥ 45 min, ESR >28 mm/h, CRP >2 mg/dL	≥ 6 SJ, ≥6 TJ	≥10 SJ, ≥12 TJ, Disease duration ≥1 year, CRP ≥1 mg/dL	≥3 SJ, ≥8 TJ, 2 of: morning stiffness ≥ 45 min, ESR >28 mm/h, CRP >1.5 mg/dL	≥6 SJ, ≥6 TJ, 2 of: Morning stiffness ≥ 45 min, ESR >28 mm/h, CRP >2 mg/dL	≥6 SJ, ≥6 TJ, ESR ≥ 28 mm/hr or CRP > 1 mg/dL

Anti-TNF experience allowed	No	No	No	Yes	No	Yes
Concomitant DMARDs	Stable MTX	Stable MTX + additional DMARDs allowed	Stable MTX	Stable MTX + additional DMARDs	Stable MTX (Low Dose)	Stable MTX
Region/ Country	NA, EU	NA, EU, AU, SA	NA, EU, AU, AF, SA	China	Japan	EU, NA, AS
Baseline characteristics of study population[2]	SJ: 19; TJ: 32; Disease Duration: 8 yrs.; HAQ-DI: 1.8	SJ: 15; TJ: 22 Disease Duration: 8 yrs.; HAQ-DI: 1.5	SJ: 20; TJ: 32; Disease Duration: 7 yrs.; HAQ-DI: 1.7	Disease Duration: 7 yrs.;	SJ: 15; TJ: 19; Disease Duration: 9 yrs.;	SJ: 15; TJ: 23; Disease Duration: 9 yrs.; HAQ-DI: 1.4
Time of ACR20 evaluation	Week 30	Week 22	Week 28	Week 18	Week 14	Week 22
ACR20 Response on infliximab	50%	55%	59%	76%	61%	59%
Withdrawal on infliximab	11%	7%	8%	10%	5%	14%

Source: FDA Statistical Reviewer
Abbreviations: SJ=swollen joint count; TJ=tender joint count; DMARD=disease-modifying antirheumatic
drug; HAQ-DI = Health Assessment Questionnaire; MTX = Methotrexate; NA=North America;
EU=Europe; AS=Asia; AF = Africa; AU = Australia; SA = South America
[1] Based on best attempts to identify/estimate characteristics from literature review
[2] Means or medians, depending on what was reported in publication

7.4. Review of Safety Data

7.4.1. Methods

The safety of ABP 710 compared to US-Remicade was assessed in the single dose, healthy subject, comparative PK study, 20140108 as well as Study 20140111, the comparative clinical study in patients with RA. The overall design of each is described in

Sections 7.3.1 and 7.3.2, respectively. All analyses were performed using the safety population, defined as any subject who received at least one dose of study drug. In addition to analyses of the standard safety assessments, this review also focuses on the known safety issues with TNFα inhibitors, such as infection and malignancy. Study 20140108 was a single dose study and provided information regarding short term exposure to ABP 710. Study 20140111 provided information regarding longer term exposure to ABP 710, up to 46 weeks, as well as data for subjects who underwent a single transition from US-Remicade to ABP 710. Given the differences in exposure and treatment duration, these studies were analyzed separately.

Clinical Studies to Evaluate Safety

The applicant collected safety data from two clinical studies described in Table 3. Study 20140108, a PK similarity study, was conducted in healthy subjects who received ABP 710, US-Remicade, or EU-Remicade. Information generated with EU-Remicade did not inform the comparative safety evaluation of ABP 710 and US-Remicade. Additionally, because Study 2014018 was a single dose study in healthy subjects, studies were not pooled and safety data is primarily derived from Study 20140111.

Categorization of Adverse Events

AEs were coded and presented according to the most current version of Medical Dictionary for Regulatory Activities (MedDRA) available at the time the data were completed for each study. MedDRA version 17.1 and 20.1 were employed for Study 20140108 and Study 20140111, respectively. The severity of AEs was graded by the investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 whenever possible. AEs in terms of TEAEs; treatment-related AEs; and SAEs were summarized by SOC and preferred term (PT) according to MedDRA terminology. A TEAE was defined as any AE that occurred after the beginning of the study treatment or any pre-existing AE that worsened after the beginning of the study treatment.

Adverse events of special interest (AESIs) prespecified for Study 20140111 included infusion reactions and hypersensitivities, congestive heart failure, serious infections, opportunistic infections, malignancies, demyelinating disorders, hepatitis B reactivation, autoimmunity, hepatotoxicity, and hematological reactions. The AESIs were identified using StandardizedMedDRA Queries (SMQs).

Safety Analyses

Safety analyses were performed on data from the individual studies because differences in study population and study design made pooling of the studies inappropriate. The review tools used to conduct independent reviewer analyses included MAED, JMP Clinical, JMP, JReview and OCS Toolbox Demographic Tool. For Study 20140111, this

review separately evaluated safety during two treatment time periods: through week 22 and after week 22. Analyses through week 22 compared safety between ABP 710 and US-Remicade, whereas safety analyses after week 22 include a separate subset of subjects who switched from US-Remicade to ABP 710, in addition to subjects who continued treatment with US-Remicade or ABP 710.

7.4.2. Major Safety Results

Exposure

The extent of exposure for the comparative PK study 20140108 and the comparative clinical study 20140111 are outlined in Table 32 and Table 33 **Error! Reference source not found.**below, respectively.

Table 32. Extent of Exposure to ABP 710 for Study 20140108

	ABP 710 (N=49)	US-Remicade (N=50)	EU-Remicade (N=50)
Not Treated [n (%)]	0 (0)	0 (0)	1 (2)
Treated [n (%)]			
Complete Dose	49 (100)	50 (100)	48 (96)
Incomplete Dose	0 (0)	0 (0)	1 (2)

Source: Clinical reviewer generated JMP analysis using ADSL, INFUSFL=Y SAFFL=Y.

Table 33. Extent of Exposure to ABP 710 from Study 20140111

Treatment Duration	ABP 710/ ABP 710 (N=240)	US-Remicade/ US-Remicade (N=121)	US-Remicade /ABP 710 (N=119)	ABP 710/ Not Treated (N=38)	US-Remicade/ Not Treated (N=38)
< 22 Weeks [n (%)]	0 (0)	0 (0)	0 (0)	38 (100)	38 (100)
22-46 Weeks [n (%)]	113 (47)	55 (45)	53 (44)	0 (0)	0 (0)
> 46 Weeks [n (%)]	127 (53)	66 (55)	66 (56)	0 (0)	0 (0)

Source: Clinical reviewer generated JMP analysis; ADSL, SAFFL=Y, TRTDURD < 154, TRTDUR ≥ 154 AND ≤ 322, TRTDUR > 322 (days).

Population Demographics

The baseline demographics of subjects enrolled in Study 20140108 and Study 20140111 have previously been described in Table 13 and Table 18, respectively. In general the baseline characteristics of subjects in Study 20140111 are representative of an RA population with moderate to severe active disease.

Deaths

There were two deaths that occurred during study 20140111. One in a subject that had been initially randomized to the US-Remicade 3mg/kg arm. The subject, a 59 year old white male with a past medical history of rheumatoid arthritis diagnosed in 2012, received his first dose of US-Remicade on (b) (6). On (b) (6), 40 days after receiving his first dose of US-Remicade, the subject was involved in a traffic accident and died on the same day due to "multi-organ trauma." The last dose of US-Remicade had been given on (b) (6)

The second death occurred in a 73-year-old white male that had been initially randomized to the ABP 710 3mg/kg arm and received his first dose on (b) (6). His past medical history was significant for RA, glaucoma, Parkinson's disease, hypertension, hypercholesterolemia, bradycardia, insomnia, osteoarthritis, and atrial fibrillation. On (b) (6), 97 days after receiving his first dose of ABP710, the subject experienced pneumococcal pneumonia. The event was classified as a serious adverse event and an event of interest. On (b) (6), 61 days after the last dose and 101 days after the first dose of ABP710, the subject died due to pneumococcal pneumonia.

Serious Adverse Events

No SAEs occurred in Study 20140108 in subjects treated with ABP 710 or US-Remicade.

Table 34 and Table 35 show the SAEs by system organ class (SOC) and preferred term (PT) reported in Study 20140111, up to week 22 and after week 22, respectively. Through Week 22, there were 9 SAEs in the ABP 710 arm compared to 14 SAEs in the US-Remicade arm (Table 34). The total number of SAEs reported was slightly larger in the US-Remicade than ABP 710 treatment arm; however, there was only one event (acute myocardial infarction) that occurred more than once.

Table 34. SAEs by system organ class and preferred term up to week 22 in Study 20140111

	ABP 710 (N=278) [n (%)]	**US-Remicade (N=278)** [n (%)]
Cardiac Disorders	2 (0.7)	2 (0.7)
Acute Myocardial Infarction	0	2 (0.7)
Cardiovascular insufficiency	1 (0.4)	0
Ventricular Extrasystole	1 (0.4)	0
Gastrointestinal Disorders	0	2 (0.7)
Constipation	0	1 (0.4)
Colitis	0	1 (0.4)
General Disorders and Administration Site Conditions	1 (0.4)	0
Heaviness in Chest	1 (0.4)	0

Infections and Infestations	2 (0.7)	2 (0.7)
Febrile Infection	1 (0.4)	0
Pneumococcal Pneumonia	1 (0.4)	0
Pneumonia Legionella	0	1 (0.4)
Severe Rhinovirus Pneumonitis	0	1 (0.4)
Injury, Poisoning and Procedural Complications	0	2 (0.8)
Multi-Organ Trauma	0	1 (0.4)
Right tibia fracture	0	1 (0.4)
Musculoskeletal and Connective Tissue Disorders	0	1 (0.4)
Transient Weakness of Limbs	0	1 (0.4)
Neoplasms Benign, Malignant and Unspecified	2 (0.7)	2 (0.7)
Chronic Lymphocytic Leukemia	0	1 (0.4)
Endometrial Adenocarcinoma	1 (0.4)	0
Non-Invasive Papillary Urothelial Carcinoma	0	1 (0.4)
Ovarian Atypical Proliferating Tumor	1 (0.4)	0
Nervous System Disorders	2 (0.7)	0
Sciatica Aggravated with Lumbosacral Pain	1 (0.4)	0
Transient Ischemic Attack	1 (0.4)	0
Renal and Urinary Disorders	0	1 (0.4)
Left Kidney Failure	0	1 (0.4)
Vascular Disorders	0	2 (1.0)
Orthostatic Hypotension	0	1 (0.4)
Thrombosis and Thrombophlebitis of Unspecified Site	0	1 (0.4)
Number of Subjects with any SAE*	9 (3.2)	14 (5.0)

Source: Clinical reviewer generated JMP analysis from Study 20140111 ; ADSL, ADAE, SAFFL=Y, AESER=Y, APERIOD=1.

**Subjects may have reported more than one SAE*

Table 35 shows subjects who had an SAE after Week 22. Subjects are categorized as those who were initially randomized to ABP 710 for the first 22 weeks and remained on ABP 710 after Week 22, those who started on US-Remicade and were randomized to continue on US-Remicade, and those who were on US-Remicade and randomized to switch to ABP 710 after Week 22. During the treatment period after Week 22, the percentage of subjects experiencing an SAE was relatively low and no SAE preferred term was reported more than once across treatment groups. Though there are slight differences in the percentage of subjects with an SAE, small numerical differences across treatment arms is not unexpected and does not preclude a determination of no clinically meaningful differences between ABP 710 and US-Remicade.

Table 35. SAEs by system organ class and preferred term after week 22 in Study 20140111

	ABP 710/ ABP 710 (N=240) [n (%)]	**US-Remicade/ US-Remicade (N=121)** [n (%)]	**US-Remicade/ ABP 710 (N=119)** [n (%)]
Blood and lymphatic system disorders	1 (0.4)	0	1 (0.8)
Iron deficiency anemia	0	0	1 (0.8)
Microcytic anemia	1 (0.4)	0	0
Cardiac disorders	1 (0.4)	0	0
Cardiac failure congestive	1 (0.4)	0	0
General disorders and administration site conditions	1 (0.4)	0	0
Non-cardiac chest pain	1 (0.4)	0	0
Infections and infestations	3 (1.2)	0	0
Appendicitis	1 (0.4)	0	0
Cellulitis	1 (0.4)		
Gastroenteritis	1 (0.4)	0	0
Injury, poisoning and procedural complications	3 (1.2)	0	0
Femoral neck fracture	1 (0.4)	0	0
Laceration	1 (0.4)	0	0
Hip fracture	1 (0.4)	0	0
Investigations	1 (0.4)	0	0
Transaminases increased	1 (0.4)	0	0
Musculoskeletal and connective tissue disorders	1 (0.4)	1 (0.8)	0
Arthralgia	0	1 (0.8)	0
Foot deformity	1 (0.4)	0	0
Neoplasms benign, malignant and unspecified	1 (0.4)	0	0
Malignant melanoma	1 (0.4)	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.8)	0
Pulmonary embolism	0	1 (0.8)	0
Skin and Subcutaneous tissue disorders	0	1 (0.8)	0
Dermatitis atopic	0	1 (0.8)	0
Vascular disorders	1 (0.4)	0	0

Peripheral ischemia	1 (0.4)	0	0
Number of Subjects with any SAE*	13 (5.4)	3 (2.5)	1 (0.8)

Source: Clinical reviewer generated JMP analysis from Study 20140111 ; ADSL, ADAE, SAFFL=Y, AESER=Y, APERIOD=2.

**Subjects may have reported more than one SAE*

Dropouts and/or Discontinuations

There were no premature treatment discontinuations from Study 2014018. In Study 20140111, there were a similar number of treatment discontinuations due to adverse events in the ABP 710 group compared to the US-Remicade group (6% vs 7%) up to Week 22 as shown in Table 36. Other than flares in RA symptoms, most events were reported only once in a treatment arm.

Table 36. TEAEs leading to discontinuation by system organ class and preferred term up to week 22 in Study 20140111

	ABP 710 (N=278) [n (%)]	**US-Remicade (N=278)** [n (%)]
Cardiac Disorders	1 (0.4)	1 (0.4)
Acute Transmural Myocardial Infarction	0	1 (0.4)
Chest Discomfort	1 (0.4)	0
Eye Disorders	1 (0.4)	0
Retinal Detachment Right Eye	1 (0.4)	0
Hepatobiliary Disorders	1 (0.4)	0
Hepatitis Toxic Drug-Induced	1 (0.4)	0
Immune System Disorders	1 (0.4)	2 (0.7)
Acute Allergic Reaction	1 (0.4)	2 (0.7)
Infections and Infestations	2 (0.7)	1 (0.4)
Herpes Zoster Th10-Th12	1 (0.4)	0
Infection Superimposed, Bacterial Pneumonia	0	1 (0.4)
Upper Respiratory Tract Infection	1 (0.4)	0
Injury, Poisoning and Procedural Complications	1 (0.4)	1 (0.4)
Infusion Related Reaction	1 (0.4)	0
Multi-Organ Trauma	0	1 (0.4)
Investigations	1 (0.4)	1 (0.4)
Elevated Blood Pressure	0	1 (0.4)
Positive QuantiFERON	1 (0.4)	0
Musculoskeletal and Connective Tissue Disorders	2 (0.7)	5 (1.8)
Rheumatoid Arthritis	1 (0.4)	4 (1.4)
Arthralgia	1 (0.4)	0

Osteoarthritis	0	1 (0.4)
Neoplasms Benign, Malignant and Unspecified	2 (0.7)	3 (1.1)
Benign Spinal Tumor	0	1 (0.4)
Chronic Lymphocytic Leukemia	0	1 (0.4)
Endometrial Adenocarcinoma	1 (0.4)	0
Non-Invasive Papillary Urothelial Carcinoma	0	1 (0.4)
Ovarian Atypical Proliferating Tumor	1 (0.4)	0
Nervous System Disorders	1 (0.4)	0
Numbness in Extremities	1 (0.4)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.4)	0
Nonspecific Interstitial Pneumonia	1 (0.4)	0
Skin and Subcutaneous Tissue Disorders	2 (0.7)	3 (1.1)
Allergic Contact Dermatitis	0	1 (0.4)
Cutaneous Lupus Erythematodes	0	1 (0.4)
Skin Rash	2 (0.7)	0
Urticaria Acute (Infusion Reaction)	0	1 (0.4)
Vascular Disorders	0	1 (0.4)
Skin Flushed	0	1 (0.4)
All	16 (5.8)	18 (6.5)

Source: Clinical reviewer generated JMP analysis from Study 20140111 ; ADSL, ADAE, APERIOD=1, SAFFL=Y, TRTEMFL=Y, AEACN="DOSE DISCONTINUED" OR AEACNOTH="DISCONTINUED FROM STUDY".

Table 37 includes TEAEs that led to permanent discontinuation after week 22. Eleven events occurred in the ABP 710 group, 4 events in the US-Remicade group, and 3 events in subjects who transitioned from US-Remicade to ABP 710. As with the first 22 weeks of the study, most AEs leading to treatment discontinuation occurred in single subjects and the overall frequency of premature discontinuations was similar across treatment arms. Notably, there were no treatment discontinuations due to hypersensitivity reactions in the subgroup of subjects who transitioned from US-Remicade to ABP 710. Overall, these rates of TEAEs leading to discontinuation appear comparable and the differences do not preclude a demonstration of no clinically meaningful difference.

Table 37. TEAEs leading to discontinuation by system organ class and preferred term after week 22 in Study 20140111

	ABP 710/ ABP 710 (N=240) [n (%)]	**US-Remicade/ US-Remicade (N=121)** [n (%)]	**US-Remicade/ ABP 710 (N=119)** [n (%)]
Blood and lymphatic system disorders	0	0	1 (0.8)
Iron deficiency anemia	0	0	1 (0.8)
Cardiac disorders	1 (0.4)	0	1 (0.8)

Cardiac failure congestive	1 (0.4)	0	0
Tachycardia	0	0	1 (0.8)
Immune system disorders	2 (0.8)	3 (2.5)	0
Hypersensitivity	2 (0.8)	3 (2.5)	0
Infections and infestations	1 (0.4)	1 (0.8)	0
Influenza	1 (0.4)	0	0
Pharyngitis	0	1 (0.8)	0
Musculoskeletal and connective tissue disorders	2 (0.8)	0	1 (0.8)
Rheumatoid arthritis	2 (0.8)	0	1 (0.8)
Neoplasms benign, malignant and unspecified	1 (0.4)	0	0
Malignant melanoma	1 (0.4)	0	0
Skin and subcutaneous tissue disorders	3 (1.3)	0	0
Rash	3 (1.3)	0	0
Vascular disorders	1 (0.4)	0	0
Peripheral ischemia	1 (0.4)	0	0
All	11 (4.6)	4 (3.3)	3 (2.5)

Source: Clinical reviewer generated JMP analysis from Study 20140111 ; ADSL, ADAE, APERIOD=2, SAFFL=Y, TRTEMFL=Y, AEACN="DOSE DISCONTINUED" OR AEACNOTH="DISCONTINUED FROM STUDY".

Common TEAEs

Table 38 shows the TEAEs that occurred in greater than or equal to 2% of subjects in either arm by system organ class and preferred term in Study 20140111 through week 22. The number and types of TEAEs were comparable between treatment arms. There were numerically more infections reported in the ABP 710 arm, the difference being primarily driven by nasopharyngitis and bronchitis events. However, the number of individual events was small, and therefore differences likely occurred by chance and do not preclude a demonstration of no clinically meaningful differences.

Table 38. Common TEAEs by system organ class and preferred term up to week 22 in Study 20140111 in ≥ 2% of subjects.

	ABP 710 (N=278) [n (%)]	**US-Remicade (N=278)** [n (%)]
Infections and infestations		
Bronchitis	9 (3.2)	4 (1.4)
Upper respiratory tract infection*	38 (13.7)	27 (9.7)
Urinary tract infection	5 (1.8)	6 (2.2)
Investigations		

	ABP 710 (N=278) [n (%)]	US-Remicade (N=278) [n (%)]
Transaminases Increased†	8 (2.9)	10 (3.6)
Musculoskeletal and connective tissue disorders		
Rheumatoid arthritis	14 (5)	11 (4)
Skin and subcutaneous tissue disorders		
Rash‡	9 (3.2)	16 (5.8)
Vascular disorders		
Hypertension	4 (1.4)	10 (3.6)

Source: Clinical reviewer generated JMP analysis from Study 20140111 ; ADSL, ADAE, APERIOD=1, SAFFL=Y, TRTEMFL=Y.
** Upper respiratory tract infection includes PTs: "nasopharyngitis", "laryngitis", "pharyngitis", "tonsillitis", "sinusitis", and "rhinitis"*
† Transaminases Increased includes PTs: "hepatic enzyme increased", "aspartate aminotransferase increased", and "alanine aminotransferase increased"
‡ Rash includes PTs: "dermatitis", "erythema"

Table 39 shows common TEAEs in greater than or equal to 2% of subjects in any treatment arm that occurred after week 22. The types and numbers of TEAEs were similar across treatment arms. However, there were more reports of rash and upper respiratory infections in subjects making the transition from US-Remicade to ABP 710 at week 22. Again, the number of events were very small and therefore differences likely occurred by chance and do not preclude a demonstration of no clinically meaningful differences.

Table 39. Common TEAEs by system organ class and preferred term after week 22 in Study 20140111 in ≥ 2% of subjects.

	ABP 710/ ABP 710 (N=240) [n (%)]	US-Remicade/ US-Remicade (N=121) [n (%)]	US-Remicade/ ABP 710 (N=119) [n (%)]
Blood and lymphatic system disorders			
Anemia	2 (0.8)	3 (2.5)	2 (1.7)
Neutropenia	4 (1.7)	1 (0.8)	3 (2.5)
Gastrointestinal disorders			
Diarrhea	4 (1.7)	3 (2.5)	3 (2.5)

	ABP 710/ ABP 710 (N=240) [n (%)]	US-Remicade/ US-Remicade (N=121) [n (%)]	US-Remicade/ ABP 710 (N=119) [n (%)]
Immune System Disorders			
Hypersensitivity	2 (0.8)	3 (2.5)	0
Infections and infestations			
Bronchitis	8 (3.3)	6 (5.0)	2 (1.7)
Ear infection	0	3 (2.5)	0
Upper respiratory tract infection*	38 (15.8)	26 (21.5)	33 (27.7)
Urinary tract infection	0	3 (2.5)	0
Investigations			
Transaminases Increased	8 (3.3)	2 (1.7)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (1.3)	4 (3.3)	1 (0.8)
Rheumatoid arthritis	17 (7.1)	9 (7.4)	7 (5.9)
Skin and subcutaneous tissue disorders			
Rash‡	2 (0.8)	3 (2.5)	4 (3.4)
Vascular disorders			
Hypertension	2 (0.8)	3 (2.5)	4 (1.7)

Source: Clinical reviewer generated JMP analysis from Study 20140111 ; ADSL, ADAE, APERIOD=2, SAFFL=Y, TRTEMFL=Y.
**Includes PTs "nasopharyngitis", "laryngitis", "pharyngitis", "tonsillitis", "sinusitis", and "rhinitis"*
†Includes PTs "hepatic enzyme increased", "aspartate aminotransferase increased", and "alanine aminotransferase increased"
‡Includes PTs "dermatitis", "erythema"

The overall profile of TEAEs was comparable between ABP 710 and US-Remicade and before/after the US-Remicade transition to ABP 710. No new safety signals emerged from all treatment groups during the 46-week treatment. Additionally, Table 40**Error! Reference source not found.** lists the TEAEs by system organ class and preferred term occurring in Study 2014108. The types of TEAEs were similar to those of Study 20140111. However, the number of total events was lower. This is not unexpected given Study 2014018 was shorter in duration.

Table 40. TEAEs by system organ class and preferred term in Study 20140108

	ABP 710 N=49	US-Remicade N=50
Gastrointestinal disorders		
Diarrhea	2 (4.1)	0
Nausea	3 (6.1)	1 (2.0)
General disorders and administration site conditions		
Catheter site pain	0	0
Pyrexia	0	0
Immune system disorders		
Seasonal allergy	1 (2.0)	1 (2.0)
Infections and infestations		
Oral herpes	2 (4.1)	0
Nasopharyngitis	0	7 (14)
Upper respiratory tract infection	3 (6.1)	3 (6.0)
Nervous system disorders		
Headache	16 (33)	16 (32)
Lethargy	1 (2.0)	1 (2.0)
Somnolence	27 (55)	30 (60)
Syncope	0	0
Respiratory, thoracic and mediastinal disorders		
Cough	0	1 (2.0)
Nasal congestion	0	0

Source: Clinical reviewer generated JMP analysis from Study 20140108 ; ADSL, ADAE, SAFFL=Y, TRTEMFL=Y.

7.4.3. Additional Safety Evaluations

Based on previous experience with TNFα inhibitors, the AESIs that were prespecified in this analysis included infusion reactions including hypersensitivity, congestive heart failure, serious infections, opportunistic infections, malignancies, demyelinating disorders, hepatitis B reactivation, autoimmunity, such as systemic lupus erythematosus (SLE) and sarcoid, hepatoxicity, and hematological reactions. The AESIs were defined by the applicant and retrieved using MedDRA SOCs, Amgen search strategies, or SMQs including the Cardiac Failure SMQ, Opportunistic Infections SOC, Malignancies SMQ, Demyelination SMQ, Hepatitis B Infections Amgen query and the SLE SMQ. Table 41 is a sponsor generated table that lists AESIs for the first 22 weeks of the study and Table 42**Error! Reference source not found.** lists those that occurred after week 22. There were small numerical differences observed but with inconsistent trends, which are likely due to chance alone, and do not indicate meaningful differences between ABP-710 and US-Remicade.

Table 41. Incidence of AESIs through Week 22 in Study 20140111

	ABP 710 (N = 278)		Infliximab (N = 278)	
Event of Interest	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)
Any adverse event of interest	5 (1.8)	38 (13.7)	5 (1.8)	49 (17.6)
Infusion reactions including hypersensitivity	2 (0.7)	21 (7.6)	2 (0.7)	37 (13.3)
Hematological reactions	0 (0.0)	10 (3.6)	0 (0.0)	5 (1.8)
Hepatotoxicity	0 (0.0)	9 (3.2)	0 (0.0)	9 (3.2)
Serious infections	1 (0.4)	2 (0.7)	3 (1.1)	4 (1.4)
Congestive heart failure	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Opportunistic infections	0 (0.0)	1 (0.4)	2 (0.7)	2 (0.7)
Malignancies	2 (0.7)	2 (0.7)	0 (0.0)	2 (0.7)
Demyelinating disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis B reactivation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Autoimmunity (SLE and sarcoid)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

Source: Module 5.3.5.1, Clinical Study Report 20140111, Clinical Study Report, p. 161

Table 42. Incidence of AESIs after Week 22 in Study 20140111

	ABP 710/ABP 710 (N = 240)		Infliximab/Infliximab (N = 121)		Infliximab/ABP 710 (N = 119)	
Event of Interest	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)
Any adverse event of interest	5 (2.1)	39 (16.3)	2 (1.7)	16 (13.2)	4 (3.4)	15 (12.6)
Infusion reactions including hypersensitivity	0 (0.0)	19 (7.9)	1 (0.8)	10 (8.3)	0 (0.0)	6 (5.0)
Hepatotoxicity	1 (0.4)	10 (4.2)	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)
Hematological reactions	0 (0.0)	9 (3.8)	0 (0.0)	6 (5.0)	1 (0.8)	8 (6.7)
Serious infections	3 (1.3)	4 (1.7)	1 (0.8)	1 (0.8)	3 (2.5)	3 (2.5)
Malignancies	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congestive heart failure	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Opportunistic infections	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Demyelinating disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis B reactivation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Autoimmunity (SLE and sarcoid)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Module 5.3.5.1, Clinical Study Report 20140111, p. 162

Overall, the incidence of AESIs in this study was relatively low across treatment arms and the type of AESIs reported appear comparable between ABP 710 and US-Remicade. Although there were differences in the incidence of some AESIs between the treatment

arms, this difference appears to be due to the search query methods rather than a clinically meaningful difference in the rate of any particular AESI. For example, when looking at the AESI of infusion reactions/hypersensitivity which displayed the largest difference, the PTs captured in this query are quite broad and include some nonspecific terms (e.g., vomiting, fatigue, headache, hepatic enzyme increased) that, in isolation, are not indicative of an infusion reaction or hypersensitivity event. However, the differences are less apparent when evaluating preferred terms within each SOC or SMQ, with erythema being the most commonly listed term under infusion reaction during each treatment period.

7.5. Clinical Conclusions on Immunogenicity

The immunogenicity evaluation included qualitative and quantitative measurement of anti-drug antibody (ADA) and neutralizing antibody (NAb) in healthy subjects (from a single dose PK study) and in RA patients (multiple dose up to 46 weeks). ABP 710 was similar to US-Remicade in regard to the formation of ADA and NAb and their impact on PK, efficacy, and safety. Therefore, the immunogenicity evaluation supports the demonstration of no clinically meaningful differences. Refer to Section 6.4 **Error! Reference source not found.**for more details and discussion of the results.

Authors:

Katherine Clarridge, MD
Clinical Reviewer

Stacy Chin, MD
Clinical Team Leader

7.6. Extrapolation to Support Approval of Non-Studied Indications

The collective evidence from the comparative clinical study supports a demonstration of no clinically meaningful differences between ABP 710 and US-Remicade in the studied indication (RA). However, the applicant is also seeking licensure of ABP 710 for the following indications for which US-Remicade has been previously licensed and for which ABP 710 has not been directly studied (PsA, AS, CD, pediatric CD, UC, pediatric UC, and PsO). Thus, the applicant provided a justification for extrapolating data and information submitted in the application to support licensure of ABP 710 as a biosimilar for each condition of use for which licensure is sought and for which US-Remicade has been previously approved.

Amgen's analytical characterization data support a demonstration that ABP 710 is highly similar to US-Remicade notwithstanding minor differences in clinically inactive components. In addition, the data support a demonstration there are no clinically meaningful differences between ABP 710 and US-Remicade in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in RA.

Further, the additional points considered in the scientific justification for extrapolation of data to support licensure of ABP 710 for the treatment of PsA, AS, CD, pediatric CD, UC, pediatric UC, and PsO, as referenced in Appendices 13 and 14, include:

- Similar PK was demonstrated between ABP 710 and US-Remicade, as discussed in Section 6 on Clinical Pharmacology. Importantly, ABP 710 was demonstrated to be highly similar to US-Remicade, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between ABP 710 and US-Remicade in the indications sought for licensure. Thus, a similar PK profile would be expected between ABP 710 and US-Remicade in subjects across all the indications being sought for licensure.

- The Agency has concluded that there are sufficient data to support similar immunogenicity between ABP 710 and US-Remicade with repeat dosing in subjects with RA, and between ABP 710 and US-Remicade after a single dose in healthy subjects, and both populations are considered sensitive for detecting meaningful differences. Accordingly, similar immunogenicity would be expected between ABP 710 and US-Remicade in patients with PsA, AS, CD, pediatric CD, UC, pediatric UC, and PsO.

- A similar clinical safety profile with chronic dosing was demonstrated between ABP 710 and US-Remicade in patients with RA, and between ABP 710 and US-Remicade following single doses in healthy subjects. As analytical and PK similarity was demonstrated between ABP 710 and US-Remicade, a similar safety profile would be expected between ABP 710 and US-Remicade in patients with PsA, AS, CD, pediatric CD, UC, pediatric UC, and PsO.

- Amgen addressed each of the known and potential mechanisms of action of US-Remicade and submitted data to support the conclusion that ABP 710 and US-Remicade have the same mechanisms of action for each of the sought indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Therefore, based on the above considerations, and in consultation with the DGEIP and DDDP review teams (refer to Appendices 13 and 14), the applicant has demonstrated that ABP 710 is biosimilar to US-Remicade for each of the following indications for which US-Remicade has been previously approved and for which Amgen is seeking licensure of ABP 710: RA, PsA, AS, CD, pediatric CD, UC, pediatric UC, and PsO.

Author:
Stacy Chin, MD
CDTL

8 Labeling Recommendations

8.1. Nonproprietary Name

The applicant proposed suffix, 'axxq', was found to be conditionally acceptable by the Agency.

8.2. Proprietary Name

The proposed proprietary name for ABP 710 is conditionally approved as Avsola. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the name was acceptable.

8.3. Other Labeling Recommendations

ABP 710 is a proposed biosimilar to US-Remicade. The applicant is proposing a dosage form and strength of 100 mg of lyophilized ABP 710 in a 20 mL vial for intravenous infusion.

The proposed ABP 710 prescribing information incorporated relevant data and information from the US-Remicade prescribing information, with appropriate modifications. The applicant is seeking licensure for the following indications, for which US-Remicade has been previously approved: Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

The labeling was reviewed to ensure compliance with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) and consistency with labeling guidance recommendations and CDER/OND best labeling practices and policies. The labeling was also reviewed to ensure that information is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

Amgen agreed to changes requested by the Division to improve the readability, clarity, and accuracy of the prescribing information.

Authors:

Katherine Clarridge, MD
Clinical Reviewer

Stacy Chin, MD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No advisory committee was held for this biosimilar application as it was determined that there were no issues where the Agency needed input from the committee.

Authors:

Katherine Clarridge, MD
Clinical Reviewer

Stacy Chin, MD
Clinical Team Leader

10 Pediatrics

The Applicant's initial pediatric study plan (iPSP) was presented to PeRC on July 17, 2019. No Pediatric Research Equity Act (PREA) PMRs were recommended.

The agency has determined at this time that no pediatric studies will be required under PREA for this applicant's BLA. Refer to memo dated November 22, 2019.

Authors:

Katherine Clarridge, MD
Clinical Reviewer

Stacy Chin, MD
Clinical Team Leader

11 REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

Develop and implement a control strategy for the Fc-domain-mediated effector function of antibody-dependent cell mediated cytotoxicity (ADCC) of ABP 710. The test format can either be a functional bioassay or the use of FcγRIIIa binding as a surrogate. The proposed control strategy and supporting validation data will be submitted to FDA following 21 CFR 601.12 (b).

Final Report Submission: 12/31/2020

Authors:
Katherine Clarridge, MD
Clinical Reviewer

Stacy Chin, MD
Clinical Team Leader

12 Appendices

12.1. Financial Disclosure

The applicant provided financial disclosure information on all investigators that participated in the two clinical studies listed in Table 3. Two completed Financial Certification and Disclosure Form 3454, one for Study 20140111 and one for Study 20140108, were submitted. Of the 324 clinical investigators involved in either study, all have certified to the absence of significant proprietary and/or equity interests, as required by 21CFR54.2(b). Furthermore, there were no investigators who did not provide any financial disclosure information during the conduct of the studies.

Covered Clinical Study (Name and/or Number): 20140111 and 20140108

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 324		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in Sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

12.2. Office of Clinical Pharmacology Appendices

12.2.1. Summary of Bioanalytical Method Validation and Performance

12.2.2. Pharmacokinetics

The serum concentrations of ABP 710, US-Remicade and EU-Remicade were appropriately quantified using a validated electrochemiluminescence (ECL) assay in Study 20140108 and ABP 710 and US-Remicade in Study 20140111 (validation report 119704 and 119704 addendum 1).

During the method validation, ABP 710, US-Remicade and EU-Remicade were used to establish the standard curves, and the accuracy and precision (± 20.0%, ± 25.0% for lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ)) was evaluated using ABP 710, US-Remicade and EU-Remicade as QC samples. The assay validation were summarized in **Table** 43 below.

Table 43. Summary of the bioanalytical method validation and in-study performance for measurement of US-Remicade and ABP 710

Bioanalytical method review summary	The PK method is supported by a method qualification study that was conducted prior to the start of the validation. The method qualification study was performed to establish bioanalytical comparability between ABP 710 and US-Remicade and EU-Remicade. Method qualification data was generated by (b) (4) in project RCPX4. Data was submitted from (b) (4) to the Applicant for evaluation of analytical comparability and to justify the use of a single calibrator (ABP 710); comparability was demonstrated. Standards (STD) and validation samples (VS) were prepared by spiking ABP 710 into 100% healthy human serum. When appropriate during validation, QCs were also prepared by spiking US-Remicade and EU-Remicade into 100% human serum. STD, VS, QC, blank and other validation samples were added to a plate that had been passively coated with a mouse anti-ABP 710 monoclonal antibody (b) (4), Amgen, Inc., CA). After

<table>
<tr><td></td><td>capture of ABP 710 or US-Remicade to the immobilized antibody, unbound materials were removed by a wash step. Ruthenium labeled mouse
anti-ABP 710 monoclonal antibody ((b) (4) , Amgen, Inc. CA) was added for detection of captured ABP 710 and US-Remicade.
After another wash step, a tripropylamine read buffer (MSD®) was added to the plate. Ruthenium emits light at 620 nm when electrically stimulated and co-reacts with the tripropylamine buffer to enhance the electrochemiluminescent signals (ECL counts).
The ECL counts were directly proportional to the amount of ABP 710 and US-Remicade bound by the capture reagent.
The response vs. concentration relationship was regressed according to a four parameter logistic regression model with a weighting factor of 1/response2. The conversion of ECL counts to concentrations was performed using (b) (4) LIMS ((b) (4)).</td></tr>
<tr><td>Materials used for calibration curve & concentration</td><td>ABP 710</td></tr>
<tr><td>Validated assay range</td><td>10-5000 ng/mL</td></tr>
<tr><td>Material used for QCs & concentration</td><td>ABP 710, US-Remicade , EU-Remicade</td></tr>
<tr><td>Minimum required dilutions (MRDs)</td><td>1:50</td></tr>
<tr><td>Source & lot of reagents (LBA)</td><td>
<table>
<tr><th>Name</th><th>Lot Number</th><th>Source</th></tr>
<tr><td>ABP 710 (b) (4)</td><td>0010190343</td><td>Amgen</td></tr>
<tr><td>US-Remicade
(reference test article)</td><td>EBD14013P1</td><td>Janssen
(supplied by Amgen)</td></tr>
<tr><td>EU-Remicade</td><td>3RMA62304</td><td>Janssen</td></tr>
<tr><td>EU-Remicade</td><td>3RMA70303</td><td>Janssen</td></tr>
<tr><td>Mu Anti-ABP 710 (b) (4) (Capture Antibody)</td><td>P142115.4</td><td>Amgen</td></tr>
<tr><td>Mu Anti-ABP 710 (b) (4) (Secondary Antibody)</td><td>PL-36525</td><td>Amgen</td></tr>
</table>
</td></tr>
<tr><td>Regression model & weighting</td><td>four-parameter logistic, 1/response^2 weighted</td></tr>
<tr><td>Validation Parameters</td><td>Method Validation Summary</td></tr>
<tr><td></td><td>No of standard calibrators from LLOQ to ULOQ</td><td>9</td></tr>
</table>

Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) from LLOQ to ULOQ ABP 710	 -3 to 2%
	Cumulative precision (%CV) from LLOQ to ULOQ ABP 710	 ≤ 4%
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs ABP 710 US-Remicade EU-Remicade	 -6 to 1% -4 to 9% -5 to 7%
	Inter-batch %CV ABP 710 US-Remicade EU-Remicade	 ≤ 12% ≤ 14% ≤ 15%
	Percent total error (TE) ABP 710 US-Remicade EU-Remicade	 ≤ 16% ≤ 18% ≤ 20%
Selectivity & matrix effect	10 healthy individuals and 20 with rheumatoid arthritis. No matrix effect observed.	
Interference & specificity	In the presence of other structurally similar compounds, a structurally similar IgG1 molecule, no specificity effects observed.	
Dilution linearity & hook effect	Linearity was demonstrated for all three test articles diluted in 100% healthy human serum at dilution factors of 50 to 400.	
Bench-top/process stability	Stability was demonstrated for all three test articles as follows: 1. At 2-8 °C for up to 24 hours prior to pretreatment 2. At 2-8 °C for up to 24 hours after pretreatment 3. At ART for 24 hours prior to pretreatment 4. At ART for 24 hours after pretreatment	
Freeze-Thaw stability	Stable up to four freeze-thaw cycles for all three test articles.	
Long-term storage	Stability was demonstrated up to 102 days at -25 °C ± 5 °C and up to 711 days at -80 °C ± 10 °C	
Parallelism	Parallelism was not performed	
Carry over	Carry over was not performed	
Method Performance in Study 20140108		
Assay passing rate	• 84.4% for Study 20140108	
Standard curve performance	• Cumulative bias range: -1 to 2% • Cumulative precision: ≤ 5% CV	
QC performance	• Cumulative bias range: -6 to 0%	

	• Cumulative precision: ≤ 16% CV • TE: ≤ 18% (LBA only)
Method reproducibility	• Incurred sample reanalysis was performed in 7.57% of study samples and 95.1% of samples met the pre-specified criteria
Method Performance in Study 20140111	
Assay passing rate	• 94.4%
Standard curve performance	• Cumulative bias range: -2 to 2% • Cumulative precision: ≤ 3% CV
QC performance	• Cumulative bias range: -6 to 0% • Cumulative precision: ≤ 16% CV • TE: ≤ 18% (LBA only)
Method reproducibility	• Incurred sample reanalysis was performed in 6.1% of study samples and 97.4% of samples met the pre-specified criteria
Study sample analysis/ stability	711 days at nominal -80°C 102 days at nominal -25°C
Study sample analysis/ stability	711 days at nominal -80°C 102 days at nominal -25°C

12.3. Nonclinical Pharmacology and Toxicology Appendix

12.3.1. Nonclinical Pharmacology

Primary Pharmacology

ABP 710 is a chimeric immunoglobulin of the IgG1κ isotype monoclonal antibody. It binds with high affinity and specificity to the soluble and transmembrane tumor necrosis factor alpha (TNFα) but not TNFβ [also known as lymphotoxin alpha (LT)]. Binding to TNFα inhibits the interaction of TNFα with its receptors and subsequent signal transduction resulting in the suppression of inflammation.

The Applicant's pharmacology studies were evaluated as part of the product quality assessment. Refer to the OBP Integrated Quality Assessment for detailed discussion of these studies.

The Applicant stated "Additional mechanisms of action (MOAs) that may be important for efficacy in the inflammatory bowel diseases (IBDs) ulcerative colitis and Crohn's disease (CD) include antibody- dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) (Horiuchi et al, 2010) and reverse signaling (Mitoma et al, 2005) through binding to the membrane-bound form of TNFα (mbTNFα)." The Applicant also stated "US-Remicade and ABP 710 have been observed to mediate antibody-dependent cellular phagocytosis (ADCP), although there is no indication that this activity contributes to clinical efficacy or safety."

The Applicant conducted 2 studies that evaluated some of these potential MOAs, mixed lymphocyte assay (MLR) with cells from healthy human subjects and an ADCC assay with cells from healthy human subjects and Crohn's Disease patients. Both assays were thought to be critical for therapeutic application in Crohn's Disease, in which membrane bound TNFα is thought to have a more critical role than soluble TNFα.

Study Title: Similarity Assessment of ABP 710 and US-Remicade Inhibition of Proliferation in a MLR Assay

Report R20150173

- ABP 710, EU-Remicade, and US-Remicade had similar inhibitory effects on cell proliferation in a mixed lymphocyte reaction assay using cells from 2 heathy human donors with mismatched human leukocyte antigen.

- The inhibition of cell proliferation in a MLR assay by US-Remicadewas similar to EU-Remicade, and the inhibition by ABP 710 was similar to both US-Remicade and EU-Remicade.

Methods

Two healthy human donors (#(b) (6) and #(b) (6)) contributed peripheral blood mononuclear cells. Cells from one donor were irradiated to prevent activation and proliferation of those donor cells. Cells from both donors were incubated together for 48 h in microwell plates, then ABP 710 or US-Remicade and EU-Remicade was added (5 µg/mL) and incubated for an additional 3 days. Proliferating cells are identified after newly synthesized DNA is labeled with a modified thymidine analogue, EdU (5-ethynyl-2'-deoxyuridine), in EdU during overnight incubation, followed by conjugation to AF488 involving a copper-catalyzed covalent reaction between the picolyl azide coupled to Alexa Fluor® 488 (AF488) fluorescent dye and an alkyne found in the ethynyl moiety of EdU. Cells were analyzed for the EdU-AF488 signal by flow cytometry to obtain cell counts. The mean % of control values for each antibody were compared to the ABP 710 reference standard in that assay to generate a % relative inhibition.
Seven independent studies were conducted.

Drug, Lots, and Formulations

ABP 710, Lots 0010237659, 0010301972, and 0010302149
Formulation: (b) (4) sodium phosphate, 5% sucrose (w/v), 0.005% polysorbate 80, pH 7.2

ABP 710 reference standard, Lot 0010189002
Formulation: (b) (4) sodium phosphate, (b) (4)% sucrose (w/v), (b) (4)% polysorbate 80, pH 7.2

EU-Remicade, Lots 6RMA60204, 6RMA64303, and 6RMA68806
Formulation: (b) (4) sodium phosphate, 5% sucrose (w/v), 0.005% polysorbate 80, pH 7.2

US-Remicade, Lots 16C032P1, 16JD15581, and 16LD17551
Formulation: (b) (4) sodium phosphate, 5% sucrose (w/v), 0.005% polysorbate 80, pH 7.2

Controls

Irradiated Donor (b) (6) alone – included in each assay to validate level of irradiation was sufficient to prevent any proliferation.

Donor (b) (6) alone – included in each assay to determine level of proliferation in the absence of stimulation.

Irradiated Donor (b) (6) Non-irradiated Donor (b) (6) no EdU – Control for background signal not due to EdU.

Irradiated Donor (b) (6)/Non-irradiated Donor (b) (6) with EdU, 0 µg/mL antibody – Control for maximum stimulation.

The mean % of control values for each antibody were compared to the ABP 710 reference standard in that assay to generate a % relative inhibition. One EU-Remicade lot (#6RMA68806) was excluded from the initial analysis and rerun since no TNFα-induced cytotoxicity occurred in the initial assays.

Results

The mean % of control for the lots tested ranged from 62% to 70% (% CV range 3% to 11%). The mean relative inhibition ranged from 89% to 99% (%CV range 2% to 8%). The % of control and % relative inhibition values were similar between all the lots tested. Thus, ABP 710,US-Remicade, or EU-Remicade resulted in similar inhibition of cell proliferation in the MLR assay.

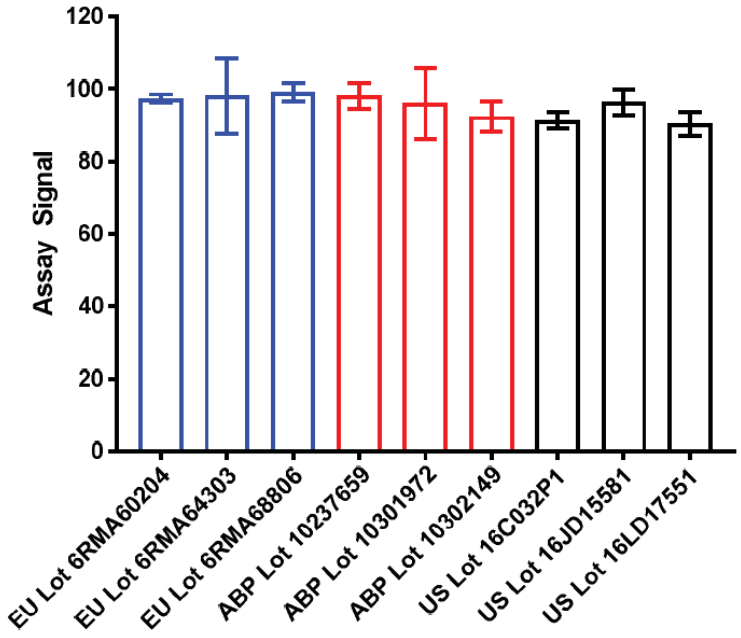


Figure 12. Summary of Relative Inhibition of EU-Remicade, ABP 710, and US-Remicade in a MLR Assay (from Applicant's Figure 4)

Summary of assay results for all tested lots. The assay signal is the mean % relative inhibition of 3 replicated assays for each lot and the error bars are standard deviation.

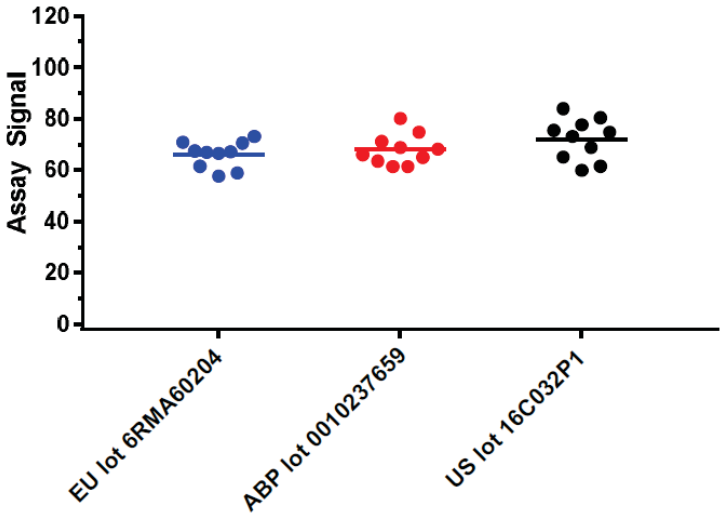


Figure 13. Summary of Representative Lots of EU-Remicade, ABP 710, and US-Remicade in a MLR Assay (from Applicant's Figure 8)

PBMC from Donor (b) (6) were mixed and incubated with irradiated PBMC from Donor (b) (6) for 48 hours to stimulate proliferation due to HLA mismatch. After 48 hours, antibody (5 g/mL) or media was added and this mixture was incubated for an additional 72 hours before adding EdU. After an overnight incubation, EdU incorporated into the DNA was labelled with AF488. EdU positive cells were measured by flow cytometry. Assay signal is % of control and each dot represents a single replicate with the lines representing the mean of all replicates. Source: ELN ID 20170803-00011

Study Title: Assessment of ABP 710 and US-Remicade in an ADCC Assay Using PBMC From Healthy Subjects and Crohn's Disease Donors

Report TA-009389

Methods

The ADCC activity of ABP 710, US-Remicade, and EU-Remicade was evaluated using peripheral blood mononuclear cells (PBMC) isolated from healthy volunteers (n=5, 4 males, 1 female) or from Crohn's disease patients (n=3 males) as effector cells. Target cells consisted of CHO MT-3 cell line engineered to stably express mbTNFα and a proprietary housekeeping protein fused to an inactive fragment of the β-galactosidase (β-gal) reporter. The target cells were mixed with PBMC at a 1:200 ratio, respectively, in the presence of varying concentrations of ABP 710, US-Remicade, or EU-Remicade. Dose-response curves were generated for each lot of ABP 710, US-Remicade, EU-Remicade and an ABP 710 reference standard (0.0214 – 6000 ng/mL, or for one healthy donor 0.1286 – 36000 ng/mL), then assessed quantitatively.

Test article: ABP 710 Reference Standard,
Lot No: 0010189002
Test article: ABP 710
Lot No(s): 0010190343; 0010201184

Test article US-Remicade

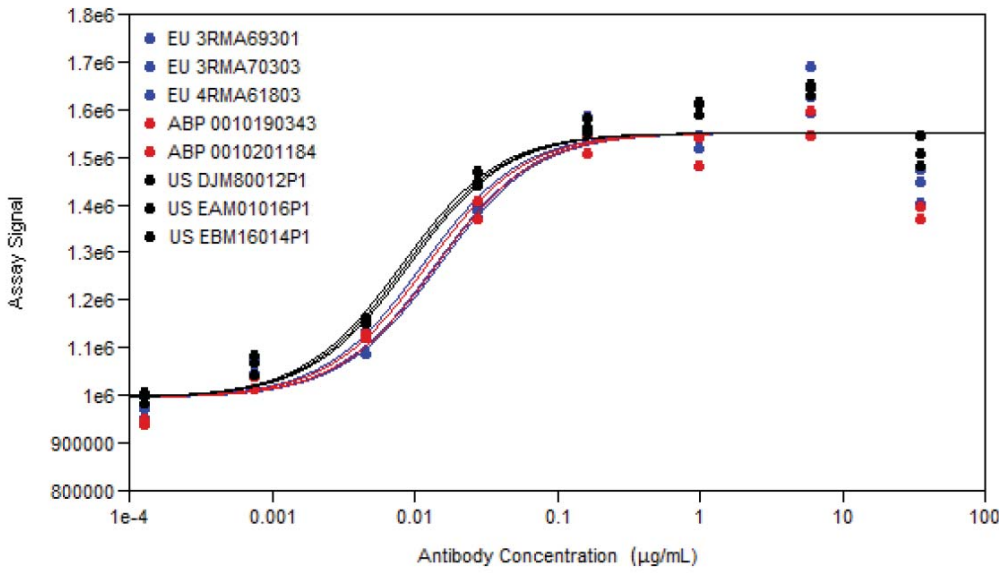
Lot No(s): DJM80012P1; EAM01016P1; EBM16014P1

Test article: EU-Remicade

Lot No(s): 3RMA69301; 3RMA70303; 4RMA61803

Results

PBMC isolated from 5 healthy volunteers showed similar, dose-dependent ADCC activity in the presence of ABP 710, US-Remicade, and EU-Remicade. Two of three donor PBMC isolated from Crohn's disease patients showed similar, dose-dependent ADCC activity in the presence of ABP 710, US-Remicade, and EU-Remicade, while PBMC from the remaining Crohn's disease patient did not respond to any of the drugs.



Assay Signal = RLU (Relative Luminescence Units); Data Source = wbretzla.01-004

Figure 14. ADCC Activity in Healthy PBMCs with ABP 710, EU-Remicade, and US-Remicade, (from Applicant's Figure 2)

Dose-response curves for 2 lots of ABP 710 and 3 lots each of US-Remicade and EU-Remicade in PBMC from 2 representative healthy donors. Assay signal = relative luminescence units
ADCC = antibody-dependent cell-mediated cytotoxicity; infliximab (EU) = EU-Remicade; infliximab (US) = US-Remicade; PBMC = peripheral blood mononuclear cells.

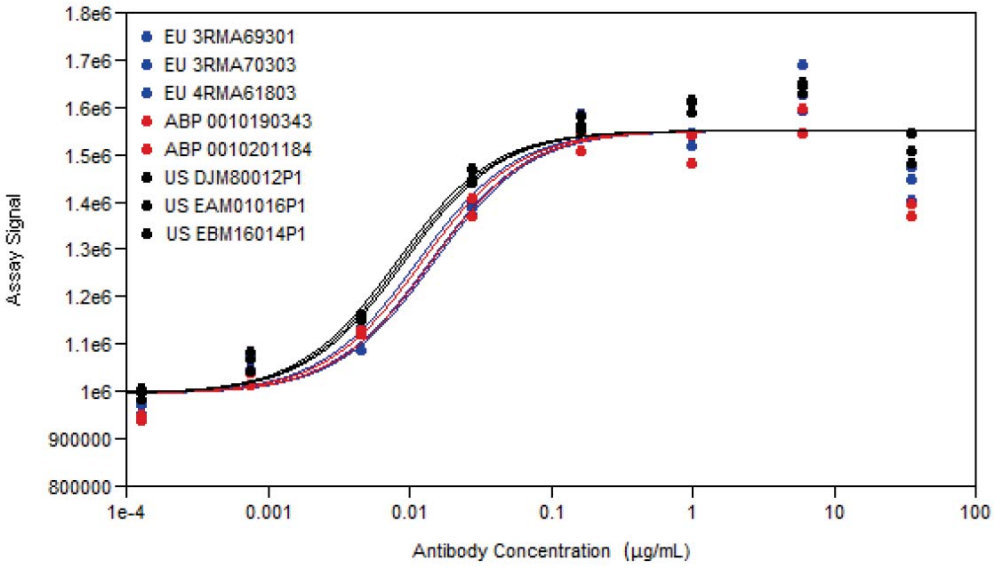


Figure 15. ADCC Activity in Crohn's Disease PBMCs with ABP 710, EU-Remicade, and US-Remicade, (from Applicant's Figure 2)

Dose-response curves for 2 lots of EU-Remicade, ABP 710, and US-Remicade in PBMC from a Crohn's disease donor. Assay signal = relative luminescence units
ADCC = antibody-dependent cell-mediated cytotoxicity; infliximab (EU) = EU-Remicade; infliximab (US) = US-Remicade; PBMC = peripheral blood mononuclear cells.

12.3.2. Nonclinical Pharmacokinetics and Pharmacodynamics

Nonclinical toxicokinetics from the 2-week toxicity study in rats (Report 118849, discussed below) demonstrated ABP 710 and US-Remicade resulted in similar toxicokinetic parameters (Cmax, Tmax, AUC) as presented in the following table. Anti-drug antibodies were not assessed in the study. Separate nonclinical ADME studies were not conducted.

Table 44. Toxicokinetic Parameter Values in Sprague Dawley Rats After Intravenous Administration of ABP 710 or US-Remicade Once Weekly for 2 Weeks (Report 118849, from Module 2.6.4 Summary, Table 2)

Sprague Dawley Rats[a]				
TK Parameter	ABP 710 10 mg/kg	US-Remicade 10 mg/kg	ABP 710 50 mg/kg	US-Remicade 50 mg/kg
Day 1				
C_{max} (µg/mL)	296 (38.9)	275 (53.8)	1430 (110)	1290 (144)
AUC_{0-t} (µg•hr/mL)	19900 (1680)	19900 (2600)	98300 (8720)	87800 (7020)
Day 8				

C_{max} (µg/mL)	300 (89.0)	315 (76.2)[b]	1360 (366)	1570 (387)
AUC_{0-t} (µg•hr/mL)	27700 (3540)	28500 (3730)[b]	124000 (17100)	130000 (11600)
AR	1.39 (0.151)	1.47 (0.199)[b]	1.27 (0.165)	1.48 (0.103)

AR = accumulation ratio; AUC = area under the serum drug concentration-time curve; AUC_{0-t} = AUC from time 0 to the time of the last quantifiable concentration; C_{max} = maximum concentration; infliximab (US) = Remicade®, which is approved and marketed in the United States; SD = standard deviation; TK = toxicokinetic.

[a] TK parameters are reported as mean (SD) (n = 4/sex/dose group).

[b] One outlier was excluded from summary statistics; see Appendix 10 of Study 118849 for details. Source: Table 4-1 in Appendix 10 of Study 118849

12.3.3. General Toxicology

A toxicity study in rats was conducted to support the safety of ABP 710 prior to the clinical study. The Applicant was informed at the preIND meeting that specific studies for pregnancy and fertility labeling, mutagenicity and carcinogenicity of its proposed biosimilar would be unnecessary, and relevant information from the labeling of US-Remicade, with appropriate modifications, could be incorporated into the proposed product's labeling.

Repeat-Dose Toxicity/Toxicokinetics

A toxicity study was conducted in rats to compare the effects of ABP 710 and US-Remicade. The study was an examination of off-target (non-pharmacodynamic) effects, since neither drug binds non-human TNFα, except for chimpanzee TNFα.

Sprague-Dawley rats (n= 10/sex/dose group) were administered 10 or 50 mg/kg ABP 710 or US-Remicade, intravenously once weekly on day 1 or day 8 and animals were sacrificed on day 15. The control animals received vehicle comprising (b) (4) phosphate, 5% sucrose and
0.005% (v/v) polysorbate 80 at pH 7.2. Toxicokinetic samples were obtained from another set of rats (n=4/sex/dose group). There were no recovery groups.

Both ABP 710 and US-Remicade produced similar toxicokinetic parameter values and similar off-target effects. There were small increases in platelet numbers and a reduction in triglycerides which were similar in magnitude and occurred at the same dose levels and same sexes. The small changes were not considered to be toxicologically significant. There was a small increase in the incidence of lung granulomas of minimal severity in both drug groups at the high dose. The low doses were not examined histologically unless macroscopic lesions were apparent. The low incidence at the high dose made interpretation of dose-related effects difficult even if the low dose was evaluated, since the US-Remicade female group had no granulomas. While rarely observed in young animals, lung granulomas sometimes occur with tail vein intravenous injection of protein solutions in rats since injected material travels directly to the heart then the lung; however, the lack of an obvious dose response, the absence

of associated inflammation, and the comparable effects across drug groups provides reasonable assurance of clinical safety.

The toxicity study demonstrated similar off-target responses and magnitudes of both ABP 710 and US-Remicade. The study supports a determination of biosimilarity.

Study title: ABP 710: 14-Day Intravenous Toxicology Study in the Sprague Dawley Rat

Study no.:	**118849**
Study report location:	Module 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 29, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ABP 710, Batch 0010189023, Purity 99.1% (0.9% HMW, <0.1% LMW) US-Remicade, Batch DJM80012P1, Purity not provided

Key Study Findings

- ABP 710 and US-Remicade produced similar results when administered IV to Sprague-Dawley, once weekly for two weeks (day 1 and day 8), at dosages of 10 or 50 mg/kg (n=10 animals/sex/dose group).
- Similar drug toxicokinetic parameters were obtained between both drugs at each dose level.
- There was a small increase in platelets in males and increase in triglycerides in males and females at the 50 mg/kg dose for both drugs, but the changes were not considered to be toxicologically significant.
- There were similar low incidences of lung granulomas in the high dose males and females groups of ABP 710 and in males of US-Remicade. These were associated with an increase in alveolar macrophages, but there were no signs of inflammation or other pathology.
- Although there are limitations of the study due to the lack of a pharmacodynamic effect, the off-target findings support the biosimilarity of ABP 710 and US-Remicade.

Methods

Doses:	ABP710: 0, 10, or 50 mg/kg US-Remicade: 0, 10, or 50 mg/kg The dose levels were based on 2- and 10-fold the clinical dose of 5 mg/kg and too enable graded effect responses.
Frequency of dosing:	Once weekly for 2 injections
Route of administration:	Intravenous (tail vein, slow bolus)
Dose volume:	5 mL/kg
Formulation/Vehicle:	(b) (4) phosphate, 5% sucrose and 0.005% (v/v) polysorbate 80 at pH 7.2

Species/Strain: Sprague Dawley rats
Number/Sex/Group: 10/sex/dose
Age: 10 weeks at receipt
Weight: 200 to 400 g
Satellite groups: Toxicokinetics, n=4/sex/dose
Unique study design: The dose levels were based in an attempt to produce graded responses to the test article. The high- and low-dose levels were selected as 10- and 2-fold the clinical dose of 5 mg/kg, respectively.

Experimental Design

Main Study Groups 1-5

Group No.	Test Material	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	No. of Animals	
					Males	Fema
					Main	Mai
1	Control	0	5	0	10	10
2	Infliximab	10	5	2	10	10
3	Infliximab	50	5	10	10	10
4	ABP 710	10	5	2	10	10
5	ABP 710	50	5	10	10	10

TK Groups 6-10

Group No.	Test Material	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	No. of Animals	
					Males	Female
					Toxicokinetic	Toxicokin
6	Control	0	5	0	4	4
7	Infliximab	10	5	2	4	4
8	Infliximab	50	5	10	4	4
9	ABP 710	10	5	2	4	4
10	ABP 710	50	5	10	4	4

Infliximab=US-Remicade
Deviation from study protocol: There were no deviations that affected the interpretation or conclusion of the study.

Observations and Results

Mortality

Animals were checked twice daily.

There were no mortalities.

Clinical Signs

Animals were checked at cageside at least once daily, at 30 min postdose.

There were no clinical signs attributed to ABP 710 or US-Remicade.

Body Weights

Animals were weighed once weekly.

There were no changes in body weight or weight change attributed to ABP 710 or US-Remicade.

Feed Consumption

Food consumption was monitored qualitatively once weekly.

There were no changes in food consumption attributed to ABP 710 or US-Remicade.

Ophthalmoscopy

Ophthalmic examinations were conducted at prestudy and in the final week of the study using slit lamp biomicroscopy and indirect ophthalmoscopy.

There were no changes in ophthalmic findings that were considered treatment-related.

Hematology

Blood was collected from the jugular or lateral tail vein on day 15. Bone marrow smears were also collected at necropsy but were not evaluated.

ABP 710 and US-Remicade treatments both resulted in small increase in platelets in males at the 50 mg/kg dose but not at 10 mg/kg/week. There were no US-Remicade- or ABP 710-related changes in other hematological or coagulation parameters.

Table 45. Hematology Findings

Dose (mg/kg/week)	**0**		**ABP 710**				**US-Remicade**			
			10		**50**		**10**		**50**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
N	**10**	**10**	**10**	**9**	**10**	**10**	**10**	**10**	**9**	**10**
Platelets (10^3/µL)	953	1173	1016	1070	**1199*** **126%**	1230 1.05%	1010	1014	1071 113%	1255 107%
* P<0.05										

Clinical Chemistry

Blood was collected from the jugular or lateral tail vein on day 15.

ABP 710 and US-Remicade treatments resulted in small decreases of triglycerides at the high doses. These changes are not considered to be toxicologically significant. There were no other clinical chemistry effects.

Table 46. Clinical Chemistry Findings (values rounded by reviewer)

Dose (mg/kg/week)	**0**		**ABP 710**				**US-Remicade**			
			10		**50**		**10**		**50**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
N	**10**	**10**	**10**	**8**	**10**	**10**	**10**	**10**	**9**	**10**
Triglycerides (mg/dL)	45	38	40 88%	38 100%	**34** **76%**	**34** **89%**	46 102%	38 100%	**41** **91%**	**34** **89%**
Actual values rounded up or down by the Reviewer. No statistical significance was indicated between control and ABP 710 or US-Remicade in the summary tables despite an indication of this by the Applicant.										

Urinalysis

Urine was collected overnight before necropsy.

There were no ABP 710 or US-Remicade treatment effect of urinalysis parameters.

Gross Pathology

Main study animals were subjected to a complete necropsy examination after euthanasia on study day 15.

There were no ABP 710- or US-Remicade related macroscopic changes.

Organ Weights

The weighed organs are listed below.

Organs Weighed at Necropsy

Brain Epididymis[a] Gland, adrenal[a] Gland, pituitary Gland, prostate Gland, thyroid[a] Heart	Kidney[a] Liver Ovary[a] Spleen Testis[a] Thymus

[a] Paired organ weight.

There were no ABP 710- or US-Remicade -related organ weight changes.

Histopathology

Adequate Battery:

Only the high dose (50 mg/kg/week) US-Remicade and ABP 710 and control treatment tissues were examined histopathologically. Low dose (10 mg/kg/week) group tissues were planned to be examined only if there were macroscopic lesions present and none were present. The standard list of tissues was collected and examined.

Peer Review: Yes, by the applicant's pathologist, thus not considered an independent reviewer. Examined and discussed with the study pathologist were the first 5 males and females in the control and the first 5 males and females in high dose groups given ABP 710 and US-Remicade at 50 mg/kg/week and any tissues with gross lesions. This was acceptable and did not affect the validity of the study.

Histological Findings

There were no ABP 710- or US-Remicade treatment-related microscopic changes based on examination of tissues from the 50 mg/kg/week ABP 710 and US-Remicade doses and control groups. There was a low incidence of lung granuloma of minimal severity in males and females at the 50 mg/kg/week groups of both ABP 710 and US-Remicade. These were associated with the presence of alveolar macrophages, but there were no signs of inflammation or other pathologies. Control animals and high dose females lacked granulomas.

Only tissues from the 10 mg/kg/week dose groups with macroscopic findings were examined histologically. One female (#4506) in the 10 mg/kg/week ABP 710 group had moderately severe pyogranulomatous inflammation of the spleen without detectable bacteria, and with focal, pale, tan discoloration noted macroscopically. This was judged to be unrelated to ABP 710 treatment and the reviewer concurs.

Table 47. Summary of Histological Findings

Dose (mg/kg/week)		**0**		**50 ABP 710**		**50 US-Remicade**	
Sex		**M**	**F**	**M**	**F**	**M**	**F**
N		**10**	**10**	**10**	**10**	**10**	**10**
Lung							
Focal granuloma	minimal	0	0	1	2	2	0
Alveolar Macrophages	minimal	1	3	2	1	2	4

Toxicokinetics

Blood was collected from the jugular or lateral tail vein on days 1 and 8 at 1, 24, 48, 72, and 168 hrs postdose (168 hr corresponds to day 8 and day 15 respectively). Serum was harvested and analyzed for ABP 710 and US-Remicade. ABP 710 and US-Remicade iconcentrations were measured using a validated electrochemiluminescent immunoassay method (Report 119411, titled "Method Validation Report for the Quantification of ABP 710 and US-Remicade in Sprague-Dawley Rat Serum by Electrochemiluminescence Assay") that had an LLOQ of 1000 ng/mL. Samples were collected for the presence of anti-drug antibodies, but these were not analyzed.

The day 8 values for the male #7003 dosed at 10 mg/kg/week ABP 710 were excluded from the summary table presented below due to extremely high concentrations of ABP 710 (3- to 4-fold higher concentrations than other animals' values at each time point). The reviewer concurs with excluding these values from the analysis.

There were no sex differences in exposure (within 1.4-fold) and the data between sexes was combined in the table below. Control treatment samples or day 1 predose samples lacked detectable ABP 710 or US-Remicade. For both the 10 and 50 mg/kg/week dose groups, C_{max} and AUC values for ABP 710 and US-Remicade were similar. There was minimal accumulation over the 2-week study.

Table 48. Mean (SD) Toxicokinetic Parameters for ABP 710 and US-Remicade in Rats

Route	Treatment. Desc	Day	N	t_{max} (hr)[1]	C_{max} (ug/mL)	AUC_{0-t} (ug*hr/mL)	AR
IV	ABP 710 10 mpk	1	8	1.00 (1.00-1.00)	296 (38.9)	19900 (1680)	NC
		8	8	1.00 (1.00-24.00)	300 (89.0)	27700 (3540)	1.39 (0.151)
	ABP 710 50 mpk	1	8	1.00 (1.00-1.00)	1430 (110)	98300 (8720)	NC
		8	8	1.00 (1.00-24.00)	1360 (366)	124000 (17100)	1.27 (0.165)
	infliximab 10 mpk	1	8	1.00 (1.00-1.00)	275 (53.8)	19900 (2600)	NC
		8	7[a]	1.00[a] (1.00-1.00)	315[a] (76.2)	28500[a] (3730)	1.47[a] (0.199)
	infliximab 50 mpk	1	8	1.00 (1.00-1.00)	1290 (144)	87800 (7020)	NC
		8	8	1.00 (1.00-24.00)	1570 (387)	130000 (11600)	1.48 (0.103)

[1] t_{max} (hr) is Median (min - max)
[a] Select individual parameters were excluded from summary statistics. See Summary of Exclusions table.
Source Data: 118849 - 118849_(b) (4) Description-ABP 710: 14-Day Intravenous Toxicology Study in the Sprague Dawley Rat
Scenario Source Data: NCA Version- 3 Description- Save with flag column and AR calculated
Date Generated by PK Reporter S-PLUS: Fri Jun 20 13:27:21 PDT 2014 User: (b) (4)

Infliximab=US-Remicade

Dosing Solution Analysis

Dosing samples were collected pretest (comparing pre and post filtering effects), day 1 and day 8. All samples were within acceptable limits (mean values within ±10% of expected concentrations). The drug was stable at room temperature under study conditions and duration of dose administration.

13 Division of Dermatology and Dental Products

Type: Biosimilar 351(k)
eCTD: 001
Supporting Document Number: 001

Correspondence date: 14-DEC-2018
CDER Stamp date: 14-DEC-2018
Review Date: 7-NOV-2019

Applicant: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320

Drug: ABP-710, a proposed biosimilar to US-licensed Remicade (infliximab)
Name: AVSOLA (infliximab-axxq)
Route of Administration: Intravenous
Dosage Form: lyophilized 100mg/20 mL vial for reconstitution
Pharmacologic Category: Anti-human tumor necrosis factor alpha (TNFα) human-murine immunoglobulin G1 (IgG1) monoclonal antibody
Proposed Indication:

1) Crohn's Disease (CD):
    - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
    - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
2) Pediatric Crohn's Disease:
    - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
3) Ulcerative Colitis (UC):
    - reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.
4) Pediatric Ulcerative Colitis:
    - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active

ulcerative colitis who have had an inadequate response to conventional therapy.[16]

5) Rheumatoid Arthritis (RA) in combination with methotrexate:
    - reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.
6) Ankylosing Spondylitis (AS):
    - reducing signs and symptoms in patients with active ankylosing spondylitis
7) Psoriatic Arthritis (PsA):
    - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
8) Plaque Psoriasis (PsO):
    - treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

DDDP Project Manager: Barbara Gould
Team Leader: David Kettl, MD
Medical Officer: Gary Chiang, MD, MPH.

Executive Summary

The Division of Dermatology and Dental Products has concluded that the Applicant for the proposed drug product AVSOLA, a proposed biosimilar to US-licensed Remicade (infliximab), has provided adequate scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (rheumatoid arthritis), to support licensure of AVSOLA as a biosimilar, under section 351(k) of the PHS Act, for plaque psoriasis.

No clinical data was submitted specifically related to the psoriasis indication. To support licensure of AVSOLA for plaque psoriasis, Amgen Inc. has provided adequate scientific justification for the extrapolation of the data and information, including clinical data from the studied patient population, to support licensure under section 351(k) of the PHS Act of AVSOLA as a biosimilar for the non-studied indication, plaque psoriasis. For additional information on the clinical data submitted to support the indications evaluated in this application, please refer to the clinical review from DPARP (located in the multidisciplinary review) and the review

[16] We note that US-licensed Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

memo from the Division of Gastrointestinal and Inborn Errors Products (DGIEP) for details of the submitted application.

Introduction

Amgen Inc. is developing AVSOLA as a proposed biosimilar to US-licensed Remicade (infliximab). REMICADE was licensed in the United States (US) in 1998.

AVSOLA is a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to human tumor necrosis factor alpha (TNF α), a cytokine which mediates inflammatory response. Binding of AVSOLA to TNFα with its receptors and subsequent signal transduction results in the suppression of inflammation central to several chronic inflammatory diseases.

As part of the totality of the evidence for a demonstration of biosimilarity, the clinical development program for AVSOLA support a demonstration that no clinically meaningful differences exist between AVSOLA and US-licensed Remicade, in terms of its pharmacokinetics, efficacy, safety, and immunogenicity. The clinical evidence supporting the demonstration of no clinically meaningful differences between AVSOLA and US-licensed Remicade, includes a 3-arm, single dose pharmacokinetic (PK) and tolerability similarity study in healthy subjects comparing AVSOLA to US-licensed Remicade and EU-approved Remicade (20140108); and a randomized, double-blind, active-controlled comparative clinical study comparing efficacy, safety, PK, and immunogenicity of AVSOLA to US-licensed Remicade in subjects with moderate to severe RA, who have an inadequate response to MTX (2014011).

Extrapolation to Plaque Psoriasis

Amgen Inc. is seeking licensure for the indication studied in the clinical program, RA, as well as for ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis[1] for which they did not conduct a comparative clinical study. To support licensure of AVSOLA (infliximab-axxq) for the non-studied indications, Amgen Inc. has provided scientific justification for the extrapolation of the data and information to support a demonstration of biosimilarity for those indications.

The justification addresses the following issues outlined in Guidance for Industry: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product:* [17]

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought
- The PK and bio-distribution of the product in different patient populations

[17] Guidance for Industry "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", April 2015
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

- The immunogenicity of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population
- Any other factor that may affect the safety and efficacy of the product in each condition of use and patient population for which licensure is sought.

Consistent with the principles outlined in this Guidance, Amgen Inc. provided a justification to extrapolate data and information to support licensure of AVSOLA for the plaque psoriasis indication for which US-licensed Remicade is licensed and for which the applicant is seeking licensure. Considerations specific to plaque psoriasis include:

- The primary mechanism of action (MOA) of infliximab is direct binding and blocking of TNF receptor-mediated biological activities. Infliximab binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The scientific literature indicates that this MOA is the primary MOA in RA and PsO. The data provided by Amgen Inc. showed similar TNF binding and potency to neutralize TNFα, supporting that US-licensed Remicade and AVSOLA have the same MOA.

- Because similar PK was demonstrated between AVSOLA and US-licensed Remicade, a similar PK profile would be expected for AVSOLA in adult patients with chronic severe plaque psoriasis.

- In general, immunogenicity of the US-licensed Remicade was affected primarily by the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used. US-licensed Remicade is used without methotrexate in plaque psoriasis. The applicant provided sufficient data to indicate similar immunogenicity between AVSOLA and US-Remicade, including in the setting of a repeat dosing in patients with RA. Accordingly, similar immunogenicity would be expected between AVSOLA and US-Remicade in plaque psoriasis.

- No differences in expected toxicities that are relevant to the plaque psoriasis population were noted between AVSOLA and US-licensed Remicade in the submitted clinical studies.

Based on the above considerations, the Division concluded Amgen provided sufficient justification to extrapolate data and information to support licensure of AVSOLA for the plaque psoriasis indication for which US-licensed Remicade is licensed..

Overall Conclusion:

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires a demonstration that the proposed biological product is highly similar to the reference

product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of the safety, purity and potency of the product.

This review from DDDP concludes that the applicant has provided adequate data and information to support licensure of AVSOLA (infliximab-axxq) under section 351(k) of the PHS Act for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate, an indication for which US-licensed Remicade has been previously licensed and for which Amgen is seeking licensure of AVSOLA.

Authors:

Gary Chiang, MD, MPH
Clinical Reviewer

David Kettl, MD
Clinical Team Leader

14 Division of Gastroenterology and Inborn Errors Products

Application Type and Number:	351(k); BLA 761,086
Applicant:	Amgen
Date of Submission:	12/14/2018
Goal Date:	12/14/2019
DGIEP Clinical Reviewer:	Sandhya Apparaju, Ph.D.
DGIEP Clinical Team Leader:	Juli Tomaino, M.D.
DGIEP Associate Director:	Jessica Lee, M.D.
Date Review Completed:	August 13, 2019
Drug:	ABP710[18] / "AVSOLA" (infliximab-axxq); Proposed biosimilar to US-licensed Remicade
Drug Class:	Tumor Necrosis Factor-alpha (TNF- α) blocker
Dosage Form/Presentation:	20 mL vial containing 100 mg of sterile lyophilized powder for reconstitution with 10 mL sterile water for injection
Route of Administration:	Intravenous infusion
Proposed Indications:	Same as those previously approved for US-licensed Remicade: Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis

Executive Summary

[18] In this document, Amgen's proposed product is referred to as ABP710, which was the name used to refer to this product during development. The proposed proprietary name (AVSOLA) and the proposed nonproprietary name (infliximab-axxq) are only conditionally accepted for this product until the application is approved.

The Division of Gastroenterology and Inborn Errors Products concludes that the Applicant provided adequate scientific justification (based on mechanism of action, pharmacokinetics, immunogenicity, and toxicity) to support extrapolation of data and information submitted, including clinical data from the studied population (rheumatoid arthritis), to support licensure of ABP710 as a biosimilar, under section 351(k) of the PHS Act, to US-licensed Remicade for the inflammatory bowel disease indications (ulcerative colitis and Crohn's disease) in adult and pediatric patients (≥ 6 years of age).

Introduction

On December 14, 2018, Amgen, Inc. (the Applicant) submitted a Biologics License Application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for ABP710, a proposed biosimilar to the United States (US) licensed Remicade (infliximab). The US-licensed Remicade (BLA103772) received initial marketing approval on August 24, 1998 and its license is currently held by Janssen Biotech, Inc.

This application (BLA 761086) was submitted to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for review. In addition to comprehensive analytical assessments to evaluate structural and functional similarity to support the BLA, the Applicant also submitted data from a comparative pharmacokinetic (PK) study 20140108 in healthy subjects to assess the safety, tolerability, immunogenicity and PK similarity of ABP710, US-licensed Remicade, and the European Union (EU)-approved Remicade. In addition, the Applicant submitted results from a comparative clinical study (Study 20140111) evaluating the efficacy, safety and immunogenicity of ABP710 relative to US-licensed Remicade in patients with moderate to severe rheumatoid arthritis (RA) who are on stable doses of methotrexate. The following table summarizes the clinical studies included in the BLA for ABP710:

Table 49. ABP710 Clinical Studies

Study	Objectives	Study Design	Test products Dose/Route/ Treatment Duration	Population and Number of Subjects
20140108	PK Similarity of ABP710 relative to US-licensed Remicade and EU-approved Remicade; Similarity of US-Licensed Remicade *vs.* EU-approved Remicade; Safety, tolerability, immunogenicity	Randomized, single-blind, single-dose, 3-arm, parallel-group study	ABP710, US-licensed Remicade, EU-approved Remicade; 5 mg/kg IV infusion; Single dose	149 Healthy Subjects; [49 ABP710, 50 US-licensed Remicade, 50 EU-approved Remicade]

20140111	Comparative clinical study evaluating efficacy, safety and immunogenicity of ABP710 relative to US-licensed Remicade	Randomized, multicenter, double-blind, active-controlled study	ABP-710, US-licensed Remicade; 3 mg/kg IV infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter through Week 46	558 patients with moderate to severe RA; [279 ABP710, 279 US-licensed Remicade]

Source: BLA 761086, Tabular listing of clinical studies (Module 5.2)

The collective evidence from the comparative clinical study in patients with RA supports a demonstration of no clinically meaningful differences between ABP710 and US-licensed Remicade. The clinical reviewer for this BLA, Dr. Katherine Clarridge, concluded, among other things, that Study 20140111 met its primary objective of demonstrating that the proportion of patients achieving ACR20 response at week 22 was similar between the ABP710 and the US-licensed Remicade treatment groups. For additional information on the clinical study in RA, please refer to the multidisciplinary review from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP).

Although the inflammatory bowel disease (IBD) indications were not directly studied in the ABP710 clinical program, the rationale for extrapolating data and information submitted in the BLA, including the RA data, to other indications, including IBD was included in the submission for review. This memorandum provides DGIEP's assessment of the extrapolation rationale to support the approval of ABP710 for the following IBD indications, for which the applicant is seeking licensure and that have been previously approved for US-licensed Remicade: Crohn's disease (CD), pediatric CD, ulcerative colitis (UC) and pediatric UC.

Extrapolation of Existing Data to Support Biosimilarity to IBD Indications

The applicant seeks licensure for ABP710 for the same indications for which US-licensed Remicade has been previously approved (Crohn's disease, pediatric Crohn's disease (≥ 6 years of age), ulcerative colitis, pediatric ulcerative colitis (≥ 6 years of age), rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis).

To support licensure of ABP710 as a biosimilar for each condition of use for which licensure is sought and for which US-licensed Remicade has been previously approved, the Applicant needed to provide sufficient justification for extrapolating data and information submitted in the application. Such a scientific justification for extrapolation should consider the following issues that are described in the FDA guidance - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product[19]:

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought
- The PK and bio-distribution of the product in different patient populations

[19] Guidance for Industry- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

- The immunogenicity of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population
- Any other factor that may affect the safety and efficacy of the product in each condition of use and patient population for which licensure is sought.

All of these factors were adequately addressed by the Applicant, as summarized below, for the IBD indications. The totality of the evidence provides support for licensure of ABP710 for the IBD indications (Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis) under section 351(k) of the PHS Act.

Mechanism of Action

The mechanisms of action of infliximab that are relevant to RA (the comparative clinical study population) are also relevant to IBD. The Applicant provided data to support that ABP710 has the same known and potential mechanisms of action as US-licensed Remicade, which supports extrapolation to these other indications.

Infliximab belongs to the pharmacologic class of tumor necrosis factor alpha (TNF-□) blockers. Infliximab neutralizes the biological activity of TNF-α by binding with high affinity to the soluble (s) and transmembrane (tm) forms of TNF-α and inhibits binding of TNF-α with its receptors.[20] Similar to the studied indication (RA), TNF-α plays a central role in the pathogenesis of IBD. TNF-α inhibition is important in treating the disease, as evidenced by the efficacy of approved TNF-α inhibitors in the treatment of IBD.[21] In addition, the efficacy of infliximab in the treatment of IBD is thought to involve reverse signaling via binding to tmTNF, and other plausible mechanisms of action involving the Fc region of the antibody.[21,22] Table 2 summarizes the known and potential mechanisms of action of US-licensed Remicade. Binding to sTNF-α and tmTNF-α involves the fragment antigen-binding (Fab) region of the antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

[20] BLA 103772 US-licensed Remicade Labeling
[21] Oikonomopoulos A, et al., Current Drug Targets 2013; 14:1421-32.
[22] Tracey D, et al., Pharmacology & Therapeutics 2008; 117:244–79.

Table 50. Known and Potential Mechanisms of Action of US-licensed Remicade

MOA of Remicade	RA	AS	PsA	PsO	CD, Pediatric CD	UC, Pediatric UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible

ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors[21,22,23]

The biological activities of ABP710 and US-licensed Remicade were evaluated by a comprehensive set of comparative functional and binding assays. The Product Quality reviewers determined that the Applicant has adequately addressed the known and potential mechanisms of action of US-licensed Remicade. TNF-α binding and neutralization, believed to be the primary function of infliximab, as well as other mechanisms of action, such as reverse signaling, antibody dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), were found to be similar between ABP710 and US-licensed Remicade. These data support the conclusion that ABP710 and US-licensed Remicade utilize the same mechanism(s) of action, to the extent such mechanism(s) are known. Refer to the Product Quality reviews for additional details in this regard.

Pharmacokinetics (PK)

Study 20140108 was a randomized, single dose, 3-arm, parallel group, PK similarity study conducted in healthy adult male and female subjects. The clinical pharmacology reviewers concluded that the data from this study support a demonstration of PK similarity of ABP710 to US-licensed Remicade in healthy subjects. Refer to the clinical pharmacology review for additional details in this regard. Available data on US-licensed Remicade do not indicate any major differences in PK based on disease state.[20] Therefore, it is reasonable to conclude that PK for the ABP710 is expected to be similar between patients with RA (the studied population) and those with IBD. In addition, it should be noted that the PK of infliximab products is also

[23] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

influenced by immunogenicity. Specifically, the clearance of infliximab has been shown to be higher in patients who developed anti-drug-antibodies (ADA).[20] Immunogenicity considerations are discussed further below.

Immunogenicity

In the ABP710 development program, immunogenicity was evaluated in populations that were considered sensitive for detecting meaningful differences (RA and healthy subjects). Immunogenicity was found to be similar when comparing ABP710 and US-licensed Remicade, in the PK similarity study 20140108 in healthy subjects and between ABP710 and US-licensed Remicade in the comparative clinical study 20140111 conducted in patients with RA. Specifically, the rates of binding and neutralizing anti-drug antibodies, were found to be similar between ABP710 and US-licensed Remicade. These results support a demonstration of no clinically meaningful differences between ABP710 and US-licensed Remicade. Study 20140111 also provided information regarding subjects who underwent a single transition from US-licensed Remicade to ABP710 after Week 22. The transition was used to specifically assess potential risks in safety and immunogenicity as a result of switching from US-licensed Remicade to ABP710. There were no meaningful differences in the rates of binding and neutralizing anti-drug antibodies in those subjects that underwent a single transition from US-licensed Remicade to ABP710 after Week 22, compared to those that remained on their randomized treatment (US-licensed Remicade or ABP710). Therefore, it is reasonable to conclude that immunogenicity in IBD patients receiving ABP710 would be similar to that observed in IBD patients receiving US-licensed Remicade.

Toxicity

The safety of ABP710 compared to US-licensed Remicade was assessed in a comparative clinical study (Study 20140111), as well as a single dose, healthy subject, comparative PK study (Study 20140108). Safety assessments in these two studies included adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory testing, and immunogenicity assessments. In addition, as previously noted study 20140111 included a single transition from US-licensed Remicade to ABP710. No meaningful differences in the incidence of adverse events, including hypersensitivity were observed in RA patients that underwent a single transition from US-licensed Remicade to ABP710 after Week 22, compared to those that remained on their randomized treatments (ABP710 or US-licensed Remicade). As described in the labeling for US-licensed Remicade, in controlled clinical trials that supported approval of the US-licensed Remicade, patients with IBD experienced similar adverse reactions as other indications, including RA. Additionally, as further described in the approved labeling of US-licensed Remicade, similar common and serious adverse reactions have been reported across licensed indications.[20] Since the safety profile of ABP710 has been shown to be similar to that of US-licensed Remicade in patients with RA and, given the similar product quality attributes, PK, and immunogenicity, we expect that the safety profile in the IBD population would not be different from that observed in patients with RA.

Summary and Conclusions

Consistent with the principles of the FDA Guidance outlined above[19], DGIEP concludes that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity and toxicity profile), data and sufficient information, including clinical data from the studied population (patients with RA on concomitant methotrexate therapy), to support licensure of ABP710 for the inflammatory bowel disease indications (Crohn's disease, pediatric Crohn's disease, ulcerative colitis, and pediatric ulcerative colitis).

Authors

Sandhya Apparaju, PhD	Juli Tomaino, MD	Jessica Lee, MD
Clinical Reviewer	Clinical Team Leader	Associate Director

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STACY J CHIN
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SALLY M SEYMOUR
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