1 TITLE PAGE

A RANDOMIZED, DOUBLE-BLIND PHASE 3 STUDY TO ASSESS THE EFFICACY AND SAFETY OF ABP 710 COMPARED TO INFLIXIMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS

Test Drug: ABP 710

Protocol Number:	20140111	**EudraCT Number:**	2014-004704-29
Study Phase:	3		
Date and Version:	**17 March 2017, version 2.0**		

Sponsor:

Amgen Inc.
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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Council for Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

NCT Number: 02937701
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

SIGNATURES

Representatives of Sponsor and Clinical Research Organization

I have read and agree to the **Protocol 20140111, entitled "A RANDOMIZED, DOUBLE-BLIND PHASE 3 STUDY TO ASSESS THE EFFICACY AND SAFETY OF ABP 710 COMPARED TO INFLIXIMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS."** I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities.

Accepted for the Sponsor – Amgen Inc.:

PPD

Print Name

MEDICAL DIRECTOR

Title

PPD

Signature

3/17/2017

Date

Accepted for the Clinical Research Organization - PRA:

PPD

Print Name

MEDICAL DIRECTOR

Title

PPD

Signature

03/20/2017

Date

Investigator

I have read and agree to the Protocol 20140111, entitled "A RANDOMIZED, DOUBLE-BLIND PHASE 3 STUDY TO ASSESS THE EFFICACY AND SAFETY OF ABP 710 COMPARED TO INFLIXIMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS." I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Study Center: _____

Study Center Number: _____

Study Center Principal Investigator

_____ _____

Print Name Title

_____ _____

Signature Date

Coordinating Investigator Signature:

_____ _____

Print Name Title

_____ _____

Signature Date

2 SYNOPSIS

NAME OF SPONSOR: Amgen Inc.	**PROTOCOL No.:** 20140111
NAME OF STUDY TREATMENT: ABP 710	
TITLE OF STUDY: A Randomized, Double-blind Phase 3 Study to Assess the Efficacy and Safety of ABP 710 Compared to Infliximab in Subjects With Moderate to Severe Rheumatoid Arthritis	
STUDY CENTERS: Approximately 90 study centers in Europe, North America, and Australia	
STUDY PERIOD: A total of up to 54 weeks, consisting of a screening period of up to 4 weeks, a treatment period of 46 weeks, and a safety, immunogenicity, and efficacy follow-up period of 4 weeks. The end of the study will be the date when the last subject has completed the last study assessment.	**PHASE OF DEVELOPMENT:** Phase 3
PLANNED STUDY DATES: The expected enrollment duration is 10.5 months, and each subject will participate for up to 54 weeks.	
OBJECTIVES: **Primary Objective:** The primary objective for this study is to assess the efficacy of ABP 710 compared with US-licensed infliximab (infliximab). **Secondary Objectives:** The secondary objectives are to assess the safety and immunogenicity of ABP 710 compared with infliximab.	
STUDY DESIGN AND METHODOLOGY: This is a randomized, double-blind, active-controlled study in adult subjects with moderate to severe rheumatoid arthritis (RA) who have an inadequate response to methotrexate (MTX). Approximately 550 subjects (275 per treatment group) will be enrolled. The subjects will be randomized in a 1:1 ratio to receive either ABP 710 3 mg/kg infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter (treatment group A), or infliximab 3 mg/kg infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter (treatment group B), until week 22. At week 22, subjects initially randomized to the infliximab group will be re-randomized in a 1:1 ratio to either continue receiving infliximab infusion every 8 weeks (treatment group B1), or to switch to ABP 710 (treatment group B2) every 8 weeks. Subjects initially randomized to ABP 710 (treatment group A) will continue on the same treatment. Re-randomization will be managed to ensure that the blind to the initial study group is maintained. **Subjects who are unable to complete the week 22 visit within the visit window of ± 3 days will be 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.** The last treatment for all subjects **who do not discontinue early** will be at week 46. Subjects will be considered study completers when they finish the week 50 end-of-study assessments. An independent data monitoring committee will evaluate the safety data throughout the study.	
STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION: Subjects cannot be randomized before all entry criteria (including test results) are confirmed. **Inclusion Criteria:** 1. Subject has signed an institutional review board/independent ethics committee-approved informed consent form before any study specific procedures are performed. 2. Subject (man or woman) is ≥ 18 and ≤ 80 years old.	

3. Subject is diagnosed with RA as determined by meeting the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria for RA.
4. Subject has RA duration of at least 3 months.
5. Subject has active RA defined as ≥ 6 swollen joints and ≥ 6 tender joints (based on 66/68 joint count excluding distal interphalangeal joints) at screening and baseline and at least 1 of the following at screening:
   - erythrocyte sedimentation rate ≥ 28 mm/hr
   - serum C-reactive protein > 1.0 mg/dL
6. Subject has **at least one of the following:** a positive rheumatoid factor or anti-cyclic citrullinated peptide at screening.
7. Subject has taken MTX for ≥ 12 consecutive weeks and is on a stable dose of oral or subcutaneous MTX 7.5 to 25 mg/week for ≥ 8 weeks before receiving the investigational product and is willing to remain on a stable dose throughout the study.
8. For a subject on nonsteroidal anti-inflammatory drugs or low potency analgesics such as tramadol, Soma Compounds, Fioricet, or Fiorinal, the dose should be stable for ≥ 2 weeks before screening.
9. For a subject on oral corticosteroids (≤ 10 mg prednisone or equivalent), the dose should be stable for ≥ 4 weeks before screening.
10. Subject has no known history of active tuberculosis.

Subject must meet any 1 of the following 3 criteria:

11. Subject has a negative test for tuberculosis during screening defined as either:
    - negative purified protein derivative (PPD) defined as < 5 mm of induration at 48 to 72 hours after test is placed

    OR

    - negative Quantiferon test
12. Subject with a positive PPD and a history of Bacillus Calmette-Guérin vaccination is allowed with a negative Quantiferon test.
13. Subject with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or a subject with a positive or indeterminate Quantiferon test is allowed if they have all of the following:
    - no symptoms of tuberculosis according to the worksheet provided by the sponsor, Amgen Inc.
    - documented history of adequate prophylaxis initiation before receiving investigational product in accordance with local recommendations
    - no known exposure to a case of active tuberculosis after most recent prophylaxis

Exclusion Criteria:

Rheumatoid arthritis related

1. Subject has Class IV RA (Hochberg et al, 1992) according to the ACR revised response criteria.
2. Subject has Felty's syndrome (RA, splenomegaly, and granulocytopenia).
3. Subject has a history of prosthetic or native joint infection.

Other medical conditions

4. Subject has a planned surgical intervention during the duration of the study.
5. Subject has an active infection or history of infections as follows:
   - any active infection for which systemic anti-infectives were used within 28 days before first dose of investigational product
   - a serious infection, defined as requiring hospitalization or intravenous (IV) anti-infective(s) within 8 weeks before the first dose of investigational product
   - recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject
6. Subject has a positive blood test for human immunodeficiency virus.
7. Subject has a positive hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody result at screening.
8. Subject has uncontrolled, clinically significant systemic disease such as diabetes mellitus, cardiovascular disease including moderate or severe heart failure (New York Heart Association Class III/IV), renal disease, liver disease, or hypertension.
9. Subject had a malignancy within 5 years EXCEPT for treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma.
10. Subject has a history of neurologic symptoms suggestive of central or peripheral nervous system demyelinating disease.
11. Subject has a major chronic inflammatory disease or connective tissue disease other than RA, with the exception of secondary Sjögren's syndrome.
12. Subject has a concurrent medical condition that, in the opinion of the investigator, could cause this study to be detrimental to the subject.

Laboratory abnormalities

13. Subject has laboratory abnormalities at screening, including any of the following:
   - hemoglobin < 9 g/dL
   - platelet count < 100 000/mm^3
   - white blood cell count < 3000/mm^3
   - aspartate aminotransferase and/or alanine aminotransferase ≥ 2.0 x the upper limit of normal
   - creatinine clearance < 50 mL/min (Cockroft-Gault formula)
   - any other laboratory abnormality, that, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.

Washouts and nonpermitted drugs

14. Subject has used any of the following within 28 days before the first dose of investigational product:
   - intra-articular (IA) hyaluronic acid injections
   - intramuscular (IM), IA, or IV corticosteroids, including adrenocorticotropic hormone

15. Subject has used nonbiologic disease-modifying antirheumatic drugs other than MTX within 28 days before the first dose of investigational product, except as below:
    - leflunomide (unless an active washout with cholestyramine has been performed), cyclosporine, azathioprine, tacrolimus excluded within 3 months before the first dose of investigational product
    - intramuscular or oral gold excluded within 6 months before the first dose of investigational product
    - cytotoxic agents such as cyclophosphamide, D-penicillamine excluded within 6 months before the first dose of investigational product
    - intravenous gamma-globulin or Prosorba column therapy excluded within 3 months before the first dose of investigational product
    - Janus kinase inhibitor eg, tofacitinib; excluded within 28 days before the first dose of investigational product.
16. Subject has prior use of 2 or more **distinct** biologic therapies for RA.
17. Subject has used commercially available or investigational biologic therapies for RA as follows:
    - anakinra, etanercept within 1 month before the first dose of investigational product
    - abatacept, tocilizumab, adalimumab, golimumab, certolizumab within 3 months before the first dose of investigational product
    - other experimental or commercially available biologic therapies for RA within 3 months or 5 half-lives (whichever is longer) before the first dose of investigational product
    - rituximab within 9 months before the investigational product along with evidence of incomplete B cell recovery
18. Subject has received live vaccines within 28 days before the first dose of investigational product or plans to receive live vaccines during the course of the study.
19. Subject has chronic use of high potency narcotic analgesics such as morphine or morphine-derived medications, fentanyl, codeine, hydromorphone, levorphanol, meperidine, methadone, oxycodone, or hydrocodone at screening.
20. Subject who has taken any of the above agents in the past must have recovered from all drug-related adverse events.
21. Subject has previously received Remicade® (infliximab) or a biosimilar of infliximab.
22. Subject is currently enrolled in or has not yet completed at least 30 days or 5 half-lives (whichever is longer) since ending other investigational device or investigational drug(s), including vaccines, or subject is receiving other investigational agent(s).

General

23. Woman who is pregnant or breast feeding, or plans to become pregnant while enrolled in the study and for 6 months after the last dose of investigational product.
24. Woman who is of childbearing potential (ie, neither surgically sterile nor postmenopausal) and does not agree to use adequate contraception (eg, true abstinence, sterilization, birth control pills, Depo-Provera® [medroxyprogesterone] injections, contraceptive implants**, or other effective methods**) while on study and for 6 months after the last dose of investigational product.
25. Subject has a known sensitivity to mammalian cell-derived drug products or hypersensitivity to the active substance or to any of the excipients of ABP 710 or infliximab.

26. Subject has any physical or psychiatric disorder that, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.
27. Subject has any disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures.
28. Subject has active substance abuse (within 24 weeks of screening).

NUMBER OF SUBJECTS: Approximately 550 subjects will be randomized in a 1:1 ratio to receive either ABP 710 or infliximab. Subjects will be stratified based on geographic region and prior biologic use for RA (with prior biologic use capped at 30% of the study population). The sample size is chosen to achieve > 90% power to demonstrate equivalence at a 0.05 significance level on the primary efficacy endpoint, response difference (RD) of 20% improvement in ACR core set measurements (ACR20) at week 22 between ABP 710 and infliximab, with an equivalence margin of (-15%, 15%), assuming an expected ACR20 rate for both ABP 710 and infliximab of 52% at week 22. This sample size will also achieve approximately 85% power to demonstrate equivalence on the RD of ACR20 between ABP 710 and infliximab with an equivalence margin of (-12%, 15%) at a significance level of 0.05 at week 22.

STUDY TREATMENT(S):

Test Product, Dose and Mode of Administration:

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

Reference Therapy, Dose and Mode of Administration:

Infliximab 3 mg/kg infusion given on day 1, weeks 2 and 6, and every 8 weeks thereafter

DURATION OF TREATMENT: 46 weeks

STUDY EVALUATIONS:

Primary Endpoint:

- response difference of ACR20 at week 22

Secondary Endpoints:

- response difference of ACR20 at weeks 2, 6, 14, 30, 34, 38, 46, and 50
- response difference of 50% improvement in ACR core set measurements (ACR50) and 70% improvement in ACR core set measurements (ACR70) 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, 38, 46, and 50

Safety Endpoints:

- treatment-emergent adverse events, serious adverse events, and adverse events of special interest
- clinically significant changes in laboratory values and vital signs
- incidence of antidrug antibodies

Exploratory Endpoint:

- CCI [redacted]

STATISTICAL METHODS: All efficacy analyses will be performed using the intention-to-treat analysis set based on the subject's randomized treatment. As a sensitivity analysis,

the equivalence test on the primary endpoint will be also performed using the per-protocol analysis set.

Clinical equivalence for the primary endpoint, RD of ACR20 at week 22, will be sequentially evaluated: first by comparing the 2-sided 90% CI of the RD of ACR20 between ABP 710 and infliximab with an equivalence margin of (-15%, 15%). The CIs will be estimated from the stratified Newcombe confidence limits for the common RD to adjust for stratification factors. If the first equivalence is established, the primary endpoint, RD of ACR20 at week 22 will be further evaluated by comparing the same 2-sided 90% CI between ABP 710 and infliximab with an equivalence margin of (-12%, 15%). **In addition to the 90% CI, the 95% CI for all primary and secondary efficacy endpoints will also be provided descriptively.**

Inferential analyses will only be performed for the primary endpoint. Secondary efficacy endpoints, ACR20 at scheduled visits other than week 22, ACR50/ACR70, and DAS28-CRP will be analyzed descriptively at various time points.

All safety analyses will be performed using the safety analysis set based on actual treatment received. Safety analysis will include analyses of adverse events, clinical laboratory test results, vital signs, and antidrug antibodies. In general, summaries will be provided separately as follows: from day 1 (first investigational product administration) until week 22, from week 22 through the end of the study, and for the entire study period (from day 1 [first investigational product administration] through the end of the study).

The number and percentage of subjects developing binding antidrug antibodies and those developing neutralizing antidrug antibodies will be tabulated separately for day 1 until week 22, from week 22 through the end of the study, and for the entire study by actual treatment received.

DATE AND VERSION: 17 March 2017, version 2.0

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
ACR	American College of Rheumatology
ACR20	20% improvement in ACR core set measurements
ACR50	50% improvement in ACR core set measurements
ACR70	70% improvement in ACR core set measurements
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CCP	cyclic citrullinated peptide
CFR	Code of Federal Regulations
CI	confidence interval
COX-2	cyclooxygenase-2
CRO	clinical research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DAS	disease activity score
DAS28	disease activity score in 28 joints
DAS28-CRP	disease activity score in 28 joints - C-reactive protein
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
EU	European Union
Fc	fragment crystallizable

FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire - Disability Index
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
IA	intra-articular
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
Infliximab	US-licensed infliximab
IL	interleukin
IL-1	interleukin-1
IL-1β	interleukin-1 beta
IL-6	interleukin-6
IL-8	interleukin-8
IM	intramuscular
IRB	institutional review board
IV	intravenous(ly)
IXRS	interactive voice and web response system
MedDRA	Medical Dictionary for Regulatory Activities
MMP	matrix metalloproteinase
MTX	methotrexate
NSAID	nonsteroidal anti-inflammatory drug
PIN	Personal Identification Number
PPD	purified protein derivative

RA	rheumatoid arthritis
RD	response difference
SAP	statistical analysis plan
SJC	swollen joint count
SUSAR	suspected unexpected serious adverse reactions
TJC	tender joint count
TNFα	tumor necrosis factor alpha
US	United States
VAS	visual analogue scale
WHO-DD	World Health Organization-Drug Dictionary

5 ETHICS

5.1 Ethics Committee

This study will be conducted in compliance with institutional review board (IRB)/independent ethics committee (IEC) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines including Title 21 Part 56 of the United States (US) Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B[R3]), European Union (EU) Community Directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition, this study will adhere to all local regulatory requirements and requirements for data protection.

Before initiating a trial/study, the investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the study protocol/amendment(s), written informed consent form (ICF), any consent form updates, subject recruitment procedures (eg, advertisements), and any written information to be provided to subjects, and a statement from the IRB/IEC that they comply with GCP requirements. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 [R1]; FDA CFR [21 CFR § 50, 56, 312]) and all applicable regulatory requirements.

5.3 Subject Information and Consent

The investigator will explain the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative and obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study and before initiation of any study-related procedure (including administration of investigational product).

The sponsor will provide a sample ICF, based on the elements of informed consent in Section 17.1. The final, version-dated form must be agreed to by the sponsor and the IRB/IEC and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form (personally signed and dated by the

subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion) will be retained by the investigator. The investigator will supply all enrolled subjects with a copy of their signed ICF.

The ICF may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance, approval should always be given by the IRB/IEC, and existing subjects will need to be informed of the changes and be re-consented. This is documented in the same way as previously described.

The investigator should, with the consent of the subject, inform the subject's primary physician about the subject's participation in the clinical study as needed.

6 INTRODUCTION

6.1 Disease Review

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology in which patients exhibit systemic features such as fatigue, low-grade fever, weight loss, anemia, and increased systemic measures of acute phase reactants (eg, erythrocyte sedimentation rates [ESRs] and C-reactive protein [CRP]; Aletaha et al, 2010). Although the disease is systemic in nature, the primary target tissues are the synovial membrane, cartilage, and bone (McInnes and Schett, 2007), which exhibit uncontrolled synovium/pannus proliferation and excess fluid production, and ultimately undergo progressive destructive arthropathy (Aletaha et al, 2010; Choy and Panayi, 2001).

The destruction of the cartilage seen in RA, and related inflammatory diseases, is considered to be due to the activity of matrix metalloproteinases (MMPs) that are produced by resident and infiltrating cells in inflamed synovium (Feldmann M et al, 1996).

Tumor necrosis factor alpha (TNFα), in conjunction with interleukin (IL)-1, plays a key role in synovial inflammation by increasing expression of endothelial-cell adhesion molecules, which cause retention of lymphocytes in the affected joint (Chin JE et al, 1990). Tumor necrosis factor alpha promotes joint damage by increasing the release of MMPs, particularly MMP-3 (Carrasco R et al, 2010), involved in the breakdown of the connective tissue matrix and by decreasing production of tissue inhibitor of metalloproteinase (Shingu M et al, 1993). Tumor necrosis factor alpha also has a role in the bone damage seen in RA, by promoting development of osteoclasts, either directly through tumor necrosis factor receptor 1 or indirectly through additive effects with receptor activator of nuclear factor-KB ligand (McInnes and Schett, 2007).

In an in vitro study conducted with synovial tissue isolated and cultured from the joints of patients with RA (thus containing a mixture of synovial cell types, eg, macrophages, T cells, fibroblasts, endothelial cells, and plasma cells), blockage of TNFα diminished the production of proinflammatory cytokines **interleukin-1 beta (**IL-1β**), interleukin -6 (**IL-6**),** and **interleukin-8 (**IL-8**),** and granulocyte- macrophage colony-stimulating factor, suggesting that TNFα can modulate proinflammatory cytokine production within the local synovial environment (Butler DM et al, 1995). Conversely, blocking **interleukin-1 (**IL-1**)** activity had no effect on TNFα concentrations, indicating that IL-1 was not solely involved in regulating TNFα production in RA (Butler DM et al, 1995).

Angiogenesis and increased expression of endothelial molecules are also prominent features in RA, as they are in other chronic inflammatory disorders. This is manifested by increased blood vessel density, facilitating cell trafficking in and out of the inflamed tissue (Tracey D et al, 2008).

6.2 Infliximab

Remicade® (infliximab) is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα, but not to lymphotoxin α (REMICADE Prescribing Information). Elevated concentrations of TNFα have been found in the joints of patients with RA and correlate with elevated disease activity. In RA, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint, as well as reduced expression of molecules mediating cellular adhesion, chemo-attraction, and tissue degradation. After infliximab treatment, patients with RA exhibited decreased concentrations of serum IL-6 and CRP; and patients with reduced hemoglobin concentrations had increased hemoglobin concentrations compared with baseline. Peripheral blood lymphocytes showed no significant decrease in number or in proliferative responses to in vitro mitogenic stimulation when compared with untreated patients' cells.

Infliximab, in combination with methotrexate (MTX), is indicated for the reduction of signs and symptoms of RA, as well as the improvement in physical function in adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including MTX, has been inadequate and in adult patients with severe, active and progressive disease not previously treated with MTX or other DMARDs (REMICADE Prescribing Information).

6.3 Compound Review

ABP 710 is being developed as a biosimilar candidate to Remicade® (infliximab) for the treatment of RA and other indications: Crohn's disease (adults/pediatrics), ulcerative colitis (adults/pediatrics), ankylosing spondylitis (adults), psoriatic arthritis (adults), and plaque psoriasis (adults). The active ingredient of ABP 710 is a monoclonal antibody that has the same amino acid sequence as infliximab. ABP 710 has the same pharmaceutical form and dosage strength as infliximab.

Similarity of ABP 710 to infliximab has been shown in analytical assessments. ABP 710 and infliximab have similar binding affinity for human TNFα and comparable inhibition of TNFα as assessed in vitro in the human histiocytic lymphoma cell line U-937. ABP 710

and infliximab also show similar in vitro binding to the fragment crystallizable (Fc) neonatal receptor and Fc gamma receptor Type IIIa, and similar antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity activity in vitro. In a toxicology study in rats, administration of ABP 710 or infliximab was similarly well tolerated at doses of up to 50 mg/kg for 2 weeks. In the absence of pharmacologically relevant preclinical species to evaluate on-target effects in vivo, ABP 710 and infliximab demonstrated a similar lack of activity in an in vitro cytokine release assay with human peripheral blood leukocytes and endothelial cells. Refer to the investigator's brochure (IB) for additional information about ABP 710 and its comparability with infliximab.

CCI

[redacted]

Adverse events that may be serious or fatal include serious infections including new onset or reactivation of tuberculosis, reactivation of hepatitis B, sepsis, malignancies including lymphomas (such as hepatosplenic T-cell lymphoma), serious infusion reactions including delayed **hypersensitivity**, hepatotoxicity, heart failure, hematologic reactions, and demyelinating disorders. Based on clinical trial experience in infliximab-treated adult subjects across multiple indications, frequently reported (≥ 10% subject incidence) adverse reactions included viral infections, headache, upper respiratory tract infection, sinusitis, abdominal pain, nausea, infusion-related reaction, and pain. Based on clinical trial experience in subjects with RA, the most common (≥ 10% subject incidence) adverse reactions in those receiving 4 or more infusions of infliximab were nausea, abdominal pain, diarrhea, dyspepsia, upper respiratory tract infection, sinusitis, pharyngitis, coughing, bronchitis, rash, and headache (ABP 710 Investigator's Brochure, Edition 3, 17 Mar 2016).

6.4 Study Rationale

In the US, EU, and much of the world, laws, regulations, and guidances have been or are being put in place to increase availability of biological treatments by developing and licensing biosimilar products (EMA/CHMP/437/04 Rev 1; EMA/CHMP/BWP/247713/2012 Rev 1; EMEA/CHMP/BMWP/42832/2005 Rev.1; EMEA/CHMP/BMWP/403543/2010 Rev. 1; US FDA 2015a; US FDA 2015b). A biosimilar product, generally, is highly similar to a licensed biologic reference product, and there are no clinically meaningful differences between the biosimilar and reference products in terms of safety, purity, and potency. Biosimilarity is demonstrated by the totality of the evidence, including analytical, nonclinical, and clinical evidence. The analytical and pharmacokinetic similarity of ABP 710 and infliximab are summarized briefly in more detail in the IB.

A phase 1 study of ABP 710 compared with infliximab (US) and infliximab (EU) (Study 20140108) was conducted in 148 healthy adult men and women. Subjects received a single 5 mg/kg IV infusion of ABP 710, infliximab (US), or infliximab (EU), and were followed for 57 days after infusion. A similar safety profile was seen across the 3 treatment groups. Overall, all treatments were safe and well tolerated. The most common treatment-emergent adverse events were somnolence (53.4%), headache (31.8%), nasopharyngitis (8.8%), upper respiratory tract infection (4.7%), and nausea (4.2%). The percentage of subjects who were positive for binding antibodies was 42.9%, 36.0% and 32.7% for ABP 710, infliximab (US) and infliximab (EU), respectively. Thus, it is expected that the safety profile of ABP 710 is similar to that of infliximab.

The current study is designed to demonstrate the clinical similarity between ABP 710 and infliximab in terms of efficacy, safety, and immunogenicity for moderate and severe RA and in accordance with the biosimilar regulations and guidance (EMA/CHMP/437/04 Rev.1; EMA/CHMP/BWP/247713/2012 Rev 1; EMEA/CHMP/BMWP/42832/2005 Rev.1; EMEA/CHMP/BMWP/403543/2010 Rev 1; US FDA 2015a; US FDA 2015b).

7 STUDY OBJECTIVES

7.1 Primary Study Objective

The primary objective for this study is to assess the efficacy of ABP 710 compared with US-licensed infliximab (infliximab).

7.2 Secondary Study Objectives

The secondary objectives are to assess the safety and immunogenicity of ABP 710 compared with infliximab.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a randomized, double-blind, active-controlled study in adult subjects with moderate to severe RA who have an inadequate response to MTX. Approximately 550 subjects (275 per treatment group) will be enrolled. The subjects will be randomized in a 1:1 ratio to receive either ABP 710 3 mg/kg infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter (treatment group A), or infliximab 3 mg/kg infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter (treatment group B), until week 22.

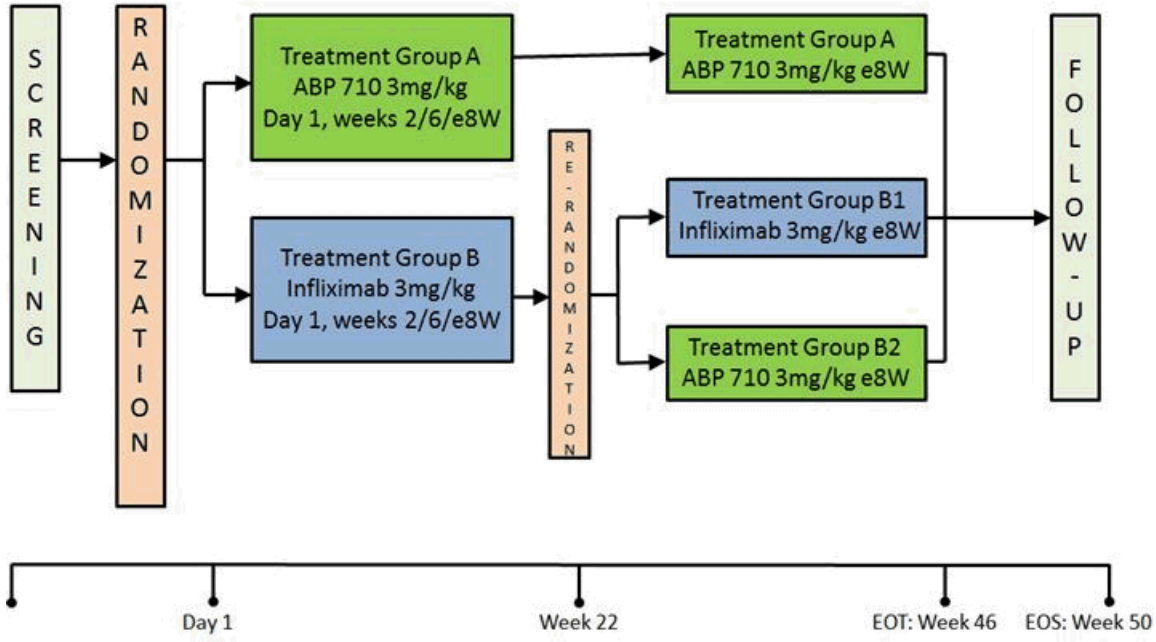
At week 22, subjects initially randomized to the infliximab group will be re-randomized in a 1:1 ratio to either continue receiving infliximab infusion every 8 weeks (treatment group B1), or to switch to ABP 710 (treatment group B2). Subjects initially randomized to ABP 710 (treatment group A) will continue on the same treatment. Re-randomization will be managed to ensure that the blind to the initial study group is maintained. **Subjects who are unable to complete the week 22 visit within the visit window of ± 3 days will be 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.** The last treatment for all subjects **who do not discontinue early** will be at week 46. Subjects will be considered study completers when they finish the week 50 end-of-study assessments.

Subjects will complete a screening period of up to 4 weeks, receive investigational product for 46 weeks, and complete an efficacy, safety, and immunogenicity follow-up period of 4 weeks for a total study duration of up to 54 weeks.

An independent data monitoring committee (DMC) will evaluate the safety data throughout the study. The primary analysis will be conducted at week 34. The end of the study will be at week 50, and a final analysis will be conducted when all subjects have completed the week 50/end-of-study assessments (or are terminated early from the study). Study completion is defined as completion of the week 50 visit.

Figure 8-1 is a summary of the study design.

Figure 8-1. Study Diagram



e8W = every 8 weeks; EOS = end-of-study (week 50); EOT = end-of-treatment (week 46).

Note: the primary analysis will be conducted at week 34.

8.2 Discussion of Study Design

This study is randomized and double-blinded to prevent bias in treatment allocation and in the subjective assessment of effect. The primary analysis will be conducted after all subjects have either completed the week 34 assessments, or been terminated from the study before week 34.

8.3 Study Duration

The study consists of a screening period of up to 4 weeks, a treatment period of 46 weeks, and a safety, immunogenicity, and efficacy follow-up period through to week 50 for a total of up to 54 weeks.

Enrollment will continue until approximately 550 subjects (275 per treatment group) have been randomized to treatment. The end of the study will be the date when the last subject has completed the last study assessment.

8.4 Study Population

8.4.1 Inclusion Criteria

Subjects **MUST** satisfy all of the following entry criteria before they will be allowed to participate in the study:

1. Subject has signed an IRB/IEC-approved ICF before any study-specific procedures are performed.
2. Subject (man or woman) is ≥ 18 and ≤ 80 years old.
3. Subject is diagnosed with RA as determined by meeting the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria for RA.
4. Subject has RA duration of at least 3 months.
5. Subject has active RA defined as ≥ 6 swollen joints and ≥ 6 tender joints (based on 66/68 joint count, excluding distal interphalangeal joints) at screening and baseline and at least 1 of the following at screening:
   - erythrocyte sedimentation rate ≥ 28 mm/hr
   - serum CRP > 1.0 mg/dL
6. Subject has **at least one of the following:** a positive rheumatoid factor or anti-cyclic citrullinated peptide (CCP) at screening.
7. Subject has taken MTX for ≥ 12 consecutive weeks and is on a stable dose of oral or subcutaneous MTX 7.5 to 25 mg/week for ≥ 8 weeks before receiving the investigational product and is willing to remain on a stable dose throughout the study.
8. For a subject on nonsteroidal anti-inflammatory drugs (NSAIDs) or low potency analgesics such as tramadol, Soma Compounds, Fioricet, or Fiorinal, the dose should be stable for ≥ 2 weeks before screening.
9. For a subject on oral corticosteroids (≤ 10 mg prednisone or equivalent), the dose should be stable for ≥ 4 weeks before screening.
10. Subject has no known history of active tuberculosis.

Subject must meet any 1 of the following 3 criteria:

11. Subject has a negative test for tuberculosis during screening defined as either:
    - negative purified protein derivative (PPD) defined as < 5 mm of induration at 48 to 72 hours after test is placed

    OR

- negative Quantiferon test

12. Subject with a positive PPD and a history of Bacillus Calmette-Guérin vaccination is allowed with a negative Quantiferon test.
13. Subject with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or a subject with a positive or indeterminate Quantiferon test is allowed if they have all of the following:
    - no symptoms of tuberculosis according to the worksheet provided by the sponsor, Amgen Inc.
    - documented history of adequate prophylaxis initiation before receiving investigational product in accordance with local recommendations
    - no known exposure to a case of active tuberculosis after most recent prophylaxis

8.4.2 Exclusion Criteria

If any of the following apply, the subject **MUST NOT** enter the study:

Rheumatoid arthritis related

1. Subject has Class IV RA (Hochberg et al, 1992) according to the ACR revised response criteria (Section 17.2).
2. Subjects has Felty's syndrome (RA, splenomegaly, and granulocytopenia).
3. Subject has a history of prosthetic or native joint infection.

Other medical conditions

4. Subject has a planned surgical intervention during the duration of the study.
5. Subject has an active infection or history of infections as follows:
    - any active infection for which systemic anti-infective(s) were used within 28 days before the first dose of investigational product
    - a serious infection, defined as requiring hospitalization or IV anti-infective(s) within 8 weeks before the first dose of investigational product
    - recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject
6. Subject has a positive blood test for human immunodeficiency virus.
7. Subject has a positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody, or hepatitis C virus (HCV) antibody result at screening.

8. Subject has uncontrolled, clinically significant systemic disease such as diabetes mellitus, cardiovascular disease, including moderate or severe heart failure (New York Heart Association Class III/IV), renal disease, liver disease, or hypertension.
9. Subject had a malignancy within 5 years EXCEPT for treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma.
10. Subject has a history of neurologic symptoms suggestive of central or peripheral nervous system demyelinating disease.
11. Subject has a major chronic inflammatory disease or connective tissue disease other than RA, with the exception of secondary Sjögren's syndrome.
12. Subject has a concurrent medical condition that, in the opinion of the investigator, could cause this study to be detrimental to the subject.

Laboratory abnormalities

13. Subject has laboratory abnormalities at screening, including any of the following:
    - hemoglobin < 9 g/dL
    - platelet count < 100 000/mm^3
    - white blood cell count < 3000/mm^3
    - aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 2.0 x the upper limit of normal
    - creatinine clearance < 50 mL/min (Cockroft-Gault formula)
    - any other laboratory abnormality, that, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results

Washouts and nonpermitted drugs

14. Subject has used any of the following within 28 days before the first dose of investigational product:
    - intra-articular (IA) hyaluronic acid injections
    - intramuscular (IM), IA, or IV corticosteroids, including adrenocorticotropic hormone
15. Subject has used nonbiologic DMARDs other than MTX within 28 days before the first dose of investigational product, except as below:

- leflunomide (unless an active washout with cholestyramine has been performed), cyclosporine, azathioprine, tacrolimus excluded within 3 months before the first dose of investigational product
- intramuscular or oral gold excluded within 6 months before the first dose of investigational product
- cytotoxic agents such as cyclophosphamide, D-penicillamine excluded within 6 months before the first dose of investigational product
- intravenous gamma-globulin or Prosorba column therapy excluded within 3 months before the first dose of investigational product
- Janus kinase inhibitor, eg, tofacitinib; excluded within 28 days before the first dose of investigational product

16. Subject has prior use of 2 or more **distinct** biologic therapies for RA.
17. Subject has used commercially available or investigational biologic therapies for RA as follows:
    - anakinra, etanercept within 1 month before the first dose of investigational product
    - abatacept, tocilizumab, adalimumab, golimumab, certolizumab within 3 months before the first dose of investigational product
    - other experimental or commercially available biologic therapies for RA within 3 months or 5 half-lives (whichever is longer) before the first dose of investigational product
    - rituximab within 9 months before the investigational product along with evidence of incomplete B cell recovery.
18. Subject has received live vaccines within 28 days before the first dose of investigational product or plans to receive live vaccines during the course of the study.
19. Subject has chronic use of high potency narcotic analgesics such as morphine or morphine-derived medications, fentanyl, codeine, hydromorphone, levorphanol, meperidine, methadone, oxycodone, or hydrocodone at screening.
20. Subject who has taken any of the above agents in the past must have recovered from all drug-related adverse events.
21. Subject has previously taken Remicade® (infliximab) or a biosimilar of infliximab.

22. Subject is currently enrolled in or has not yet completed at least 30 days or 5 half-lives (whichever is longer) since ending other investigational device or investigational drug(s), including vaccines, or subject is receiving other investigational agent(s).

General

23. Woman who is pregnant or breast feeding, or plans to become pregnant while enrolled in the study and for 6 months after the last dose of investigational product.
24. Woman who is of childbearing potential (ie, neither surgically sterile nor postmenopausal) and who does not agree to use adequate contraception (eg, true abstinence, sterilization, birth control pills, Depo-Provera® (medroxyprogesterone) injections, contraceptive implants**, or other effective methods**) while on study and for 6 months after the last dose of investigational product.
25. Subject has a known sensitivity to mammalian cell-derived drug products or hypersensitivity to the active substance or to any of the excipients of ABP 710 or infliximab.
26. Subject has any physical or psychiatric disorder that, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.
27. Subject has any disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures.
28. Subject has active substance abuse (within 24 weeks of screening).

8.4.3 Withdrawal and Replacement of Subjects

8.4.3.1 Criteria for Subject Withdrawal

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study, but continue participating in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments and Procedures (Table 8-1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments and

Procedures (Table 8-1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

Reasons for removal from protocol-required investigational products or procedural assessments might include:

- **inability to complete the week 22 visit within the allowed visit window**
- subject request to end investigational product administration
- safety concern (eg, an adverse event, failure to follow contraception, and/or protocol requirements)
- pregnancy

Subjects who discontinued treatment because of inability to complete the week 22 visit within the allowed visit window should return for an end-of-study visit to complete the end-of-study assessments within 28 days, if possible.

Reasons for removal of a subject from the study might include:

- withdrawal of consent from study
- lost to follow-up
- decision by sponsor

8.4.3.2 Evaluations at Withdrawal

For any subject who is withdrawn before completing all study visits, the investigator should:

- Perform all the procedures scheduled for the week 50/end-of-study visit. These assessments will be performed no later than 28 days after withdrawal/discontinuation (unless the subject withdraws consent to do so).
- Complete all appropriate electronic case report form (eCRF) screens, providing the date of and explanation for the subject's withdrawal/discontinuation.

- When indicated, arrange for appropriate follow-up and/or alternative medical care for the discontinued subject.

If the subject fails to attend a scheduled termination or follow-up visit, there will be at least 2 attempts to contact the subject via telephone and 2 written communications. If these receive no reply, the subject will be considered lost to follow-up.

8.4.3.3 Replacement of Subjects

Subjects who are withdrawn will not be replaced. However, a sufficient number of subjects will be included to ensure that the minimum defined sample size is reached (see Section 12.2).

8.5 Treatments

8.5.1 Treatments Administered

The investigator must ensure that the investigational products will be used only in accordance with the protocol.

ABP 710 is a chimeric human/murine monoclonal antibody with the same amino acid sequence as infliximab.

Subjects will initially be randomly assigned at baseline (day 1) to 1 of 2 treatment groups, as follows:

- treatment A: ABP 710, 3 mg/kg IV infusion
- treatment B: Infliximab, 3 mg/kg IV infusion

In both treatment groups, doses will be administered by study center staff on day 1, weeks 2 and 6, and then every 8 weeks thereafter until week 22. At week 22, subjects initially randomized to the infliximab group will be re-randomized in a 1:1 ratio to either continue receiving infliximab infusion every 8 weeks (treatment group B1), or switch to ABP 710 (treatment group B2) every 8 weeks. Subjects initially randomized to ABP 710 will continue on the same treatment.

No dose reductions or changes will be allowed, except for weight-based dosing changes.

Premedications **must** be given**. Premedications should be selected** according to local practice and**/or** the approved product label for infliximab. These medications should generally include acetaminophen and an antihistamine and methylprednisone 100 mg IV

or equivalent **approximately** 30 minutes before each infusion **but should be selected according to the individual subject's needs.**

Intravenous infusions should be performed according to local practice and the approved product label for infliximab.

Investigational product infusion reactions should be handled according to local practice and the approved product label for infliximab.

ABP 710/infliximab will be administered after all other procedures have been completed for each visit. If the subject presents with an infection at the dosing visit(s), the administration of investigational product may be delayed (up to 5 days). If a dose is delayed or missed for any reason, subsequent doses should be administered at the original scheduled dosing dates in relation to the first dose date.

All subjects will continue on a stable dose of MTX (7.5 to 25 mg/week, oral, or subcutaneous) for the duration of their participation in the study, as prescribed by the treating physician. When possible, the dose of MTX should be taken on the same day of the week. In the event that a subject develops MTX-related side effects (eg, mucositis/stomatitis), a dose reduction or change of route should be considered, as deemed appropriate by the investigator. Please see Section 8.5.7.4 for folate/folinic acid.

8.5.2 Study Treatment Formulation

8.5.2.1 Study Drug

ABP 710 is a human/murine chimeric monoclonal IgG1 antibody that binds with high affinity to both soluble and transmembrane forms of TNFα and has the same amino acid sequence as infliximab. ABP 710 and infliximab are manufactured by recombinant DNA technology, and ABP 710 is expressed in a Chinese hamster ovary cell line and purified by a suitable process.

ABP 710 is supplied as a sterile, white, lyophilized powder for IV infusion requiring reconstitution prior to infusion with 10 mL of Sterile Water for injection. Each single-use vial contains 100 mg ABP 710, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate.

8.5.2.2 Comparator

Infliximab, the active ingredient in Remicade®, is a chimeric IgG1 kappa monoclonal antibody (composed of human constant and murine variable regions) specific for human TNFα. It has a molecular weight of approximately 149.1 kD and a binding affinity for soluble TNFα of approximately K(D)=4.2 picomolars, as measured by KinExA technology. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

Infliximab is supplied as a sterile, white, lyophilized powder for IV infusion. After reconstitution with C mL Sterile Water for Injection, USP, the resulting pH is approximately CCI. Each single-use vial contains 100 mg infliximab, CCI mg sucrose, CCI mg polysorbate 80, CC mg monobasic sodium phosphate, monohydrate, and CCI mg dibasic sodium phosphate, dihydrate. No preservatives are present.

Infliximab will be provided from commercial supplies.

8.5.2.3 Methotrexate

Investigators will prescribe MTX according to standard local practice. Additional details are provided in Section 8.5.1.

8.5.3 Study Treatment Labeling and Packaging

A manual containing detailed information regarding the labeling, packaging, storage, preparation, and administration of each investigational product (eg, test and comparator product) and brief information about other protocol-required therapies will be provided separately in the Pharmacy Guide.

8.5.4 Blinding of Study Medication

The investigational product containers are different for ABP 710 and infliximab, therefore, investigational product (ABP 710 or infliximab) will be prepared by an unblinded pharmacist or designee for administration to the subject. The subjects, the sponsor (Amgen Inc.), designated PRA study personnel, and other study center staff will be blinded to the investigational product allocation for each subject. Randomization data will be kept strictly confidential, filed securely by the sponsor (or designee), and accessible only to authorized persons per sponsor's (or designee's) standard operating procedures until the time of unblinding. Select PRA staff (eg, unblinded clinical research associates) who will not be involved in the monitoring or the daily operations of the study

will be unblinded to subject investigational product allocation to perform investigational product accountability.

For details on the emergency procedure for unblinding of individual subjects see Section 8.5.10, below.

At randomization, randomization numbers will be assigned to each subject by the interactive voice and web response system (IXRS).

8.5.5 Study Treatment Storage and Accountability

Investigational product must not be used for purposes other than those defined in this protocol.

8.5.5.1 Study Treatment Storage

The investigational product should be stored at [redacted]°C to [redacted]°C in a secure limited access location. ABP 710 and infliximab should be stored protected from light and according to the storage and expiration information (where required) provided on the label that is affixed to the package containing the investigational product. After reconstitution, the investigational product should be stored in a refrigerator ([redacted]°C to [redacted]°C).

8.5.5.2 Study Treatment Accountability

All supplies of investigational product will be accounted for in accordance with GCP. **There will be a master study drug accountability record completed,** and the pharmacist, or designee, should maintain accurate records of the disposition of all investigational product supplies received during the study. These records should include the amounts and dates that investigational products were received and destroyed/returned to the sponsor or its designee. If errors or damages in the investigational product shipments occur, the investigator should contact the sponsor or its designee immediately. Copies of the investigational product accountability records will be provided by each investigator for inclusion in the Trial Master File after database lock. The unblinded study monitor will periodically check the supplies of investigational product held by the investigator or pharmacist to verify accountability of investigational product used.

The investigator **(or designee)** will administer the investigational product only to the identified subjects of this study, according to the procedures described in this study protocol. After the end of the study, all unused investigational product and all medication containers should be destroyed at the study center or returned to the sponsor or its

designee for destruction. In either instance, complete documentation will be returned to the sponsor.

8.5.6 Dose Adjustments and Dose Escalation

No dose reductions or escalations are planned for the investigational products used in this study, except for weight-based dosing changes.

8.5.7 Prior and Concomitant Therapy

8.5.7.1 Permitted Concomitant Treatments (Medications and Therapies)

The following concomitant medications are permitted:

- methotrexate as specified in Section 8.5.1
- oral corticosteroids at a dose of ≤ 10 mg prednisone, or equivalent, per day are permitted provided they are at a stable dose for at least 4 weeks before initiation of investigational product. The dose of oral corticosteroids may be reduced according to local guidelines during the conduct of the study
- nonlive vaccinations are allowed any time throughout the study

If at any time a subject clinically needs additional therapy (other than those specified in Section 8.5.7.3), including a significant increase in the MTX dose to treat RA, the investigator should contact the Amgen medical monitor (or designee) to determine if the subject is eligible to remain on investigational product. If the subject is no longer eligible to remain on investigational product, then the subject should undergo the evaluations and procedures described in Section 8.4.3.2.

8.5.7.2 Prohibited Concomitant Medications

All of the following are prohibited at any time during the study:

- nonbiologic DMARDs (other than MTX; as per exclusion criteria)
- any biologic treatment for RA (eg, anakinra, soluble IL-1 type II receptor, etanercept, infliximab [except for investigational product], onercept, abatacept, tocilzumab, golimumab, certolizumab, rituximab, and adalimumab)
- chronic minocycline or tetracycline (except use for ≤ 10 days to treat infection, or for nonarthritis indications, eg, acne), hydroxychloroquine, mycophenolate mofetil, or sulfasalazine
- live and attenuated vaccinations are not allowed while subjects are enrolled in the study and receiving investigational product

- any experimental (biological or nonbiological) therapy (within or outside a clinical study)
- intra-articular hyaluronic acid
- intra-articular, IM, or IV corticosteroids, including adrenocorticotropic hormone
- Janus kinase inhibitor (eg**,** tofacitinib)

8.5.7.3 Rescue Medication

The definition of rescue medication is any medication other than prohibited medication that is used to treat RA. The use of rescue medication is allowed in this study under the following conditions:

- oral corticosteroids: the maximum dose allowed is 10 mg prednisone (or equivalent) per day; the dose can be decreased if needed, per the investigator's clinical judgment
- acetaminophen, hydrocodone, codeine, tramadol, and/or propoxyphene may be used by the subject as rescue analgesics. However, no rescue analgesics will be allowed within 12 hours before clinical efficacy assessments (ie, at **baseline and** weeks 2, 6, 14, 22, 30, 34, 38, 46, and 50)
- NSAIDs/cyclooxygenase-2 (COX-2) inhibitors: If the subject enters the study taking an NSAID/COX-2 inhibitor, the dose of NSAIDs/COX-2 inhibitors can be reduced or discontinued during the study if necessary for safety reasons or standard of care. In cases of flare, the dose of NSAIDs/COX-2 inhibitors can be temporarily increased as needed. However, the subject must return to the maintenance dose (the dose at baseline) as soon as the flare resolves. In subjects not taking an NSAID/COX-2 inhibitor, one may be added temporarily to treat a flare in RA. It should be tapered and discontinued with resolution of flare. In all cases, **these agents will** not **be** allowed within 12 hours before clinical efficacy assessments (ie, at **baseline and** weeks 2, 6, 14, 22, 30, 34, 38, 46, and 50)
- topical anesthetic creams (eg, lidocaine/prilocaine creams and licensed NSAID creams) are permitted. However, these agents will not be allowed within 12 hours before clinical efficacy assessments (ie, at **baseline and** weeks 2, 6, 14, 22, 30, 34, 38, 46, and 50)

8.5.7.4 Prophylactic Treatment

Certain adverse events are commonly associated with MTX treatment. To minimize MTX toxicity, subjects may receive a stable dose of oral folate or folinic acid. This can either be given as a single dose given weekly or as a divided weekly dose, at the investigator's discretion.

8.5.7.5 Other Concomitant Medications and Treatments

Any other treatment (not explicitly excluded) considered necessary for the subject's welfare may be given at the discretion of the investigator. Administration of concomitant medications must be recorded. Generic names for concomitant medication should be used, if possible.

All subjects who discontinue the investigational product should be offered alternative treatment if applicable. Treatment should be given according to normal clinical practice, after an end-of-study visit (see Section 8.4.3.2).

8.5.8 Treatment Compliance

Records of investigational product used and intervals between visits will be kept during the study. Drug accountability will be noted by the unblinded field monitor during study center visits and at the completion of the study. The investigational product should be dispensed by the investigator or by a qualified individual under the investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained.

8.5.9 Assignment to Treatment

When subjects enter the screening period for the study, the investigator (or designee) will contact the IXRS and receive a unique 11-digit subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. PPD [redacted]

The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, enrollment, randomization, or re-randomization. This number will not necessarily be the same as the randomization number assigned for the study.

Upon completion of screening, the investigator (or designee) will contact the IXRS to randomize the subject centrally to receive either ABP 710 or infliximab in a 1:1 manner. The randomization will be stratified based on geographic region and prior biologic use (yes versus no) for RA (with prior biologic use capped at 30% of the study population). At week 22, subjects initially randomized to the infliximab group will be re-randomized in a 1:1 ratio (via IXRS) to either continue receiving infliximab every 8 weeks or switch to the ABP 710 group. Re-randomization will be managed to ensure that the blind to the initial study group is maintained.

8.5.10 Unblinding Procedures

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study center for any other reason will be considered a protocol violation. The investigator is strongly encouraged to contact the Amgen medical monitor (or designee) before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

The identity of investigational product assigned to subject numbers or to individual boxes of investigational product will be available for emergency situations through the IXRS. Authorized study center staff will be provided with a unique Personal Identification Number (PIN) to access the IXRS to obtain unblinding information. This PIN is unique to the individual and must not be shared.

8.6 Efficacy and Safety Variables

8.6.1 Efficacy and Safety Measurements Assessed

A schedule of procedures and assessments is presented in Table 8-1.

Table 8-1. Schedule of Assessments and Procedures

	Screening (≤ 28 days)	Baseline	Week								
		Day 1	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

See abbreviations and footnotes on following page

Table 8-1. Schedule of Assessments and Procedures

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

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BP = blood pressure (systolic and diastolic); CRP = C-reactive protein; ECG = electrocardiogram; EOS = end-of-study; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; RR = respiratory rate; temp = temperature.

[a] For subjects who terminate early, perform the evaluations and procedures for end-of-study.

[b] Weight will be measured before infusion at each dosing visit. The dose will be adjusted based on weight changes at each visit, if required.

[c] Vital signs will be measured before and after infusion at all dosing visits.

[d] Chest radiography within 3 months before screening is acceptable (both anteroposterior and lateral incidences are required).

[e] Only serious adverse events are reported during the screening period.

[f] ABP 710/infliximab will be administered after all other procedures are completed for each visit. If the subject presents with an infection at the dosing visit(s), the administration of investigational product may be delayed (up to 5 days).

[g] Purified protein derivative (PPD); < 5 mm of induration at 48 to 72 hours after test is placed OR negative Quantiferon test; subjects with positive PPD/Quantiferon test may be eligible based on the sponsor's worksheet and the other criteria listed in inclusion criterion 13.

[h] Includes rheumatoid factor and anti-CCP.

[i] C-reactive protein will be performed by the central laboratory and results will be blinded from the study centers at the baseline visit and onward. Erythrocyte sedimentation rate may be used instead of CRP at screening only.

[j] CCI

[k] During the weeks when antidrug antibody samples are drawn, predose samples will be collected, with the exception of week 34 and week 50/end-of-study time points which do not have investigational product administration. Therefore, at these time points, the time of sample collection will be recorded.

[l] Pregnancy testing required for women of childbearing potential. Serum pregnancy test will be done at screening by the central laboratory. Urine pregnancy test performed locally at subsequent time points.

8.6.1.1 Efficacy Measurements

8.6.1.1.1 Primary Efficacy Criterion

The primary endpoint is the response difference (RD) of 20% improvement in ACR core set measurements (ACR20) at week 22.

ACR20

To achieve ACR20 response, at least 20% improvement compared with baseline is required for both swollen joint count (SJC) and tender joint count (TJC) (66/68 joint counts; Section 17.3), as well as for 3 out of the following 5 additional parameters:

- Subject's Global Health Assessment (on a 100-mm visual analogue scale [VAS]; Section 17.4)
- Investigator's Global Health Assessment (on a 100-mm VAS; Section 17.4)
- subject's assessment of pain (on a 100-mm VAS; Section 17.4)
- Health Assessment Questionnaire-Disability Index (HAQ-DI) (Section 17.4)
- serum CRP

8.6.1.1.2 Secondary Efficacy Criteria

The secondary endpoints are:

- response difference of ACR20 at weeks 2, 6, 14, 30, 34, 38, 46, and 50
- response difference of at least 50% improvement in ACR core set measurements (ACR50), and at least 70% improvement in ACR core set measurements (ACR70) 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, 38, 46, and 50

ACR50 and ACR70

ACR50 and ACR70 are defined in a similar fashion to ACR20, but require at least 50% and 70% improvement respectively, compared with baseline for both swollen and tender joint counts, as well as for 3 out of 5 additional parameters (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, HAQ-DI, and CRP).

DAS28-CRP

The DAS28-CRP is a composite measure of disease activity in RA. It is a continuous measure based on 28 Disease Activity Score (DAS) joints from the ACR, the Subject's Global Health Assessment score and CRP, as follows:

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

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.

8.6.1.2 Safety Measurements

The safety endpoints are:

- treatment-emergent adverse events, serious adverse events, and adverse events of special interest
- clinically significant changes in laboratory values and vital signs
- incidence of antidrug antibodies

8.6.1.3 Exploratory Measurements

CCI [redacted]

- [redacted]

9 STUDY EVALUATIONS BY VISIT

After signing of the informed consent at the screening visit, there will be 10 additional visits. Treatment visits will occur on day 1 (day of first treatment), and weeks 2, 6, 14, 22, 30, 38, and 46. Disease assessments will be performed on day 1, at weeks 2, 6, 14, 22, 30, 34, 38, 46, and at the follow-up week 50/end-of-study visit.

9.1 Screening

After subjects have provided informed consent, the following assessments/procedures at the screening visit must be completed within 28 days of the baseline visit:

- subject's assessment of pain (Section 17.4); subjective assessments will be the first assessments performed at the visit
- targeted medical history, including history of all prior treatments for RA within the past 3 years and any prior biologic therapy for RA
- physical examination including evaluation of body systems, height, and weight
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- standard 12-lead electrocardiogram (ECG)
- chest radiography, including anteroposterior and lateral views (prior radiography or formal reports signed off by a radiologist within 3 months of screening is acceptable)
- screening joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- tuberculosis testing (PPD or Quantiferon test)
- clinical laboratory testing, including serology, serum chemistry, hematology, ESR and/or CRP, rheumatoid factor, and anti-CCP
- collection of urine sample for urinalysis
- serum pregnancy test for women of childbearing potential

At the screening assessment, all concomitant medications from 3 months before the planned start of investigational product, all prior treatments for RA within the past 3 years, and any prior biologic therapy for RA will be recorded. Any adverse events occurring during the screening period will be recorded as medical history. Serious adverse events will be reported as outlined in Section 11.2.2.

Subjects will continue on their stable prestudy MTX regimen and folate or folinic acid regimen during the screening period.

9.1.1 Screen Failures

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Laboratory assessments used to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure. Screen failed subjects may be rescreened up to 2 times at the investigator's discretion (ie, a total of 3 screens including initial screening). **If screening procedures cannot be completed within 28 days before day 1, the subject will be considered a screen failure but may be eligible for rescreening. These subjects can be rescreened under the same ICF if rescreening occurs within 30 days of initial consent date.** The subject will retain the same subject identification number provided at the initial screening. Subjects must be re-consented if more than 30 days have elapsed between date of initial informed consent and date of rescreen/randomization.

9.2 Baseline (Day 1, first day of treatment, Week 0)

Day 1 will be defined as the first day of treatment. After subjects are confirmed to meet the entry criteria (Section 8.4), the investigator (or designee) will contact the IXRS to randomize the subject centrally to receive either ABP 710 or infliximab. The following assessments/procedures will be performed before treatment:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI, Section 17.4); subjective assessments will be the first assessments performed at the visit
- weight (dose will be calculated based on measured weight)
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- baseline joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3); **the baseline joint assessment must be performed before randomization**
- clinical laboratory testing, including serum chemistry, hematology, and CRP
- urine pregnancy test for women of childbearing potential

- collection of pretreatment pharmacokinetic sample and pretreatment sample for antidrug antibodies

Any changes in concomitant medications since the screening visit will be recorded. Any pretreatment adverse events will be recorded using the medical history eCRF; any pretreatment serious adverse events will be recorded using the adverse event eCRF. Serious adverse events will be reported as outlined in Section 11.2.2. Premedications **must** be given. **Premedications should be selected** according to local practice and**/or** the approved product label. These medications should generally include acetaminophen, an antihistamine, and methylprednisone 100 mg IV or equivalent 30 minutes before each infusion **but should be selected according to the individual subject's needs**.

After completion of pretreatment procedures (including predose pharmacokinetic sample and antidrug antibody collection), ABP 710 or infliximab will be administered as an IV infusion in a double-blinded fashion; investigational product will be assigned based on box numbers provided by the IXRS. Starting at the time of first treatment, all adverse events, including increases in severity or frequency of pre-existing conditions, will be recorded in the adverse event eCRF.

At the end of infusion, the following assessments will be performed:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- collection of postdose pharmacokinetic sample (within 10 minutes after the end of infusion)

Subjects will continue on their stable MTX regimen.

9.3 Week 2 (± 2 days), Week 6 (± 3 days), and Week 14 (± 3 days)

The subject will return to the study center at week 2 (± 2 day**s**), week 6 (± 3 days), and week 14 (± 3 days). The following assessments/procedures will be performed before treatment:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI, Section 17.4); subjective assessments will be the first assessments performed at the visit
- weight (dose will be adjusted based on weight changes, if required)

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- clinical laboratory testing, including serum chemistry, hematology, and CRP
- CCI [redacted] and sample for antidrug antibodies
- urine pregnancy test for women of childbearing potential (required only at week 6)

Any changes in concomitant medications since the last assessment will be recorded. All adverse events, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF. Serious adverse events will be reported as outlined in Section 11.2.2.

After completion of pretreatment procedures, ABP 710 or infliximab will be administered as an IV infusion in a double-blinded fashion.

At the end of infusion, the following assessments will be performed:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- collection of postdose pharmacokinetic sample (within 10 minutes after the end of infusion)

Subjects will continue on their stable MTX regimen.

9.4 Week 22 (± 3 days)

The subject will return to the study center at week 22 (± 3 days). The following assessments will be performed before re-randomization and treatment:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI); subjective assessments will be the first assessments performed at the visit
- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- physical examination, including evaluation of body systems
- weight (dose will be adjusted based on weight changes, if required)
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)

- clinical laboratory testing, including serum chemistry, hematology, and CRP
- CCI [redacted] and sample for antidrug antibodies
- collection of urine sample for urinalysis
- urine pregnancy test for women of childbearing potential

In addition, any changes in concomitant medications since the last assessment will be recorded. All adverse events, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF. Serious adverse events will be reported as outlined in Section 11.2.2.

After completion of pretreatment procedures, the investigator (or designee) will contact the IXRS, and subjects initially randomized to the infliximab group will be re-randomized (in a 1:1 ratio) to either continue to receive infliximab (treatment group B1) or switch to ABP 710 (treatment group B2). Subjects initially randomized to ABP 710 (treatment group A) will continue on the same treatment. Re-randomization will be managed to ensure that the blind to the initial study group is maintained.

Investigational product will be administered by IV infusion in a double-blinded fashion. At the end of infusion, the following assessments will be performed:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- collection of postdose pharmacokinetic sample (within 10 minutes after the end of infusion)

Subjects will continue on their stable MTX regimen.

9.5 Week 30 (± 5 days)

The subject will return to the study center at week 30 (± 5 days). The following assessments/procedures will be performed before treatment:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI, Section 17.4); subjective assessments will be the first assessments performed at the visit
- weight (dose will be adjusted based on weight changes, if required)
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)

- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- clinical laboratory testing for hematology and CRP
- collection of predose pharmacokinetic sample and sample for antidrug antibodies

Any changes in concomitant medications since the last assessment will be recorded. All adverse events, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF. Serious adverse events will be reported as outlined in Section 11.2.2.

After completion of pretreatment procedures, ABP 710 or infliximab will be administered as an IV infusion in a double-blinded fashion.

At the end of infusion, the following assessments will be performed:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)

Subjects will continue on their stable MTX regimen.

9.6 Week 34 (± 5 days)

The subject will return to the study center at week 34 (± 5 days), but will not be administered investigational product at this visit. The following assessments/procedures will be performed:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI, Section 17.4); subjective assessments will be the first assessments performed at the visit
- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- clinical laboratory testing, including serum chemistry, hematology, and CRP
- collection of pharmacokinetic sample and sample for antidrug antibodies
- collection of urine sample for urinalysis
- urine pregnancy test for women of childbearing potential

Any changes in concomitant medications since the last assessment will be recorded. All adverse events, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF. Serious adverse events will be reported as outlined in Section 11.2.2.

Subjects will continue on their stable MTX regimen.

9.7 Weeks 38 and 46 (± 5 days)

The subject will return to the study center at weeks 38 and 46 (± 5 days). The following assessments/procedures will be performed before treatment:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI, Section 17.4); subjective assessments will be the first assessments performed at the visit
- weight (dose will be adjusted based on weight changes, if required)
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- clinical laboratory testing for hematology and CRP
- collection of predose pharmacokinetic sample and sample for antidrug antibodies (required only at week 38)
- urine pregnancy test for women of childbearing potential (required only at week 46)

Any changes in concomitant medications since the last assessment will be recorded. All adverse events, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF. Serious adverse events will be reported as outlined in Section 11.2.2.

After completion of pretreatment procedures, ABP 710 or infliximab will be administered as an IV infusion in a double-blinded fashion. Week 46 is the final dose of investigational product in this study.

At the end of infusion, the following assessments will be performed:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)

Subjects will continue on their stable MTX regimen.

9.8 Week 50/End-of-Study (± 5 days)

The subject will return to the study center at week 50/end-of-study (± 5 days). Subjects who terminate early will also attend this visit. The following assessments/procedures will be performed:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI, Section 17.4); subjective assessments will be the first assessments performed at the visit
- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- clinical laboratory testing, including serum chemistry, hematology, urinalysis, and CRP
- collection of pharmacokinetic blood sample and sample for antidrug antibodies
- physical examination, including evaluation of body systems
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- urine pregnancy test (for women of childbearing potential)

Any changes in concomitant medications since the last assessment will be recorded. All adverse events, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF through 28 days after the last treatment with ABP 710/infliximab. Serious adverse events will be reported as outlined in Section 11.2.2. On completion of the week 50 visit assessments, subjects will be considered study completers. Any serious adverse events ongoing at week 50 or at the end of the study will be followed until they resolve or are considered chronic or stable.

10 METHODS OF ASSESSMENT

10.1 Efficacy Assessments

At each time point for RA assessments, the Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI (Section 17.4) will be completed. These assessments should be the first assessments performed at the visits for which they are scheduled.

At these same time points, joints will be assessed and classified as swollen/not swollen and tender/not tender by pressure and joint manipulation on physical examination. Joint prosthesis, arthrodesis, or fused joints will not be assessed for swelling or tenderness.

The joints to be assessed for swelling and tenderness are given in Section 17.3, including the 66/68 joint set for ACR and the 28 joint count for DAS. All joint assessments will be performed by an experienced joint evaluator. The evaluator cannot be the treating physician and cannot interact with the subject on the study beyond the assessment of joints. The evaluator should not discuss the subject's clinical status nor should the evaluator have access to subject medical records or eCRFs, including prior joint assessments. The same evaluator should perform joint assessments across all time points for a subject where possible.

For the screening and baseline joint counts, the distal interphalanges should be evaluated, but should not be included in the total joint count to determine eligibility.

The Investigator's Global Health Assessment will also be completed at the times indicated in Table 8-1. The independent joint assessor may not complete the Investigator's Global Disease Assessment. The physician completing the Investigator's Global Disease Assessment will have access to the joint assessments. The subject and physician must complete the global assessments independently from each other.

10.2 Safety Assessments

10.2.1 Pregnancy Test

Pregnancy will be determined by evaluation of beta-human chorionic gonadotrophin in serum at screening by the central laboratory and in urine at subsequent time points locally for all women of childbearing potential. Subjects who are pregnant will be excluded from the study.

The investigator will inform the sponsor immediately of any case of pregnancy and collect information on any female subject who becomes pregnant while participating in this study and in case of pregnancy among female partners of male subjects. The subject will also be followed to determine the outcome of the pregnancy.

10.2.2 Physical Examination

Physical examinations will be performed by a physician and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and nervous system. For each body system, an assessment of normal or abnormal will be recorded. Clinically relevant changes from baseline will be reported as adverse events.

Body weight (kg) will be measured without shoes or jacket at screening, baseline, and before infusion at each dosing visit, and dose of investigational product will be adjusted for weight changes, if required. Height will be determined at screening.

10.2.3 Vital Signs

Systolic blood pressure and diastolic blood pressure will be measured on the same arm (preferentially on the left arm) after the subject has been in a supine/sitting position for 5 minutes. Pulse will be recorded simultaneously with blood pressure measurements. Respiration rate and temperature will also be recorded. Vital signs will be measured at screening, before and after infusion at each dosing visit, and at the end-of-study visit.

During the study, measurement of vital signs may be repeated at the discretion of the investigator for safety reasons. Clinically relevant abnormal findings will be reported as adverse events.

10.2.4 Electrocardiogram

Computerized 12-lead ECG recordings will be obtained after the subject has been supine for 5 minutes. Each lead will be recorded for at least 3 to 5 beats at a speed of 25 mm/sec paper speed and 10 mm/mV amplitude. At a minimum, heart rate, P-wave, PR-interval, QRS-wave, QT-interval, and corrected QT-intervals (msec) will be recorded from the 12-lead ECG. A copy of the ECGs will be retained at the study center. For the purposes of screening, the investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically acceptable for inclusion, if abnormal.

10.2.5 Tuberculosis Testing

A tuberculosis test will be performed at screening by PPD or Quantiferon test. PPD tests will be performed locally, and Quantiferon tests will be performed by the central or local laboratory. Subjects with positive PPD/Quantiferon test may be eligible based on the sponsor's tuberculosis risk assessment worksheet and the other criteria listed in the Inclusion Criteria, Section 8.4.1.

10.2.6 Chest Radiography

Chest radiography will be performed at screening as indicated in Table 8-1 and will include anterior/posterior or posterior/anterior and lateral views. Chest X-ray performed at the study center can be read by the investigator. A formal report, signed off by the investigator, will be filed in the subject's medical records. If the X-ray is performed off site, then formal reports signed off by a radiologist should be acceptable. Historical films obtained or formal reports signed off by a radiologist within the 3 months prior to receiving investigational product are acceptable for screening as well.

10.3 Clinical Laboratory Testing

Venous blood samples will be taken for clinical laboratory tests at the time points indicated in Table 8-1. The following parameters will be determined:

Serology: HBsAg, hepatitis B core antibody, and HCV antibody.

Hematology: Hemoglobin, hematocrit or packed cell volume, red blood cell count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count, differential white cell count, platelet count.

Clinical chemistry: Sodium, potassium, urea, creatinine, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, gamma glutamyl transferase, and nonfasting glucose. Rheumatoid factor and anti-CCP will be assessed at screening. C-reactive protein will be assessed at the time points indicated in Table 8-1. C-reactive protein results from the baseline visit and onwards will be blinded and not included in the central laboratory reports to the study center. Subjects with any abnormal liver function tests should be followed for potential hepatotoxicity. The investigational product should be stopped in cases of jaundice and/or marked liver enzyme elevations. Please see FDA guidance on drug-induced liver injury (US FDA 2009) or applicable local country guidance for additional guidance.

Urinalysis (fresh urine): pH, protein, glucose, bilirubin, blood, urine pregnancy test for women of childbearing potential.

Immunology: Blood samples for antidrug antibody (binding and neutralizing) assessments will be collected at the time points indicated in Table 8-1. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity, and presence of immune complexes. Additional blood samples may be obtained to rule out antidrug antibodies during the study.

The above clinical laboratory tests will be sent to and assessed at a central laboratory, except urine pregnancy, which will be assessed locally, and immunology, which will be sent to central laboratory and analyzed by Amgen or a designee. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a Laboratory Manual.

Additional and repeat laboratory safety testing may be performed at the discretion of the investigator. Any clinically relevant changes from baseline will be reported as adverse events.

10.4 Pharmacokinetic Analysis

During treatment, serum samples will be taken according to Table 8-1. The exact times of blood sampling will be recorded.

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Details of the procedures to be followed for sample collection, storage, and shipment will be documented in the Laboratory Manual.

11 SAFETY DATA COLLECTION, RECORDING, AND REPORTING

11.1 Adverse Events

11.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with investigational product. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record as well as in the eCRF.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, and gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. In the case of worsening of a pre-existing condition, the start date of the event is the date when the first signs of worsening were observed. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

11.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from the day of randomization until the week 50 visit (or through 28 days after the last dose of investigational product for subjects who discontinue study early) are reported using the applicable eCRF Adverse Event Summary page. Adverse events observed by the investigator or reported by the subject, that occur after signing of informed consent but before randomization would be recorded.

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- dates of onset and resolution
- severity
- assessment of relatedness to investigational product
- action taken

Adverse events must be graded for severity according to the National Cancer Institute (US) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

The investigator must assess whether the adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?"

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. A subject, or subject's legal guardian, can also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws consent, the subject is encouraged to undergo, at a minimum, an end-of- study assessment.

11.2 Serious Adverse Events

11.2.1 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life-threatening (places the subject at immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of “other medically important serious event.” Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

11.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through 28 days after the last dose of investigational product are recorded in the subject’s medical record and are submitted to Amgen.

The serious adverse event must be submitted to Amgen, or its designee, within 24 hours following the investigator’s knowledge of the event via the applicable eCRF or via paper serious adverse event report form if it occurs prior to randomization, ie, during screening.

If the electronic data capture (EDC) system is not functional, the serious adverse event can be reported by faxing a completed paper Serious Adverse Event Fax Cover Sheet and serious adverse event report form or by direct telephone communication with PRA Safety Risk Management at the numbers provided below. The event must be updated electronically in the EDC system by the clinical study center once the EDC function resumes.

Fax information to Safety Risk Management/PRA, for the attention of:

PRA Drug Safety Center

For Europe, Asia, and Pacific Region Clinical Study Centers:
FAX: +44 1792 525 720
Phone: +49.621.8782.154
CHOSafety@praintl.com

For North America, Latin America, and South America Clinical Study Centers:

FAX: 1.888.772.6919 (North America); 1.434.951.3482 (Latin and South America)
Phone: 1.800.772.2215 (North America); 1.434.951.3489 (Latin and South America)
CHOSafety@praintl.com

New information relating to a previously reported serious adverse event must be submitted to Amgen, or its designee, within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

Elective hospitalizations are not considered serious adverse events. If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen, or its designee.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen, or its designee, before submission to regulatory authorities. Investigators will receive notification of related serious adverse event reports sent to regulatory authorities in accordance with local requirements.

Determination of expectedness for Amgen products will be based on the IB for the investigational product and the regional prescribing information for products being studied for an approved use. Expectedness assessments are to be made for all investigational products (Amgen and non-Amgen) using the appropriate reference safety information per local regulatory reporting requirements. Suspected unexpected serious adverse reactions (SUSARs) reported for subjects receiving a non-Amgen investigational product are to be expedited according to local requirements.

Amgen, or its designee, reports serious adverse events and/or SUSARs as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and GCPs.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the study center and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of

the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

11.3 Adverse Events of Special Interest

Adverse events of special interest for ABP 710/infliximab are defined in the IB and analyzed from the clinical database using search strategies. There are no expedited reporting requirements for adverse events of special interest (other than those that meet other reporting requirements).

11.4 Pregnancy Reporting

Pregnancy in itself is not regarded as an adverse event unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are serious adverse events. Spontaneous miscarriages should also be reported and handled as serious adverse events. Elective abortions without complications should not be handled as adverse events. All outcomes of pregnancy must be reported to Amgen, or its designee. Pregnancy surveillance will include a pregnancy questionnaire that also addresses lactation surveillance. Any pregnancy that is ongoing or reported after completion of the study will be followed up by the sponsor.

Pregnancies in female partners of male subjects will also be reported and followed for outcome.

12 DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by an external clinical research organization (CRO), PRA.

12.1 Data Management

Previous and concomitant medications will be coded using the latest available World Health Organization-Drug Dictionary (WHO-DD). Coexistent diseases and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, it will be locked.

12.2 Sample Size Estimation

Approximately 550 subjects will be randomized in a 1:1 ratio to receive either ABP 710 or infliximab. Subjects will be stratified based on geographic region and prior biologic use for RA (with prior biologic use capped at 30% of the study population). The sample size is chosen to achieve > 90% power to demonstrate equivalence at a 0.05 significance level on the primary efficacy endpoint, RD of ACR20 at week 22 between ABP 710 and infliximab, with an equivalence margin of (-15%, 15%), assuming an expected ACR20 rate for both ABP 710 and infliximab of 52% at week 22. The sample size will also achieve approximately 85% power to demonstrate equivalence on the RD of ACR20 between ABP 710 and infliximab with an equivalence margin of (-12%, 15%) at a significance level of 0.05 at week 22.

12.3 Statistical Analysis Plan

A statistical analysis plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Table, listing, and figure shells will also be included.

12.4 Randomization

Randomization will be performed by an IXRS. The randomization schedule will be prepared by a statistician not involved in the conduct of the study. Upon completion of screening, approximately 550 eligible subjects will be randomized in a 1:1 ratio to receive either ABP 710 3 mg/kg infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter (treatment group A), or infliximab 3 mg/kg infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter (treatment group B), until week 22. Randomization will be

stratified based on geographic region and prior biologic use for RA (with prior biologic use capped at 30% of the study population).

At week 22, subjects initially randomized to the infliximab group (treatment group B) will be re-randomized in a 1:1 ratio (via IXRS) to either continue receiving infliximab every 8 weeks (treatment group B1) or switch to the ABP 710 group (treatment group B2). Subjects initially randomized to ABP 710 (treatment group A) will continue on the same treatment. Re-randomization will be managed to ensure that the blind to the initial study group is maintained. **Subjects unable to complete the week 22 visit within the allowed visit window will not be re-randomized and will be discontinued from the study.**

12.5 Analysis Sets

The primary analysis for the efficacy endpoints will be performed using the intention-to- treat analysis set. The per-protocol analysis set will be used for sensitivity analyses of the efficacy endpoints. The analysis of safety endpoints will be based on the safety analysis set. Information about the analysis of pharmacokinetic concentration summaries will be provided in the SAP.

12.5.1 Intention-to-treat Analysis Set

The intention-to-treat analysis set includes all subjects randomized in the study. Analyses will be based on randomized treatment (regardless of actual treatment received).

12.5.2 Per-protocol Analysis Set

The per-protocol analysis set includes 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. Analyses will be based on actual treatment received. Per-protocol analysis sets will be determined separately for the primary analysis conducted at week 34, and for the additional analysis conducted at the end of the study. The protocol deviations that affect evaluation of the primary objective will be determined based on a blinded data review prior to database lock.

12.5.3 Safety Analysis Set

The safety analysis set includes all randomized subjects who received any amount of investigational product. Analyses will be based on actual treatment received.

12.6 Statistical Methods

The primary analysis will be conducted at week 34, when all subjects have either completed the week 34 visit or been terminated before the week 34 visit. The end of the study will be at week 50, and a final analysis will be conducted when all subjects have completed the week 50/end-of-study assessments or been terminated early from the study.

For binary endpoints (eg, ACR 20/50/70), the difference in percentages and their CIs will be estimated using Mantel-Haenszel estimate of common RDs and stratified Newcombe confidence limits for the common RDs to adjust for the stratification factors. For continuous endpoints (eg, DAS28-CRP), the CI of the mean difference will be estimated using analysis of covariance model with relevant baseline values and stratification factors as covariates.

All categorical variables will be summarized using the number and percentage of subjects falling into each category and all continuous variables will be summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects with observations. Safety endpoints will be summarized descriptively. Subgroup analyses (by age, race, sex, and stratification factors) will be presented if deemed necessary.

12.6.1 Missing Data

Imputation rules will be presented in the SAP, which will be finalized before unblinding of the study.

12.6.2 Demographic and Baseline Data

The following demographic data will be summarized: age (in years, at time of signing informed consent), race, sex, ethnicity, height, and weight. Disease history and baseline disease characteristics will also be summarized.

12.6.3 Subject Disposition

The following information will be summarized for subject disposition and accountability:

- number of subjects randomized at the initial and second randomizations will be tabulated by country, center, and stratification factor
- subject disposition at week 22 and at the end of the study (including number of subjects who were randomized, treated with ABP 710/infliximab before and after week 22, completed treatment, discontinued treatment with

reason for discontinuation, completed study, and discontinued study with reason for discontinuation)

- summaries of analysis populations with reason for exclusion at week 22 and at the end of the study
- important protocol deviations
- randomization list of subjects and their actual versus randomized treatment group

12.6.4 Efficacy

All efficacy **analyses** will be performed using the intention-to-treat analysis set based on the subject's randomized treatment. As a sensitivity analysis, the equivalence test on the primary endpoint will also **be** performed using the per-protocol analysis set.

Clinical equivalence for the primary endpoint, RD of ACR20 at week 22, will be sequentially evaluated: first by comparing the 2-sided 90% CI of the RD of ACR20 between ABP 710 and infliximab with the equivalence margin of (-15%, 15%). The CIs will be estimated from the stratified Newcombe confidence limits for the common RD to adjust for stratification factors. If the first equivalence is established, the primary endpoint, RD of ACR20 at week 22, will be further evaluated by comparing the same 2-sided 90% CI between ABP 710 and infliximab with an equivalence margin of (-12%, 15%). **In addition to the 90% CI, the 95% CI for all primary and secondary efficacy endpoints will also be provided descriptively.**

Inferential analyses will only be performed for the primary endpoint. Secondary efficacy endpoints, ACR20 at scheduled visits other than week 22, ACR50/ACR70, and DAS28-CRP will be analyzed descriptively at various time points.

12.6.5 Safety

All safety analyses will be performed using the safety analysis set based on actual treatment received. Safety analysis will include analyses of adverse events, clinical laboratory test results, vital signs, and antidrug antibodies. In general, summaries will be provided separately as follows: from day 1 (first investigational product administration) until week 22, from week 22 through the end of the study, and for the entire study period (from day 1 [first investigational product administration] through the end of the study).

The DMC will review safety data at regular intervals throughout the length of the study.

12.6.5.1 Investigational Product Administration

For the investigational product (ABP 710 or infliximab), summary statistics will be provided for the total number of doses and total duration of exposure throughout the treatment exposure period.

12.6.5.2 Adverse Events

Safety analyses will focus on treatment-emergent adverse events. Treatment-emergent adverse events are those that begin or increase in severity or frequency at or after the time of first treatment up to 28 days following the last dose of study treatment (ie, the week 50 visit or, if subject discontinues study early, the end-of-study visit). All treatment-emergent adverse events will be summarized by treatment group and according to the MedDRA system organ class and preferred term. Summaries will be provided for the incidence of all treatment-emergent adverse events and specific subgroups. Additional summaries will be presented for serious adverse events.

All adverse event data will be listed by subject, and a separate listing will include all serious adverse events, including any deaths on study.

Adverse events of special interest will be summarized separately.

12.6.5.3 Immunogenicity

The number and percentage of subjects developing binding antidrug antibodies and those developing neutralizing antidrug antibodies will be tabulated separately for day 1 until week 22, from week 22 through the end of the study, and for the entire study by actual treatment received.

12.6.5.4 Concomitant Medications and Therapies

Concomitant medications will be coded by WHO-DD and will be summarized by treatment group with number and percentage of subjects receiving each category of medication.

12.6.5.5 Clinical Laboratory Tests

Clinical laboratory test results and change from baseline will be summarized by time point. In addition, shift tables, from baseline to the worst on-study laboratory toxicity based on CTCAE version 4.03 grading, will be presented.

12.6.5.6 Vital Signs and Physical Examinations

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment.

Abnormal findings from physical examinations will be listed by subject and assessed for clinical significance, and will be included in the adverse event listings and summaries.

12.6.6 Pharmacokinetics

CCI [redacted]

12.6.7 Primary Analysis

The primary analysis will be conducted after all subjects have completed the week 34 assessments, or have terminated the study before week 34. Additional information on the primary analysis will be available in the SAP.

12.6.8 Data Monitoring Committee

A DMC external to Amgen and PRA (Independent DMC) will be formed with members consisting of individuals chosen for their expertise. Members of the DMC will include, at a minimum, physicians external to Amgen and PRA, and appropriate statistical representation external to Amgen and PRA. The primary role of this independent DMC will be to monitor safety data.

The DMC will review unblinded safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates). In addition, the DMC will communicate major safety concerns and recommendations regarding study modification or termination to Amgen management at any time during the conduct of the study.

Records of all meetings will be archived. Selected Amgen, or its designee, staff may serve as liaisons to the external DMC, but will not be voting members and will not be unblinded to the results. Details regarding the DMC will be provided in the DMC charter.

13 MONITORING PROCEDURES (QUALITY ASSURANCE)

Amgen has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, to fulfill these obligations and to maintain current of study progress, Amgen monitors, or Amgen's designees, will visit the study centers during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of adverse events. The investigator must provide the monitor with full access to all source and study documents.

13.1 Routine Monitoring

Amgen, or its designee, assigned monitors will conduct regular study center visits to the investigational facilities for the purpose of monitoring various aspects of the study. The investigator must agree to Amgen, or its designee, authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested.

Adequate time and space for monitoring visits should be made available by the investigator.

The study center must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Whenever a subject name is revealed on a document that is to be collected for the sponsor, the name must be blacked out permanently by the study center personnel, leaving the initials visible, and must be annotated with the subject number as identification.

13.2 Inspections and Auditing Procedures

Amgen, or its designee, may conduct audits at the study centers, including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the investigator during or after the study. The investigator or designee should contact Amgen, or its designee, immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are fulfilled.

14 STUDY MANAGEMENT AND MATERIALS

14.1 Electronic Case Report Forms

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by examining personnel or the appropriate study center staff. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or another reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

14.2 Data Collection

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes will contain:

- the date of the visit and the corresponding day or visit in the study schedule (eg, screening, day 1, week 2)
- general condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported adverse event, and the investigator's assessment as to whether or not the reported adverse event is investigational product-related
- changes in concomitant medications or dosages
- a general reference to the procedures completed
- the signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), CRF, and other source documents will be initialed and dated on the day the change is made by the investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

14.3 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments.

All source documents from this study will be maintained by the investigator and made available for inspection by authorized persons. The original signed informed consent for each subject shall be filed with records kept by the investigator and a copy shall be given to the subject.

14.4 Record Maintenance

All data derived from the study will remain the property of Amgen.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs, and investigational product inventory must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor.

The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

14.5 Confidentiality

All information obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The investigator must ensure that each subject's anonymity is maintained. On eCRFs and other documents submitted to the sponsor or the CRO, subjects must not be identified by name. Instead, subjects will only be known by the unique subject number allocated to them to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study. The investigator will keep a separate log of these codes.

To comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review subjects' medical records as they relate to this study. Only the subject's unique number on the eCRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the sponsor.

Documents that are not for submission to the sponsor or the CRO (eg, consent forms) will be maintained by the investigator in strict confidence, except to the extent necessary to allow monitoring by the sponsor and the CRO, and auditing by regulatory authorities. No documents identifying subjects by name will leave the study center and subject identity will remain confidential in all publications related to the study.

15 ADMINISTRATION PROCEDURES

15.1 Regulatory Approval

Amgen, or their appointed agents, will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No subject may enter the study until this approval has been obtained. A copy of the approval (where one is provided as requested, according to local country requirements) will be provided to the investigator and to the IRB(s)/IEC(s).

15.2 Protocol Amendments

In accordance with ICH Topic E 6 (R1) Guideline for GCP, the investigator should not implement any deviation from or changes to the protocol without agreement by the sponsor and documented approval from the IRB/IEC of a protocol amendment except where necessary to eliminate an immediate hazard(s) to study subjects or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor[s], change of telephone number[s]).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB/**IEC** assuming this responsibility. The investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects. In these cases, the IRB/IEC must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB/IEC, the investigator and/or sponsor, the protocol amendment alters the study design or procedures and/or increases the potential risk to the subject, the currently approved written ICF will require modification. The modified ICF must also be reviewed and approved by the sponsor, appropriate regulatory authorities, and the IRB/IEC. In such cases, repeat informed consent must be obtained from subjects enrolled in the study before participation continues.

15.3 Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the investigator or (a) responsible, appropriately trained, and credentialed professional(s) designated by the investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the investigator or designee must contact the medical monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue in the study. The investigator, sponsor, and medical monitor will document this decision.

15.4 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit is to be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors are to meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals are to fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors are to qualify for authorship, and all those who qualify are to be listed.
- Each author is to have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial

Agreement between the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

15.5 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated.

15.6 Contractual and Financial Details

The investigator (and/or the hospital administrative representative) and Amgen, or its designee, will sign a clinical study agreement prior to the start of the study, outlining overall Amgen, or its designee, and investigator responsibilities in relation to the study. Financial Disclosure Statements will be completed only as required by local regulations.

15.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

15.8 Discontinuation of the Study

This study may be terminated by Amgen at any time. In terminating the study, Amgen, the CRO (PRA), and the investigator will ensure that adequate consideration is given to protection of the subjects' interests. Amgen will not provide ABP 710 or infliximab after termination of the trial or upon discontinuation of the study for the subject.

15.9 Study Center File Management

The investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but not be limited to, the information listed below:

- investigator's brochure
- current, signed version of the protocol and any previous versions of the protocol
- protocol amendments (if applicable)
- operations manual (if applicable)
- current ICF (blank) and any previous versions of the ICF

- Curricula Vitae of investigator(s) and sub-investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug regulations), signed by all principal investigators. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by the ICH GCP and by local or national regulations
- documentation of IRB/IEC approval of the protocol, the ICF, any protocol amendments, and any ICF revisions
- all correspondence between the investigator, IRB/IEC, and the sponsor/CRO relating to study conduct
- laboratory certification(s)
- monitoring log
- investigational product invoices
- signature list of all staff completing eCRFs
- signature list of all staff completing drug accountability summaries

16 REFERENCE LIST

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United States Food and Drug Administration. Guidance for Industry: Quality considerations in demonstrating biosimilarity to a reference protein product. April 2015, US FDA.

United States Food and Drug Administration. Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009, US FDA.

17 APPENDICES

17.1 Appendix 1: Elements of Informed Consent

Both the informed consent discussion and the written ICF and any other written information to be provided to subjects should include explanations of the following:

- That the study involves research.
- The purpose of the study.
- The study treatment(s) and the probability for random assignment to each treatment.
- The study procedures to be followed including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the study that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of study-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
- The person(s) to contact for further information regarding the study and the rights of study subjects, and who to contact in the event of study-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The expected duration of the subject's participation in the study.
- The approximate number of subjects involved in the study.

17.2 Appendix 2: American College of Rheumatology Revised Criteria for the Classification of Functional Capacity in RA

American College of Rheumatology revised criteria for classification of functional status in rheumatoid arthritis [a]

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

[a] Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.

Hochberg MC, Rowland WC, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 Revised Criteria for the Classification of Global Functional Status in Rheumatoid Arthritis. *Arthritis Rheum*. 1992;35(5):498-502.

17.3 Appendix 3: American College of Rheumatology Core Set Measurements

American College of Rheumatology (ACR) Core Set Measurements:

- Tender joint count
- Swollen joint count
- Subject's Global Health Assessment
- Investigator's Global Health Assessment
- Subject's assessment of pain
- Health Assessment Questionnaire – Disability Index (HAQ-DI)
- CRP

Joints to be Assessed for Swelling and Tenderness

The joints to be assessed for tenderness (68 joints) and swelling (66 joints) consist of the following:

- Temporomandibular joint
- Sternoclavicular joint
- Acromioclavicular joint
- Shoulders*
- Elbows*
- Wrists*
- Interphalangeal on digit 1*
- Distal interphalangeal joints on digits 2 - 5
- Proximal interphalangeal joints on digits 2 - 5*
- Metacarpophalangeal joints on digits 1 - 5*
- Hips (tenderness only)
- Knees*
- Ankles
- Metatarsals
- Interphalangeal joints on toes 1 - 5
- Metatarsophalangeal joints on toes 1 - 5

Joints assessed for swelling are the same, with the exception of the hips, which are excluded.

* The 28 joints used to calculate the DAS28.

17.4 Appendix 4: Subjective Assessment Scales

Subject's Assessment of Disease Related Pain:

The subject's assessment of their current level of pain on a 100-mm horizontal VAS. The left-hand extreme of the line should be described as "no pain at all" and the right-hand extreme as "worst pain imaginable."

Subject's Global Health Assessment:

The subject's overall assessment of their disease activity in the past week on a 100 mm VAS. The left-hand extreme of the scale will be described as "no RA activity at all" (symptom-free and no arthritis symptoms) and the right-hand extreme as "worst RA activity imaginable" (maximum arthritis disease activity).

Investigator's Global Health Assessment:

The investigator's assessment of the subject's current disease activity on a 100-mm VAS. The left-hand extreme of the scale will be described as "no activity at all" (symptom-free and no arthritis symptoms) and the right-hand extreme as "worst activity imaginable" (maximum arthritis disease activity).

Health Assessment Questionnaire-Disability Index

The HAQ-DI is a questionnaire on which subjects are asked to rate their level of difficulty on daily activities (dressing and grooming, arising, eating, and walking) and personal abilities (hygiene, reach, grip, and activity), as well as their use of aids, devices, or help from another person for these activities and disabilities.

A RANDOMIZED, DOUBLE-BLIND PHASE 3 STUDY TO ASSESS THE EFFICACY AND SAFETY OF ABP 710 COMPARED TO INFLIXIMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS

Test Drug: ABP 710

Protocol Number: 20140111 **EudraCT number:** 2014-004704-29

Study Phase: 3

Date and Version: 17 March 2017, version 2.0

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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Council for Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

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Rationale:

This amendment is issued to make the following changes:

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

Summary of Changes:

Synopsis page 4, Section 8.1, Overall Study Design and Plan, page 24

Add

Subjects who are unable to complete the week 22 visit within the visit window of ± 3 days will be 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.

The last treatment **for all subjects who do not discontinue early** will be at…

Synopsis page 5, Section 8.4.1, Inclusion Criteria, page 26

Add

6. Subject has **at least one of the following:** a positive rheumatoid factor or anti-cyclic citrullinated peptide (CCP) at screening.

Synopsis page 5, Section 8.4.1, Inclusion Criteria, page 26

Add (before criterion 11)

Subject must meet any 1 of the following 3 criteria:

Synopsis page 7, Section 8.4.2, Exclusion Criteria, page 29

Change

16. Subject has prior use of 2 or more **distinct** biologic therapies for RA.

Synopsis page 7, Section 8.4.2, Exclusion Criteria, page 30

Change

24. … adequate contraception (eg, true abstinence, sterilization, birth control pills, Depo-Provera® (medroxyprogesterone) injections, ~~or~~ contraceptive implants**, or other effective methods**)...

Section: Synopsis Statistical Methods, page 9; 12.6.4, Efficacy, page 64

Add:

In addition to the 90% CI, the 95% CI for all primary and secondary efficacy endpoints will also be provided descriptively.

Section 8.4.3.1, Criteria for Subject Withdrawal, page 31

Add (under Reasons for removal from protocol-required investigational products or procedural assessments)

- **inability to complete the week 22 visit within the allowed visit window**

…

Subjects who discontinued treatment because of inability to complete the week 22 visit within the allowed visit window should return for an end-of-study visit to complete the end-of-study assessments within 28 days, if possible.

…

- ~~**adverse event**~~

Section 8.5.1, Treatments Administered, pages 32-33; 9.2, Baseline (Day 1, first day of treatment, Week 0) page 46

Change

Premedications ~~should~~ **must** be given**. Premedications should be** ~~given~~ **selected** according to local practice and**/or** the approved product label. These medications should generally include acetaminophen, an antihistamine, and methylprednisone

100 mg IV or equivalent **approximately** 30 minutes before each infusion **but should be selected according to the individual subject's needs**.

Section 8.5.5.2, Study Treatment Accountability, page 35

Change

All supplies of investigational product will be accounted for in accordance with GCP. ~~There will be an individual study drug accountability record for each subject~~ **There will be a master study drug accountability record completed,** and the pharmacist,…

The investigator **(or designee)** will administer the investigational product…

Section 8.5.7.3, Rescue Medication, page 37

Add (last 3 bullets)

(ie, at **baseline and** weeks 2, 6, 14, 22, 30, 34, 38, 46, and 50)

Change (third bullet)

- NSAIDs/cyclooxygenase-2 (COX-2) inhibitors…
  In all cases, **these agents will** ~~any dose regimen higher than the baseline dose is~~ not **be** allowed within 12 hours before clinical efficacy assessments…

Table 8-1, pages 40-41

Add (heading for the "screening" column)

Screening
(≤ 28 days)

Table 8-1, footnote j, page 41

Add

CCI [redacted]

Section 9.1.1, Screen Failures, page 45

Change

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. ~~Subjects determined to be screen failures will not be eligible for immediate participation and must be registered as a screen failure in IXRS.~~ Laboratory assessments used…
…(ie, a total of 3 screens including initial screening). **If screening procedures cannot be completed within 28 days before day 1, the subject will be considered a screen**

failure but may be eligible for rescreening. These subjects can be rescreened under the same ICF if rescreening occurs within 30 days of initial consent date. The subject will retain the same subject identification number…

Section 9.2, Baseline (Day 1, first day of treatment, Week 0), page 45

Add

- baseline joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)**; the baseline joint assessment must be performed before randomization**

Section 12.4, Randomization, page 62

Add

Subjects unable to complete the week 22 visit within the allowed window will not be re-randomized and will be discontinued from the study.

Section: Global

Replace:

Version date

~~27 April 2016~~

With:

17 March 2017