1 TITLE PAGE

A RANDOMIZED, DOUBLE-BLIND STUDY TO COMPARE PHARMACOKINETICS AND PHARMACODYNAMICS, EFFICACY AND SAFETY OF ABP 798 WITH RITUXIMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS

Test Drug: ABP 798

Protocol Number: 20130108 **EudraCT number:** 2013-005543-90

Study Phase: 1/3

Date and Version: **20 March 2018; Version 4.0**

Sponsor:
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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: 02792699
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 20130108, titled "A Randomized, Double-Blind Study to Compare Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of ABP 798 with Rituximab 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 [redacted]	CLINICAL RESEARCH MEDICAL DIRECTOR
Print Name	Title
PPD [redacted]	MARCH 22, 2018
Signature	Date

Accepted for the Clinical Research Organization - PRA:

PPD [redacted]	PRA Medical Director
Print Name	Title
PPD [redacted]	23 Mar 2018
Signature	Date

Investigator

I have read and agree to the protocol 20130108, entitled "A Randomized, Double-Blind Study to Compare Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of ABP 798 with Rituximab 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.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

_____ _____
Print Name Title

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Signature Date

Coordinating Investigator Signature:

_____ _____
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_____
Institution/ Country

_____ _____
Signature Date

2 SYNOPSIS

NAME OF SPONSOR: Amgen	**PROTOCOL No.:** 20130108
NAME OF STUDY TREATMENT: ABP 798	
TITLE OF STUDY: A Randomized, Double-Blind Study to Compare Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of ABP 798 with Rituximab in Subjects with Moderate to Severe Rheumatoid Arthritis	
STUDY CENTERS: Approximately 80 sites in Europe and North America	
STUDY PERIOD: Approximately 300 subjects will be randomized in a 1:1:1 ratio to receive ABP 798 or rituximab (US) or rituximab (EU). The end of trial will be the date when the last subject has completed their last study assessment.	**PHASE OF DEVELOPMENT:** Phase 1/3
PLANNED STUDY DATES: 29 April 2016 to 28 February 2018. The expected enrollment duration is 12 months, and each subject will participate for up to 52 weeks.	

OBJECTIVES:

Primary Objective: The primary objective for this study is to demonstrate pharmacokinetic (PK) similarity (as assessed principally by area under the serum concentration-time curve [AUC] from time 0 extrapolated to infinity [AUC_{inf}] and the maximum observed serum concentration [C_{max}] following the 2nd infusion of 1st dose) of ABP 798 following 2 intravenous (IV) infusions of 1000 mg each, relative to that of 2 IV infusions of 1000 mg each of rituximab (US) and of rituximab (EU).

Secondary Objective(s): The secondary objectives are

- **to demonstrate PK similarity between rituximab (US) and rituximab (EU) as assessed by AUC_{inf} and by C_{max} after second infusion of the first dose**
- to assess the clinical efficacy of ABP 798 compared with rituximab
- to assess the safety and immunogenicity of ABP 798 compared with rituximab.

STUDY DESIGN AND METHODOLOGY: This is a randomized, double-blind, active-controlled 3-arm study in adult subjects with moderate to severe rheumatoid arthritis (RA) who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs), which must include intolerance or inadequate response to one or more tumor necrosis factor (TNF) inhibitor therapies. Approximately 300 subjects (100 per treatment group) will be enrolled. The subjects will be randomized to receive either ABP 798 1000 mg x 2 (treatment group A) infusions given 2 weeks apart, or rituximab (US) (treatment group B), or rituximab (EU) (treatment group C) 1000 mg x 2, given 2 weeks apart in a double-blinded fashion. Randomization will be stratified by geographic region, seropositivity (rheumatoid factor [RF]-positive and/or cyclic citrullinated peptide [CCP]-positive vs. RF-negative, and CCP-negative), and number of prior biologic therapies used for RA (1 vs. > 1).

An independent data monitoring committee (DMC) will evaluate the safety data throughout the study, including an initial safety analysis after the first 18 subjects have received the first dose (1000 mg x 2 infusions of either ABP 798 or rituximab [EU] or rituximab [US]).

At week 24, the subjects in treatment groups A and C will continue with and receive the second dose of the same treatment, and the subjects in treatment group B will transition to treatment group A1 and receive ABP 798 1000 mg x 2 as their second dose. Retreatment may occur earlier, ie, anytime from week 16 to week 24, in individual subjects, if necessary in the opinion of the Investigator.

The end of study (EOS) will be at week 48 (or 24 weeks after the first infusion of the second dose for subjects retreated before week 24), and a final analysis will be performed when all subjects have completed or have had the opportunity to complete the week 48/EOS assessments.

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Subjects cannot be randomized before all inclusion criteria (including test results) are confirmed.

Inclusion Criteria:

1. Subjects must sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form before any study specific procedures are preformed
2. Men or women ≥ 18 and ≤ 80 years old
3. Subjects must be diagnosed with RA as determined by meeting 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA
4. Duration of RA of at least 6 months
5. 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 one of the following at screening:
    - erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr
    - serum C-reactive protein (CRP) > 1.0 mg/dL
6. Subjects have had an inadequate response or intolerance to other DMARDs (which must include intolerance or inadequate response to one or more TNF inhibitor therapies)
7. Subjects must be taking methotrexate (MTX) for ≥ 12 consecutive weeks and be on a stable dose of MTX 7.5 to 25 mg/week for ≥ 8 weeks prior to receiving the investigational product (IP), and be willing to remain on a stable dose throughout the study
8. Subjects on non-steroidal anti-inflammatory drugs (NSAIDs) or low potency analgesics such as tramadol, soma compounds, fioricet, fiorinal, should be on stable doses for ≥ 2 weeks prior to screening
9. Subjects on oral corticosteroids, (≤ 10 mg prednisone or equivalent), should be on stable doses for ≥ 4 weeks prior to screening
10. Subject has no known history of active tuberculosis
11. Subject has a negative test for tuberculosis during screening defined as either:
    - negative purified protein derivative (PPD) < 5 mm of induration at 48 to 72 hours after test is placed)

    OR
    - negative Quantiferon test
12. Subjects with a positive PPD and a history of Bacillus Calmette-Guérin vaccination are allowed with a negative Quantiferon test
13. Subjects with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or subjects with a positive or indeterminate Quantiferon test are allowed if they have all of the following:
    - no symptoms per tuberculosis worksheet provided by the Sponsor, Amgen
    - documented history of treatment with a TB prophylaxis regimen, with at least 4 weeks of prophylaxis therapy completed at the time of screening. If a subject has completed at least 4 weeks of prophylaxis therapy, and their regimen requires >4 weeks therapy, the subject must be deemed able and willing to complete the entire prophylaxis regimen in accordance with local guidance
    - no known exposure to a case of active tuberculosis after most recent prophylaxis
    - no evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of IP

Exclusion Criteria:

Rheumatoid arthritis related

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

Other medical conditions

4. Planned surgical intervention during the duration of the study
5. Active infection or history of infections as follows:

- any active infection for which systemic anti-infectives were used within 4 weeks prior to first dose of IP
- a serious infection, defined as requiring hospitalization or IV anti-infectives within 8 weeks prior to the first dose of IP
- 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. Known history of human immunodeficiency virus
7. Hepatitis B surface antigen (HbsAg) or Hepatitis B core antibody (anti-HBc) positivity at screening (unless documentation of hepatitis B virus immunization) or Hepatitis C virus (HCV) antibody positivity at screening
8. Uncontrolled, clinically significant systemic disease such as diabetes mellitus, cardiovascular disease including severe heart failure (New York Heart Association [NYHA] class IV), or severe uncontrolled cardiac disease, renal disease, or liver disease
9. Malignancy within 5 years EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma
10. History of neurologic symptoms suggestive of central nervous system demyelinating disease
11. Major chronic inflammatory disease or connective tissue disease other than RA, with the exception of secondary Sjögren's syndrome
12. Concurrent medical condition that, in the opinion of the Investigator, could cause this study to be detrimental to the subject

Laboratory abnormalities

13. Laboratory abnormalities at screening, including any of the following:
    - hemoglobin < 9 g/dL
    - platelet count < 100,000/mm^3
    - white blood cell count < 3,000 cells/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, which, 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 non-permitted drugs

14. Any of the following within 28 days prior to first dose of IP:
    - intra-articular (IA) hyaluronic acid injections
    - IA, intramuscular (IM), or IV corticosteroids, including adrenocorticotropic hormone
15. Non-biologic DMARDs, including Janus kinase inhibitors such as tofacitinib, other than MTX within 28 days prior to first dose of IP, except as below:
    - leflunomide (unless an active washout with cholestyramine has been performed), cyclosporine, azathioprine, tacrolimus excluded within 3 months prior to first dose of IP
    - use of IM or oral gold excluded within 6 months prior to first dose of IP
    - cytotoxic agents such as cyclophosphamide, D-penicillamine excluded within 6 months prior to first dose of IP
    - received IV gamma-globulin or Prosorba column therapy excluded within 3 months prior to first dose of IP
16. Use of commercially available or investigational biologic therapies for RA as follows:
    - anakinra, etanercept within 1 month prior to first dose of IP
    - infliximab, abatacept, tocilizumab, golimumab, certolizumab**,** adalimumab within 3 months prior to first dose of IP
    - other experimental or commercially available biologic therapies for RA within 3 months or 5 half-lives (whichever is longer) prior to first dose of IP
17. Live vaccines within 28 days prior to the first dose of IP

18. 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
19. Previous receipt of rituximab, a biosimilar of rituximab, or ocrelizumab
20. Currently is 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, including vaccines, or subject is receiving other investigational agent(s)

General

21. For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 12 months after the last dose of IP
22. Sexually active subjects and their partners who are of childbearing potential (ie, neither surgically sterile nor postmenopausal) and not agreeing to use adequate contraception (eg, true abstinence, sterilization, birth control pills, Depo-Provera injections, or contraceptive implants) while on study and for 12 months after the last dose of investigational product.
23. Known sensitivity to mammalian cell derived drug products or hypersensitivity to the active substance or to any of the excipients of ABP 798 or rituximab
24. Any physical or psychiatric disorder which, in the opinion of the Investigator, will prevent the subject from completing the study or interfere with the interpretation of the study results
25. Any disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures
26. Active substance abuse, in the opinion of the Investigator (within 24 weeks of screening)

NUMBER OF SUBJECTS: Approximately 300 subjects will be randomized in a 1:1:1 ratio to receive ABP 798, rituximab (US), or rituximab (EU), stratified by geographic region, seropositivity (RF-positive and/or CCP-positive vs. RF-negative and CCP-negative) and number of prior biologic therapies used for RA (1 vs. > 1). The sample size will provide > 90% power to demonstrate similarity on the primary PK endpoints, based on an assumption of between-subject variability (as measured by coefficient of variation) of 40%, true geometric mean ratio (GMR) of 1 among ABP 798, rituximab (US), or rituximab (EU), a margin of (0.8, 1.25), and 15% dropout by week 24. The PK similarity will be tested between ABP 798 versus rituximab (US) and ABP 798 versus rituximab (EU), each with a significance level of 0.05. The similarity between rituximab (US) and rituximab (EU) will be evaluated as well.

STUDY TREATMENT(S):
Test Product, Dose and Mode of Administration:
ABP 798 (Treatment A) 500 mg/mL given at 1000 mg IV x 2 infusions 2 weeks apart
Reference Therapy, Dose and Mode of Administration:
Rituximab (US) (Treatment B) or rituximab (EU) (Treatment C) 500 mg/mL given at 1000 mg IV x 2 infusions 2 weeks apart

DURATION OF TREATMENT: Subjects will receive a first dose (2 infusions at days 1 and 15), followed by a second dose (2 infusions 2 weeks apart beginning at week 24 or earlier, ie, anytime from week 16 to week 24, in individual subjects, if necessary in the opinion of the Investigator), with assessment until week 48 (or 24 weeks after the first infusion of the second dose for subjects retreated before week 24), plus a screening period of up to 4 weeks, for a total of up to 52 weeks. A total of 2 doses will be administered during the study; each dose will consist of 2 infusions, 2 weeks apart.

STUDY EVALUATIONS:
Primary Criteria:

- AUC_{inf}, C_{max} following the second infusion of the first dose

Secondary Criteria:

- Percent of subjects with complete depletion in CD19+ cell count from day 1 to day 3
- Disease Activity Score (DAS)28-CRP change from baseline at week 24
- **ACR20, ACR50 and ACR70**
- AUC from time 0 on day 1 prior to the first infusion of the first dose to 14 days postdose (day 15) ($AUC_{0\text{-}14\ day}$), AUC from time 0 to week 12 ($AUC_{0\text{-}12\ wk}$), C_{max} following the first infusion of the first dose

Safety Criteria:

- Treatment-emergent adverse events (AEs) and serious adverse events (SAEs)
- Clinically significant changes in laboratory values and vital signs
- Incidence of antidrug antibodies

STATISTICAL METHODS:

The PK similarity will be demonstrated by comparing the 90% confidence interval (CI) for the GMR of test (ABP 798)-to-reference (rituximab [US] or rituximab [EU]) **and rituximab [US] to rituximab [EU**] for AUC_{inf} and **for** C_{max} following the second infusion of the first dose with the bounds of 0.8 to 1.25**,** where α=0.05. PK parameters will be calculated using non-compartmental methods. Point estimates and CIs for the GMR will be estimated from an analysis of covariance model using the PK Analysis Set, consisting of all randomized subjects with an evaluable serum concentration-time profile.

Clinical equivalence will be evaluated for DAS28-CRP at week 24 using the Full Analysis Set consisting of all randomized subjects. **If PK similarity is established between rituximab (US) and rituximab (EU), the 2 arms will be combined into a single reference arm for the primary assessment of clinical equivalence between ABP 798 and rituximab. The results for ABP 798 vs. rituximab (EU) and ABP 798 vs. rituximab (US) will be provided for descriptive purposes. If PK similarity is not established, the ABP 798 arm will be compared to each of the individual rituximab arms separately to establish clinical equivalence of ABP 798 to the individual reference arms.**

With the planned sample size, there is **94% probability that the 90% CI of the difference between the ABP 798 arm and the pooled rituximab (rituximab[EU] and rituximab[US]) arm and** 83% probability that the 90% CI of the difference between test (ABP 798) and reference (US-licensed rituximab or EU-authorized rituximab) in DAS28-CRP change from baseline **at week 24** will fall into the equivalence margin of ± 0.6 (EULAR response criteria), assuming a standard deviation of 1.4 (Volkmann et al, 2010). **DAS28-CRP at other timepoints and ACR20, 50 and 70 will be summarized descriptively.**

In addition, all categorical variables will be summarized using the number and percent 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. Safety endpoints will be summarized descriptively as well, based on all randomized subjects who received at least one infusion of IP (ie, Safety Analysis Set).

DATE AND VERSION: 20 March 2018; Version 4.0

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
AE	Adverse event
ALT	Alanine aminotransferase
anti-HBc	Hepatitis B core antibody
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
$AUC_{0\text{-}14\ day}$	AUC from time 0 on day 1 prior to the first infusion of the first dose to 14 days postdose (day 15)
$AUC_{0\text{-}12wk}$	AUC from time 0 on day 1 prior to the first infusion of the first dose to week 12
AUC_{inf}	AUC from time 0 on day 1 prior to the first infusion of the first dose extrapolated to infinity
CCP	Cyclic citrullinated peptide
CDC	Complement-mediated cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum observed serum concentration
COX-2	Cyclooxygenase-2
CRO	Clinical research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DAS	Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
DMC	Data Monitoring Committee

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOI	End of infusion
EOS	End of study
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GMR	Geometric mean ratio
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCG	Human chorionic gonadotrophin
IA	Intra-articular
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IXRS	Interactive voice and web response system
λ_z	Terminal elimination rate constant

MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PIN	Personal Identification Number
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
RA	Rheumatoid arthritis
RD	Risk difference
RF	Rheumatoid factor
rituximab (EU)	European Medicines Agency EU-authorized rituximab
rituximab (US)	Food and Drug Administration US-licensed rituximab
RR	Risk ratio
SAA	Serum amyloid protein
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
Scn	Screening
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time of C_{max}
TNF	Tumor necrosis factor
VAS	Visual analogue scale
WHO	World Health Organization

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 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 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)), the general principles indicated in the Declaration of Helsinki 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 informed of the changes and 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 levels of acute phase reactants (eg, erythrocyte sedimentation rates [ESR] 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 et al, 2007), which exhibit uncontrolled synovium/pannus proliferation and excess fluid production, and ultimately undergo progressive destructive arthropathy (Aletaha et al, 2010; Choy et al, 2001).

The pathologic processes in RA appear to be primarily driven by B cells, by autoantibody production, by antigen presentation to T cells, and by promoting inflammation through the activation of macrophages and dendritic cells (Tuscano and Sands, 2009). Targeting of B cells has become a major therapeutic approach in RA. Therapeutic monoclonal antibodies have been developed with the aim of depleting B cells and reducing the RA disease process. The depleting activity of B cell-targeted monoclonal antibodies largely relies on 2 Fc-dependent mechanisms: antibody-dependent cell-mediated cytotoxicity and complement-mediated cytotoxicity (CDC). The engagement of effector cells by therapeutic monoclonal antibodies involves the interaction of the monoclonal antibodies Fc with Fcγ receptors on the surface of natural killer cells, monocytes/macrophages, or neutrophils (Blüml et al, 2013).

6.2 Rituximab

Rituximab (Rituxan®, MabThera®) is a genetically engineered chimeric murine/human monoclonal immunoglobulin (Ig) G1 kappa antibody directed against the B cell specific CD20 antigen. In RA patients, treatment with rituximab induces depletion of peripheral B lymphocytes, with the majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/μL) within 2 weeks after receiving the first dose. Most patients showed peripheral B cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B cell depletion lasting more than 3 years after a single course of treatment (Biogen Idec, 2013).

Total serum Ig levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. In RA patients during repeated rituximab treatment, 23.3%,

5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below the lower limit of normal, respectively, at any time after receiving rituximab. The clinical consequences of decreases in Ig levels in RA patients are unclear (Biogen Idec, 2013).

Treatment with rituximab in patients with RA is associated with reduction of certain biologic markers of inflammation such as interleukin (IL)-6, CRP, serum amyloid protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-cyclic citrullinated peptide (anti-CCP), and rheumatoid factor (RF; Biogen Idec, 2013).

Rituximab is indicated, in combination with methotrexate (MTX), for the treatment of adult patients with moderately- to severely-active RA who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Rituximab is approved for use in other indications such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, granulomatosis with polyangiitis, and microscopic polyangiitis (Biogen Idec, 2013).

6.3 Compound Review

ABP 798 is being developed as a biosimilar candidate to Rituxan®, MabThera® (rituximab) for the treatment of RA and other indications. The active ingredient of ABP 798 is an anti-CD20 monoclonal antibody which has the same amino acid sequence as rituximab. ABP 798 has the same pharmaceutical form and dosage strength as FDA US-licensed rituximab [rituximab (US), Rituxan®] and European Medicines Agency EU-authorized rituximab [rituximab (EU), MabThera®].

Similarity of ABP 798 to rituximab has been shown using bioanalytical methods and pre-clinical studies. As outlined in the guideline on similar biological medicinal products containing monoclonal antibodies, applicants are expected to provide data on similarity of pharmacokinetics (PK)/pharmacodynamics (PD), safety and efficacy.

Refer to the Investigator's Brochure for additional information.

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 (CHMP/437/04 Rev 1; EMEA/CHMP/BWP/247713/2012; EMEA/CHMP/BMWP/42832/2005 Rev.1; US FDA 2012a; US FDA 2012b). A biosimilar product, generally, is one that 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 quality, nonclinical, and clinical evidence. The analytical and nonclinical similarity of ABP 798 and rituximab are summarized in the Investigator's Brochure. The current study is designed to demonstrate the PK similarity and that there is no clinically meaningful difference between ABP 798 and rituximab in terms of safety, efficacy, and immunogenicity.

7 STUDY OBJECTIVES

7.1 Primary Study Objective

The primary objective for this study is to demonstrate PK similarity (as assessed principally by area under the serum concentration-time curve [AUC] from time 0 extrapolated to infinity [AUC_{inf}] and the maximum observed serum concentration [C_{max}], following the 2nd infusion of 1st dose) of ABP 798 following 2 intravenous (IV) infusions of 1000 mg each, relative to that of 2 IV infusions of 1000 mg each of rituximab (US) and of rituximab (EU).

7.2 Secondary Study Objectives

The secondary objectives are

- **to demonstrate PK similarity between rituximab (US) and rituximab (EU) as assessed by AUC_{inf} and by C_{max} after second infusion of the first dose**
- to assess the clinical efficacy of ABP 798 compared with rituximab
- to assess the safety and immunogenicity of ABP 798 compared with rituximab.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

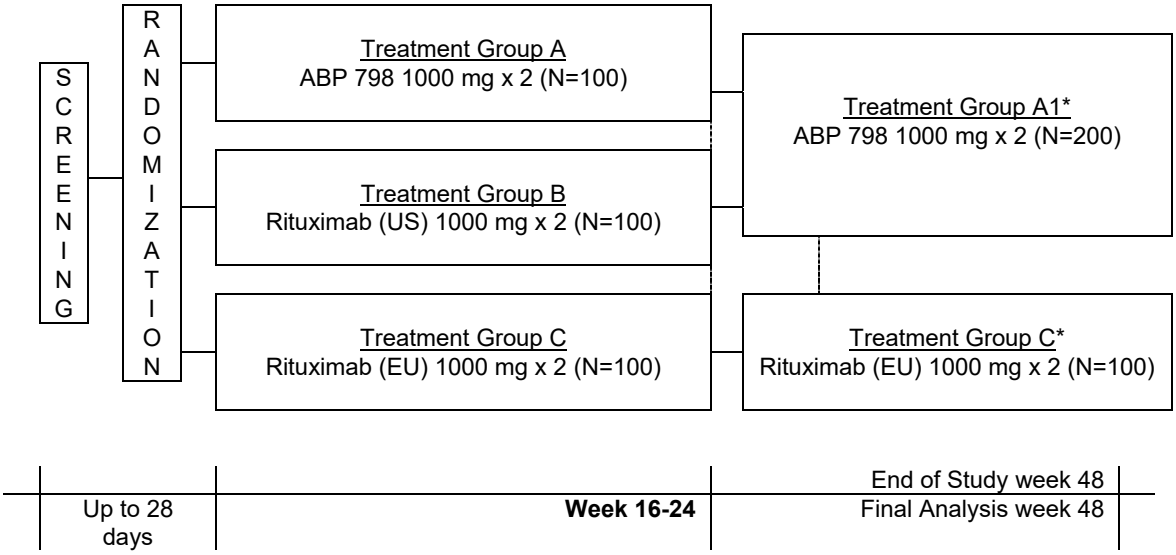
This is a randomized, double-blind, active-controlled 3-arm study in adult subjects with moderate to severe RA who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs) (which must include intolerance or inadequate response to one or more TNF inhibitor therapies). Approximately 300 subjects (100 per treatment group) will be enrolled. The subjects will be randomized to receive either 2 IV infusions of ABP 798, 1000 mg each, given 2 weeks apart (treatment group A), or 2 IV infusions of rituximab (US) 1000 mg each, given 2 weeks apart (treatment group B) or 2 IV infusions of rituximab (EU), 1000 mg each, given 2 weeks apart (treatment group C), in a double-blinded fashion. A total of 2 doses will be administered during the study; each dose consists of 2 infusions, 2 weeks apart.

An independent data monitoring committee (DMC) will evaluate the safety data throughout the study, including an initial safety analysis after the first 18 subjects have been dosed (1000 mg x 2 infusions of either ABP 798 or rituximab [EU] or rituximab [US]).

At week 24, the subjects in treatment groups A and C will continue with and receive the second dose of the same treatment, and the subjects in treatment group B will transition to become treatment group A1 and receive the second dose with ABP 798. Retreatment may occur earlier, ie, anytime from week 16 to week 24 in individual subjects if necessary in the opinion of the Investigator.

The end of study (EOS) will be at week 48 (or 24 weeks after the first infusion of the second dose for subjects retreated before week 24), and a final analysis will be performed when all subjects have completed or have had the opportunity to complete the week 48/EOS assessments. Figure 1 is a summary of the study design.

Figure 1. Study Diagram



* Retreatment will begin at week 24 or earlier, ie, anytime from week 16 to week 24 in individual subjects if necessary in the opinion of the Investigator.

8.2 Discussion of Study Design

This study is randomized and double-blind to prevent bias in treatment allocation and in the subjective assessment of effect.

8.3 Study Duration

Subjects will receive investigational product (IP) first dose (2 infusions at days 1 and 15), followed by a second dose (2 infusions 2 weeks apart beginning at week 24 or earlier, ie, anytime from week 16 to week 24 in individual subjects if necessary in the opinion of the Investigator) with assessment until week 48 (or 24 weeks after the first infusion of the second dose for subjects retreated before week 24), plus a screening period of up to 4 weeks, for a total of up to 52 weeks. A total of 2 doses will be administered during the study; each dose consists of 2 infusions, 2 weeks apart.

Enrollment will continue until approximately 300 subjects have been randomized to treatment. The end of trial will be the date when the last subject has completed their 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. Subjects must sign an IRB/IEC-approved informed consent form before any study specific procedures are preformed
2. Men or women ≥ 18 and ≤ 80 years old
3. Subjects must be diagnosed with RA as determined by meeting 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA
4. Duration of RA of at least 6 months
5. 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 one of the following at screening:
   - ESR ≥ 28 mm/hr
   - serum CRP > 1.0 mg/dL
6. Subjects have had an inadequate response or intolerance to other DMARDs (which must include intolerance or inadequate response to one or more TNF inhibitor therapies)
7. Subjects must be taking MTX for ≥ 12 consecutive weeks and be on a stable dose of MTX 7.5 to 25 mg/week for ≥ 8 weeks prior to receiving the investigational product, and be willing to remain on a stable dose throughout the study
8. Subjects on non-steroidal anti-inflammatory drugs (NSAIDs) or low potency analgesics such as tramadol, soma compounds, fioricet, fiorinal, should be on stable doses for ≥ 2 weeks prior to screening
9. Subjects on oral corticosteroids, (≤ 10 mg prednisone or equivalent), should be on stable doses for ≥ 4 weeks prior to screening
10. Subject has no known history of active tuberculosis
11. Subject has a negative test for tuberculosis during screening defined as either:
    - negative purified protein derivative (PPD) < 5 mm of induration at 48 to 72 hours after test is placed)

    OR
    - negative Quantiferon test
12. Subjects with a positive PPD and a history of Bacillus Calmette-Guérin vaccination are allowed with a negative Quantiferon test
13. Subjects with a positive PPD test (without a history of Bacillus Calmette-Guérin vaccination) or subjects with a positive or indeterminate Quantiferon test are allowed if they have all of the following:
    - no symptoms per tuberculosis worksheet provided by the Sponsor, Amgen
    - documented history of treatment with a TB prophylaxis regimen, with at least 4 weeks of prophylaxis therapy completed at the time of screening. If a subject has completed at least 4 weeks of prophylaxis therapy, and their regimen requires >4 weeks therapy, the subject must be deemed able and willing to complete the entire prophylaxis regimen in accordance with local guidance
    - no known exposure to a case of active tuberculosis after most recent prophylaxis

- no evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of investigational product

8.4.2 Exclusion Criteria

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

Rheumatoid arthritis related

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

Other medical conditions

4. Planned surgical intervention during the duration of the study
5. Active infection or history of infections as follows:
   - any active infection for which systemic anti-infectives were used within 4 weeks prior to first dose of investigational product
   - a serious infection, defined as requiring hospitalization or IV anti-infectives within 8 weeks prior to 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. Known history of human immunodeficiency virus
7. Hepatitis B surface antigen (HbsAg) or Hepatitis B core antibody (anti-HBc) positivity at screening (unless documentation of hepatitis B virus immunization) or hepatitis C virus (HCV) antibody positivity at screening
8. Uncontrolled, clinically significant systemic disease such as diabetes mellitus, cardiovascular disease including severe heart failure (New York Heart Association [NYHA] class IV), or severe uncontrolled cardiac disease, renal disease, or liver disease
9. Malignancy within 5 years EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma
10. History of neurologic symptoms suggestive of central nervous system demyelinating disease
11. Major chronic inflammatory disease or connective tissue disease other than RA, with the exception of secondary Sjögren's syndrome
12. Concurrent medical condition that, in the opinion of the Investigator, could cause this study to be detrimental to the subject

Laboratory abnormalities

13. Laboratory abnormalities at screening, including any of the following:
    - hemoglobin < 9 g/dL
    - platelet count < 100,000/mm^3
    - white blood cell count < 3,000 cells/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, which, 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 non-permitted drugs

14. Any of the following within 28 days prior to first dose of investigational product:
    - intra-articular (IA) hyaluronic acid injections
    - IA, intramuscular (IM), or IV corticosteroids, including adrenocorticotropic hormone
15. Non-biologic DMARDs, including Janus kinase inhibitors such as tofacitinib, other than MTX within 28 days prior to 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 prior to first dose of investigational product
    - use of IM or oral gold excluded within 6 months prior to first dose of IP
    - cytotoxic agents such as cyclophosphamide, D-penicillamine excluded within 6 months prior to first dose of investigational product
    - received IV gamma-globulin or Prosorba column therapy excluded within 3 months prior to first dose of investigational product
16. Use of commercially available or investigational biologic therapies for RA as follows:
    - anakinra, etanercept within 1 month prior to first dose of IP
    - infliximab, abatacept, tocilizumab, golimumab, certolizumab, adalimumab within 3 months prior to first dose of investigational product
    - other experimental or commercially available biologic therapies for RA within 3 months or 5 half-lives (whichever is longer) prior to first dose of investigational product
17. Live vaccines within 28 days prior to the first dose of investigational product
18. 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
19. Previous receipt of rituximab, a biosimilar of rituximab, or ocrelizumab
20. Currently is 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, including vaccines, or subject is receiving other investigational agent(s)

General

21. For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 12 months after the last dose of investigational product
22. Sexually active subjects and their partners who are of childbearing potential (ie, neither surgically sterile nor postmenopausal) and not agreeing to use adequate contraception (eg, true abstinence, sterilization, birth control pills, Depo-Provera injections, or contraceptive implants) while on study and for 12 months after the last dose of investigational product.
23. Known sensitivity to mammalian cell derived drug products or hypersensitivity to the active substance or to any of the excipients of ABP 798 or rituximab
24. Any physical or psychiatric disorder which, in the opinion of the Investigator, will prevent the subject from completing the study or interfere with the interpretation of the study results
25. Any disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures
26. Active substance abuse, in the opinion of the Investigator (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 1) and collection of data, including endpoints and AEs. The Investigator must document the change to the Schedule of Assessments (Table 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, publicly 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:

- subject request to end IP administration
- safety concern (eg, due to an AE, failure to follow contraception, and/or protocol requirements)
- pregnancy

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 week 48/EOS. The week 48/EOS assessments will be performed no later than 14 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 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, sufficient subjects will be included to ensure the minimum sample size defined (see Section 12.2).

8.5 Treatment

8.5.1 Treatments Administered

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

Subjects will be randomly assigned at Baseline (day 1) to 1 of 3 treatment groups. The first dose will be administered as follows:

- Treatment A: ABP 798 1000 mg IV on study days 1 and 15
- Treatment B: Rituximab (US) 1000 mg IV on study days 1 and 15
- Treatment C: Rituximab (EU) 1000 mg IV on study days 1 and 15

At week 24, the subjects in treatment groups A and C will continue with and receive the second dose with the same treatment (ABP 798 1000 mg x 2 and rituximab (EU) 1000 mg x 2, respectively), and the subjects in treatment group B will transition to treatment group A1 and receive the second dose of ABP 798 1000 mg x 2. Retreatment may occur earlier, ie, anytime from week 16 to week 24 in individual subjects, if necessary in the opinion of the Investigator. The EOS will be at week 48 (or 24 weeks after the first infusion of the second dose for subjects retreated before week 24). A total of 2 doses will be administered during the study; each dose will consist of 2 infusions.

No dose reductions or changes will be allowed.

ABP 798/rituximab will be administered after all other procedures are completed for each visit. Investigational product will be administered only as an IV infusion by a healthcare professional with appropriate medical support to manage severe infusion reactions. Do

not administer as an IV push or bolus. Subjects should receive premedications before each infusion.

Premedications should be given according to local guidance and the approved product label. These should generally include acetaminophen and an antihistamine and methylprednisone 100 mg IV or equivalent 30 minutes before each infusion.

IV infusions should be performed according to local guidance, and the approved product label (Rituxan Product Insert; MabThera Product Insert).

Investigational product infusion reactions should be handled according to local guidance and the approved product label.

All subjects will continue on a stable dose of MTX (≥ 7.5 mg/week, oral or subcutaneous [SC]) 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.

8.5.2 Study Treatment Formulation

8.5.2.1 Study Drug

ABP 798 is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. ABP 798 has an approximate molecular weight of 145 kD. ABP 798 is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium. ABP 798 is a sterile, clear, preservative-free liquid concentrate for IV administration. ABP 798 is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. Only 500 mg/50 mL vials will be used in this study. The product is formulated in polysorbate 80 (CC mg/mL), sodium citrate dihydrate (CCI mg/mL), sodium chloride (C mg/mL), and Water for Injection. The pH is CC.

Sites will prescribe MTX according to standard local guidance.

8.5.2.2 Comparator

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen, having an approximate molecular weight of 145 kD and binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Both rituximab (US) and rituximab (EU) have the same product formulation of a sterile, clear, colorless, preservative-free liquid

concentrate for IV administration. Rituximab (US) and rituximab (EU) is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. Only 500 mg/50 mL vials will be used in this study. The product is formulated in polysorbate 80 (CC mg/mL), sodium citrate dihydrate (CCI mg/mL), sodium chloride (C mg/mL), and water for injection. The pH is CC.

Rituximab (US) and rituximab (EU) will be provided from commercial supplies.

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, investigational product[s] and comparator product[s]) and brief information about other protocol required therapies will be provided separately in the Pharmacy Guide.

8.5.4 Blinding of Study Medication

Since the investigational product containers are different for ABP 798 and rituximab, investigational product (ABP 798 or rituximab) will be prepared by an unblinded Pharmacist or designee for administration to the subject. The subjects, the Sponsor (Amgen), designated PRA, and other clinical site 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 (or designee)'s standard operating procedures (SOPs) until the time of unblinding. Select PRA staff (eg, 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 in order 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

It is forbidden to use investigational drug material for purposes other than those defined in this protocol.

8.5.5.1 Study Treatment Storage

Investigational product should be stored in a secure limited access location. ABP 798 and rituximab should be stored protected from light at C°C to C°C and according to the

storage and expiration information (where required) provided on the label that is affixed to the package containing the investigational product. Do not freeze or shake.

8.5.5.2 Study Treatment Accountability

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

The Investigator will administer the medication 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 medication and all medication containers should be destroyed or returned to Amgen or its designee, as appropriate, for destruction. In either instance, complete documentation will be returned to the Sponsor.

8.5.6 Dose Adjustments and Dose Escalation

There are no recommended dose reductions or escalations for the investigational products (ABP 798 or rituximab).

All AEs should be reported in accordance with Section 11 of the protocol.

8.5.7 Prior and Concomitant Therapy

8.5.7.1 Permitted Concomitant Treatments (Medications and Therapies)

The following concomitant medications are permitted:

- MTX 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 prior to initiation of study treatment. The dose of oral corticosteroids may be reduced according to local guidelines during the conduct of the study.

If at any time a subject needs additional therapy (other than those specified in Section 8.5.7.3), including an increase in their MTX dose, to treat their RA, the Investigator should contact the Amgen Medical Monitor (or designee) to determine if the

subject is eligible to remain on study treatment. If the subject is no longer eligible to remain on study treatment, then the subject should undergo the assessments of the week 48/EOS visit before administration of any additional therapies. The subject should be withdrawn from the study treatment.

8.5.7.2 Prohibited Concomitant Medications

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

- Non-biologic DMARDs (other than MTX; as per exclusion criteria) including tofacitinib
- Any biologic treatment for RA (eg, anakinra, soluble IL-1 type II receptor, etanercept, infliximab, abatacept, tocilizumab, golimumab, certolizumab, or 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).
- IA hyaluronic acid
- IA, IM, or IV corticosteroids including adrenocorticotropic hormone (except of use as pre-medication)

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 following conditions:

- Oral corticosteroids: Maximum dose allowed is 10 mg prednisone (or equivalent) per day; dose can be decreased if needed, per Investigator's clinical judgment.
- Acetaminophen, hydrocodone, codeine, tramadol, and/or propoxyphene may be used by the subject as rescue analgesics except at least 12 hours before a scheduled study efficacy evaluation (week 8, 12, 24, 40, and 48/EOS).
- 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 such treatment may be added temporarily to treat a flare in RA. It should be tapered and discontinued with resolution of flare. In all cases, any dose regimen higher than baseline dose is not allowed at least 12 hours before the clinical efficacy assessments (week 8, 12, 24, 40, and 48/EOS).

- Topical anesthetic creams (eg, lidocaine/prilocaine creams and licensed NSAID creams) are permitted, except within 12 hours before clinical efficacy assessments (week 8, 12, 24, 40, and 48/EOS).

8.5.7.4 Prophylactic Treatment

Certain AEs are commonly associated with MTX treatment. In order 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 on a weekly basis 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) which is 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 study medication should be offered alternative treatment if applicable. Treatment should be given according to normal clinical practice, after a termination visit (see Section 8.4.3.2).

8.5.8 Treatment Compliance

Records of study medication used and intervals between visits will be kept during the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. The study treatment 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] Signing of the ICF establishes entry into the screening period.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, enrollment, or 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 798, rituximab (US), or rituximab (EU) in a 1:1:1 manner. The randomization will be stratified by geographic region, seropositivity (RF positive and/or CCP-positive vs. RF-negative and CCP-negative), and number of prior biologic therapies used for RA (1 vs. >1).

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 site for any other reason will be considered a protocol deviation. 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 site 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, Pharmacokinetic/Pharmacodynamic, and Safety Variables

8.6.1 Efficacy, Pharmacokinetic/Pharmacodynamic, and Safety Measurements Assessed

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

8.6.1.1 Pharmacokinetic/Pharmacodynamic Endpoints

The primary PK endpoints will be AUC_{inf} and C_{max} following the second infusion of the first dose. Additional PK endpoints will include AUC from time 0 on day 1 prior to the first infusion of the first dose to 14 days postdose (day 15) ($AUC_{0\text{-}14\ day}$), AUC from time 0 on day 1 prior to the first infusion of the first dose to week 12 ($AUC_{0\text{-}12\ wk}$), and C_{max} following the first infusion of the first dose.

PD endpoints will include the percent of subjects with complete depletion in CD19+ cell count from days 1 to 3.

Table 1. Schedule of Assessments and Procedures

Study Visit/Day/Week D = Day; W = Week	**Scn**	**BL/ D1/ W0**	**D1 EOI**	**D1 3 h**	**D1 6 h**	**D 2**	**D 3**	**D15/ W2**	**D15 EOI**	**D15 3 h**	**D15 6 h**	**D 16**	**D 17**	**W 4**	**W 8**	**W 12**	**W 24[a]**	**W 26**	**W 30**	**W 40**	**W48/ EOS[b]**
Visit Window														± 2 days					± 2 days	± 3 days	± 2 days
General Assessments																					
Informed consent form	X																				
Medical & medication history	X																				
Physical examination	X	X															X				X
Vital signs	X	X	X	X	X			X	X	X	X						X	X	X		X
ECG	X																				
Chest radiography	X[c]																				
Dosing of ABP 798/ rituximab [a]		X[d]						X[d]									X[d]	X[d]			
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease Assessments																					
Tender/swollen joint count	X	X													X	X	X			X	X
Subject and Investigator's global health assessment[e]		X													X	X	X			X	X
Pain VAS[e]		X													X	X	X			X	X
HAQ-DI[e]		X													X	X	X			X	X
Laboratory Assessments																					
Serology (HBsAg, anti-HBc, HCV)	X																				
Serum chemistry	X[f]	X	X					X					X		X		X	X		X	X
Hematology	X	X	X					X					X		X		X	X		X	X

Page 1 of 2

See footnotes on following page.

Table 1. Schedule of Assessments and Procedures

Study Visit/Day/Week D = Day; W = Week	**Scn**	**BL/ D1/ W0**	**D1 EOI**	**D1 3 h**	**D1 6 h**	**D 2**	**D 3**	**D15/ W2**	**D15 EOI**	**D15 3 h**	**D15 6 h**	**D 16**	**D 17**	**W 4**	**W 8**	**W 12**	**W 24[a]**	**W 26**	**W 30**	**W 40**	**W48/ EOS[b]**
Visit Window														± 2 days					± 2 days	± 3 days	± 2 days
Laboratory Assessments (*cont'd)*																					
CRP	X[g]	X													X	X	X			X	X
ESR	X[g]																				
PK sampling [h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Antidrug antibodies		X						X									X		X		X
CD19+ cell count		X				X	X							X			X				X
IgA, IgG, and IgM levels		X				X[i]	X[i]							X			X				X
Urinalysis	X	X						X									X				X
Tuberculosis testing	X																				
Pregnancy[j]	X	X						X							X		X			X	X
Anti-CCP	X																				
Rheumatoid factor	X																				

Page 2 of 2

AE = adverse event; BL = Baseline; CRP = C-Reactive Protein; EOI = End of Infusion; EOS = End of Study; ESR = Erythrocyte sedimentation rate; h = hour; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBsAg = Hepatitis B surface antigen; Anti-HBc = Hepatitis B core antibody; HCV = Hepatitis C virus antibody; Ig = Immunoglobulin, PK = Pharmacokinetic; Scn = Screening; VAS = Visual analogue scale; Anti-CCP= Anti-cyclic citrullinated peptide antibody

[a] The second dose will be administered at week 24 or earlier, ie, anytime from week 16 to week 24, in individual subjects, if necessary in the opinion of the Investigator. For subjects who receive retreatment before week 24, all week 24 and post-week-24 assessments will be moved up to the corresponding time point after treatment (eg, week 26 will be 2 weeks after retreatment, week 30 will be 6 weeks after retreatment, etc.). An infusion may be delayed up to 7 days to allow for recovery from infection.

[b] Subjects early terminating study should perform week 48 procedures.

[c] Historical radiograph performed within 3 months prior to first dose of IP may be used and does not need to be repeated at screening (section 10.7 for details)

[d] ABP 798/rituximab dosing to be administered after all other procedures are completed for each visit.

[e] Subjective assessments will be the first procedures performed at the visit.

[f] Includes any other lab tests required only for screening. Creatinine clearance calculation will be performed only at screening.

[g] Either CRP or ESR is required at screening. CRP will be performed by central lab and results will be blinded to study sites. ESR will be performed by local laboratory.

[h] PK sampling: day 1, predose, at EOI, and 3 and 6 hours postdose; day 2 (24 hours postdose); day 3 (48 hours postdose); day 15, predose, at EOI, and 3, 6, and 24 hours postdose (day 16), and 48 hours postdose (day 17). In addition, at week 4 (day 29), week 8 (day 57), week 12 (day 85), and predose week 24, week 26, and week 30, 48/EOS. Blood sampling for PK analysis during each return visit, including the EOS visit, will occur per the scheduled time point with tolerance collection

windows as follows: Day 1 predose = within 1 hour prior to dosing; days 1 and 15 at EOI = infusion should be monitored to ensure collection of the PK sample within 10 minutes after the end of the infusion; all other Day 1 sampling times = ± 10 minutes; days 2 and 3 = ± 3 hours; predose Day 15 = within 1 hour prior to dosing; all other Day 15 sampling time = ± 10 minutes; days 16 and 17 = ± 3 hours; week 4, 8 and 12 = ± 2 days; predose at weeks 24 and 26 = within 1 hour prior to dosing; and weeks 30 and 48 = ± 2 days.

[i] Only IgM required on Days 2 and 3.

[j] Pregnancy test for females of child-bearing potential. Serum pregnancy test will be done at screening by the central laboratory. Urine pregnancy test performed locally at subsequent time points.

8.6.1.2 Efficacy Measurements

8.6.1.2.1 Efficacy Criteria

Efficacy is a secondary objective in this study. The efficacy endpoint is Disease Activity Score (DAS) 28-CRP change from baseline at week 24. The endpoint will also be assessed at weeks 8, 12, 40, and 48.

In addition, ACR20 (20% improvement in ACR core set measurements), ACR50 (at least 50% improvement compared to baseline) and ACR70 (at least 70% improvement compared to baseline) will also be assessed at weeks 8, 12, 24, 40, and 48.

DAS28-CRP

The DAS28-CRP is a continuous measure based on 28 DAS joints from the ACR (indicated with * in Section 17.3), the Subject's Global Health Assessment score (as assessed as a score of 0 to 100 transformed from the results on a 100-mm VAS scale), 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 28 swollen joint count, CRP is in mg/L, and GH is the Subject's Global Health Assessment in 0 to 100 scale (van Gestel et al, 1998).

ACR

Improvement compared to baseline is required for both swollen and tender joint counts (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)
- CRP

8.6.1.3 Safety Measurements

Safety endpoints include the following:

- treatment-emergent AEs and serious adverse events (SAEs)
- clinically significant changes in laboratory values and vital signs
- incidence of antidrug antibodies

9 STUDY EVALUATIONS BY VISIT

After signing the informed consent, there are 15 visits, including a screening visit and visits on days 1, 2, 3, 15, 16, and 17 and weeks 4, 8, 12, 24, 26, 30, 40, and 48/EOS. After the first 18 subjects have received at least 1 dose of investigational product (ie, infusions on days 1 and 15) an initial safety analysis will be conducted by the DMC.

9.1 Screening

After subjects have provided informed consent, the following assessments/procedures will be performed within the 28 day screening period:

- targeted medical history, including history of all prior treatments for RA within the past 3 years and any prior biologic therapies used for RA
- physical examination, including evaluation of body systems and height and weight
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- standard 12-lead electrocardiogram (ECG)
- chest radiography (prior radiography or formal reports signed off by a radiologist within 3 months of first dose of investigational product is acceptable)
- screening joint assessments (DAS and ACR tender/swollen joint counts; Section 17.3)
- tuberculosis testing (PPD or Quantiferon test)
- clinical laboratory testing, including serology, serum chemistry, hematology, either CRP or ESR, anti-CCP, and rheumatoid factor.
- collection of samples 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 study treatment, all prior treatments for RA within the past 3 years and any prior biologic therapies used for RA will be recorded. Any AEs occurring during the screening period will be recorded as medical history; any SAEs will be recorded using the eCRF. SAEs will be reported as outlined in Section 11.2.2.

Subjects will continue on their stable pre-study MTX regimen during the screening period.

9.1.1 Screen Failures

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 to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure. Screen failed subjects may be re-screened up to 2 times at the Investigator's discretion (ie, a total of 3 screens including initial screening). The subject will retain the same subject ID 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 re-screen/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 798, rituximab (US), or rituximab (EU). The following assessments/procedures will be performed before treatment:

- subjective assessments (Subject'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
- physical examination, including evaluation of body systems
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- baseline joint assessments (DAS and ACR tender/swollen joint counts; Section 17.3)
- Investigator's Global Health Assessment
- clinical laboratory testing, including serum chemistry, hematology, and CRP
- urinalysis and urine pregnancy test (for women of childbearing potential)
- collection of pretreatment PK samples (within 1 hour predose) and samples for pretreatment antidrug antibodies, CD19+ cell count, and IgA, IgG, and IgM levels

Any changes in concomitant medications since the last assessment will be recorded. Any pretreatment AEs will be recorded as medical history; any pretreatment SAEs will be recorded using the eCRF. SAEs will be reported as outlined in Section 11.2.2.

After completion of pretreatment procedures, ABP 798, rituximab (US), or rituximab (EU) will be administered as an IV infusion in a double-blinded fashion. Starting at the time of first treatment, all AEs, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF.

At the end of infusion (EOI), blood samples for serum chemistry and hematology will be drawn.

At EOI and 3 and 6 hours after EOI, the following assessments will be performed:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- collection of PK samples (within 10 minutes after the end of the infusion, ± 10 minutes at 3 and 6 hours)

Subjects may leave the site after the 6-hour post-EOI assessment. Subjects will continue on their stable MTX regimen.

9.3 Day 2

On day 2, approximately 24 hours after EOI, a PK sample (± 3 hours) and samples for CD19+ cell count and IgM levels will be collected. Subjects will continue on their stable MTX regimen.

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

9.4 Day 3

Two days (approximately 48 hours after EOI) after the first infusion, the subject will return to the study site for collection of samples PK (± 3 hours), CD19+ cell count, and IgM levels.

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

9.5 Day 15 (Week 2)

Two weeks after the first infusion, the subject will return to the study site for the second infusion. Subjects will remain at the site for 6 hours post-treatment for sample collection. The following assessments/procedures will be performed before the infusion on day 15:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- clinical laboratory testing, including serum chemistry and hematology
- urinalysis and urine pregnancy test (for women of childbearing potential)
- collection of pretreatment PK samples (within 1 hour predose) and samples for antidrug antibodies

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

After completion of pretreatment procedures, ABP 798, rituximab (US), or rituximab (EU) will be administered as an IV infusion in a double-blinded fashion.

At the EOI and 3 and 6 hours after EOI, the following assessments will be performed:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- collection of PK samples (within 10 minutes after the end of the infusion, ± 10 minutes at 3 and 6 hours)

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

Subjects may leave the site after the 6-hour post-EOI assessment.

9.6 Day 16

On day 16, approximately 24 hours (± 3 hours) after completing the second infusion, a PK sample will be collected. Subjects will continue on their stable MTX regimen.

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

9.7 Day 17

On day 17, approximately 48 hours (± 3 hours) after the second infusion, the subject will return to the study site for collection of samples for serum chemistry, hematology, and PK.

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

9.8 Week 4 (± 2 days)

Four weeks (± 2 days) after the first infusion, the subject will return to the study site. The following assessments/procedures will be performed at week 4:

- collection of PK samples and samples for CD19+ cell count and IgA, IgG, and IgM levels

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

9.9 Week 8 (± 2 days)

Eight weeks (± 2 days) after the first infusion, the subject will return to the study site.

The following assessments/procedures will be performed at week 8:

- joint assessments (DAS and ACR tender/swollen joint counts; Section 17.3)
- subjective assessments (Subject'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

- Investigator's Global Health Assessment
- clinical laboratory testing, including serum chemistry, hematology, and CRP
- collection of PK samples
- urine pregnancy test (for women of childbearing potential)

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

9.10 Week 12 (± 2 days)

Twelve weeks (± 2 days) after the first infusion, the subject will return to the study site for safety and efficacy assessment. The following assessments/procedures will be performed at week 12:

- subjective assessments (Subject'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 (DAS and ACR tender/swollen joint counts; Section 17.3)
- Investigator's Global Health Assessment
- clinical laboratory testing including CRP
- collection of PK samples

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

9.11 Week 24

Twenty-four weeks after the first infusion (or at the time of retreatment if required before week 24), the subject will return to the study site for assessment and treatment. The following assessments/procedures will be performed before treatment at week 24:

- subjective assessments (Subject'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
- physical examination, including evaluation of body systems
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- joint assessments (DAS and ACR tender/swollen joint counts; Section 17.3)
- Investigator's Global Health Assessment
- clinical laboratory testing, including serum chemistry, hematology, and CRP
- urinalysis and urine pregnancy test (for women of childbearing potential)
- collection of pretreatment PK samples (within 1 hour predose) and samples for antidrug antibodies, CD19+ cell count, and IgA, IgG, and IgM levels

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

After completion of pretreatment procedures, ABP 798 or rituximab (EU) will be administered as an IV infusion in a double-blinded fashion. Subjects who had previously received rituximab (US) will be transitioned to ABP 798, but this change will be managed by the IXRS to maintain the blind. Subjects will continue on their stable MTX regimen.

9.12 Week 26

Twenty-six weeks after the first infusion (or 2 weeks after initiation of retreatment if retreatment occurred before week 24), the subject will return to the study site for assessment and treatment. The following assessments/procedures will be performed before treatment at week 26:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- clinical laboratory testing, including serum chemistry and hematology
- collection of pretreatment PK samples (within 1 hour predose)

After completion of pretreatment procedures, ABP 798 or rituximab (EU) will be administered as an IV infusion in a double-blinded fashion. Any changes in concomitant medications since the last assessment will be recorded. All AEs, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF and will be reported as outlined in Section 11.2.2. Subjects will continue on their stable MTX regimen.

9.13 Week 30 (± 2 days)

Thirty weeks (± 2 days) after the first infusion (or 6 weeks after initiation of retreatment if retreatment occurred before week 24), the subject will return to the study site. The following assessments/procedures will be performed at week 30:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- collection of PK samples and samples for antidrug antibodies

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

9.14 Week 40 (± 3 days)

Forty weeks (± 3 days) after the first infusion (or 16 weeks after initiation of retreatment if retreatment occurred before week 24), the subject will return to the study site. The following assessments/procedures will be performed at week 40:

- subjective assessments (Subject'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 (DAS and ACR tender/swollen joint counts; Section 17.3)
- Investigator's Global Health Assessment
- clinical laboratory testing, including serum chemistry, hematology, and CRP
- urine pregnancy test (for women of childbearing potential)

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

9.15 Week 48 (EOS)

Forty-eight weeks (± 2 days) after the first infusion (or 24 weeks after initiation of retreatment if retreatment occurred before week 24) or at the time of early discontinuation, the subject will return to the study site for a follow-up assessment. The following assessments/procedures will be performed at week 48/EOS:

- subjective assessments (Subject'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
- Investigator's Global Health Assessment
- physical examination, including evaluation of body systems
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- joint assessments (DAS and ACR tender/swollen joint counts; Section 17.3)
- clinical laboratory testing, including serum chemistry, hematology, and CRP
- urinalysis and urine pregnancy (for women of childbearing potential)
- collection of PK samples (PK sample must be within 2 days of week 48) and samples for antidrug antibodies, CD19+ cell count, and IgA, IgG, and IgM levels

Any changes in concomitant medications since the last assessment will be recorded. All AEs, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF through the week 48/EOS visit. SAEs will be reported as outlined in Section 11.2.2. Any SAEs ongoing at week 48/EOS will be followed until they resolve or are considered chronic or stable.

10 METHODS OF ASSESSMENT

10.1 Rheumatoid Arthritis Assessments

At each time point for RA assessments, the Subject'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 at 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 28 joint-count for DAS and the 66/68 joint set for ACR. 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 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 Pregnancy Test

Pregnancy will be determined by evaluation of β-human chorionic gonadotrophin (β-HCG) in serum at screening by central laboratory and in urine at subsequent time points locally for all women of childbearing potential. Subjects who are pregnant are 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.

10.3 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 AEs.

Body weight (kg) will be measured without shoes or jacket. Height will be determined at screening.

10.4 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.

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 AEs.

10.5 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, PR, QRS, and QT will be recorded from the 12-lead ECG. A copy of the ECGs will be retained on site. 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.

10.6 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 Inclusion Criterion 13.

10.7 Chest Radiography

Chest radiography will be performed at screening as indicated in Table 1 and will include anterior/posterior or posterior/anterior and lateral views. Chest x-ray performed at the site can be read by the Investigator. A formal report, signed off by the Investigator, should be filed in 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.

10.8 Clinical Laboratory Testing

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

Serology: HbsAg, anti-HBc, 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 and differential, platelet count.

Clinical chemistry: Sodium, potassium, urea, creatinine, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, gamma glutamyl transferase, nonfasting glucose, phosphate, and uric acid. Rheumatoid Factor and anti-CCP will be assessed at screening. CRP will be assessed at the time points indicated in Table 1. CRP results from the baseline visit and onwards will be blinded to study sites and not included in the central laboratory report to the site.

Urinalysis (fresh urine): pH, protein, glucose, bilirubin, blood.

Immunology: Blood samples for antidrug antibody assessments will be collected at the time points indicated in Table 1.

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.

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.

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 AEs.

IgA, IgG, and IgM levels will also be collected, as indicated in Table 1.

10.9 Blood Samples for Pharmacokinetic Analysis

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

Blood sampling for PK analysis during each return visit, including the EOS visit, will occur per the scheduled time point with tolerance collection windows as follows:

- predose day 1 = within 1 hour prior to dosing
- days 1 and 15 at EOI - infusion should be monitored to ensure collection of the PK sample within 10 minutes after the end of the infusion
- all other day 1 sampling times = ± 10 minutes
- days 2 and 3 = ± 3 hours
- predose day 15 = within 1 hour prior to dosing
- all other day 15 sampling time = ± 10 minutes
- days 16 and 17 = ± 3 hours
- weeks 4, 8, and 12 = ± 2 days
- predose at weeks 24 and 26 = within 1 hour prior to dosing
- weeks 30 and 48 = ± 2 days

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

10.10 Blood Samples for Pharmacodynamic Analysis

Pharmacodynamic analyses will include CD19+ cell count. Samples will be collected at the time points indicated in Table 1.

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 AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The Investigator is responsible for ensuring that any AEs observed by the Investigator or reported by the subject are recorded in the subject's medical record as well as the eCRF.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, 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 AE.

11.1.2 Reporting Procedures for Adverse Events

The Investigator is responsible for ensuring that all AEs observed by the Investigator or reported by the subject that occur from the day of randomization until the week 48 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. AEs observed by the Investigator or reported by the subject that occur after signing of informed consent but before randomization will be recorded.

The Investigator must assign the following AE attributes:

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

AEs 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 AE 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 AEs. However, laboratory value changes that require treatment or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

The Investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. A subject, or subject's legal guardian, can also voluntarily withdraw from treatment due to an AE. If the subject withdraws consent, the subject is encouraged to undergo, at a minimum, an EOS assessment.

11.2 Serious Adverse Events

11.2.1 Definition of Serious Adverse Events

An SAE is defined as an AE 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 AE 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 SAE 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 SAEs observed by the Investigator or reported by the subject that occur after signing of the ICF through the week 48 visit (or 28 days after the last dose of investigational product for subjects who discontinue early) are recorded in the subject's medical record and are submitted to Amgen.

The SAE must be submitted to Amgen, or its designee, within 24 hours following the Investigator's knowledge of the event via the applicable eCRF.

If the electronic data capture (EDC) system is not functional, the SAE can be reported by faxing a completed paper SAE Fax Cover Sheet and SAE report form or by direct telephone communication with PRA Safety Risk Management at the numbers provided below. The event must be updated electronically in EDC by the clinical site 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 Sites:
FAX: +44 1792 525 720
Phone: +49.621.8782.154
CHOSafety@praintl.com

For North America, Latin America, and South America Clinical Sites:
FAX: 1.888.772.6919
Phone: 1.800.772.2215
CHOSafety@praintl.com

New information relating to a previously reported SAE must be submitted to Amgen, or its designee. All new information for SAEs must be sent 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 SAE must be consistent with that recorded on the applicable eCRF (eg, AE Summary eCRF).

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

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

Determination of expectedness for Amgen products will be based on the contents of the Investigator's Brochure for investigational products 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 products are to be expedited according to local requirements.

Amgen, or its designee, reports SAEs 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 SAEs occurring at the site and other AE 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 SAEs. However, if the Investigator becomes aware of an SAE 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. SAEs 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

AEs of Special Interest for ABP 798/rituximab will be defined in the Statistical Analysis Plan (SAP) and analyzed from the clinical database. There are no expedited reporting requirements for AEs of Special Interest (other than those that meet other reporting requirements).

11.4 Pregnancy Reporting

Pregnancy in itself is not regarded as an AE 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 SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to Amgen, or its designee.

Pregnancies among 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 (WHO) Drug Reference Dictionary. Coexistent diseases and AEs will be coded using MedDRA (Medical Dictionary for Regulatory Activities).

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

12.2 Sample Size Estimation

Approximately 300 subjects will be randomized in a 1:1:1 ratio to receive ABP 798, rituximab (US), or rituximab (EU), stratified by geographic region, seropositivity (RF-positive and/or CCP-positive vs. RF-negative and CCP-negative), and number of prior biologic therapies used for RA (1 vs. > 1). The sample size will provide > 90% power to demonstrate similarity on the primary PK endpoints based on an assumption of between-subject variability (as measured by coefficient of variation) of 40%, true geometric mean ratio (GMR) of 1 among ABP 798, rituximab (US), or rituximab (EU), a margin of (0.8, 1.25) and 15% dropout by week 24. The PK similarity will be tested between ABP 798 versus rituximab (US) and ABP 798 versus rituximab (EU), each with a significance level of 0.05. The similarity between rituximab (US) and rituximab (EU) will be evaluated as well.

12.3 Statistical Analysis Plan

A 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. Randomization will be stratified by geographic region, seropositivity (RF-positive and/or CCP-positive vs. RF-negative and CCP-negative), and number of prior biologic therapies used for RA (1 vs. > 1).

12.5 Analysis Populations

The analysis for the PK endpoints will be based on the PK Analysis Set. Sensitivity analysis for the PK endpoints will be based on the per-protocol PK Analysis Set. The primary analysis for the PD endpoint and efficacy endpoints will be performed using the Full Analysis Set (FAS). The Per-protocol Analysis Set will be used for sensitivity analyses of the key efficacy endpoints. The analysis of safety endpoints will be based on the Safety Analysis Set.

12.5.1 Full Analysis Set

The FAS includes all subjects randomized in the study. It will be analyzed according to randomized treatment group (regardless of actual treatment received).

12.5.2 Per-protocol Set

The Per-protocol Analysis Set includes all subjects randomized in the study who have completed the week 24 disease assessment and did not experience a protocol deviation that affects their evaluation of the secondary objectives of the study to assess clinical efficacy. It will be analyzed according to actual treatment received. The protocol deviations that affect evaluation of efficacy endpoints 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 at least 1 infusion of investigational product. It will be analyzed according to actual treatment received.

12.5.4 Pharmacokinetic Analysis Set

The PK Analysis Set includes all randomized subjects who received **the full protocol-specified dose on Day 1** and had an evaluable serum concentration-time profile. It will be analyzed according to actual treatment received.

12.5.5 Per-protocol Pharmacokinetic Analysis Set

The Per-protocol PK Analysis Set consists of a subset of subjects in the PK Analysis Set who do not experience a protocol deviation that affects their evaluation. It will be analyzed according to actual treatment received. The protocol deviations that affect evaluation of PK endpoints will be determined based on a blinded data review prior to database lock.

12.6 Statistical Methods

The final analysis will be performed after all subjects have completed or have had the opportunity to complete the week 48/EOS assessment. Secondary analyses of long-term effects and safety will be performed after all subjects have had the opportunity to complete the week 48/EOS assessment.

All categorical variables will be summarized using the number and percent 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 as appropriate) will be presented if deemed necessary.

The PK similarity for each primary PK endpoint will be tested between ABP 798 versus rituximab (US) and ABP 798 versus rituximab (EU), each with a significance level of 0.05.

12.6.1 Missing Data

Imputation rules will be presented in the SAP before unblinding of the study for the **final** analysis.

12.6.2 Demographic and Baseline Data

The following demographic and baseline characteristics will be summarized: age (in years, at time of signing informed consent), race, gender, 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 will be tabulated by country, center, and stratification factor
- subject disposition (including number of subjects who were screened, randomized, treated with ABP 798/rituximab [US]/rituximab [EU], 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
- important protocol deviations
- number and percent of subjects on study at each visit
- randomization list of subjects and their actual versus randomized treatment group

12.6.4 Pharmacokinetics

The PK similarity will be demonstrated by comparing the 90% confidence interval (CI) for the GMR of test (ABP 798)-to-reference (US-licensed rituximab or EU-authorized rituximab) **and rituximab [US] to rituximab [EU]** for AUC_{inf} **and for C_{max} following the second** infusion of the first dose with the bounds of 0.8 to 1.25, where α=0.05. PK parameters will be calculated using non-compartmental methods. Point estimates and CIs for the GMR will be estimated from an analysis of covariance model using the PK Analysis Set.

Other PK endpoints, $AUC_{0\text{-}14\ day}$ after first infusion, $AUC_{0\text{-}12\ wk}$ after the first and second infusions of the first dose and C_{max} after the first infusion of the first dose, will be analyzed using the same methods as stated above. Additional PK parameters including the time of C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), and the terminal elimination rate constant (λ_z) will be summarized descriptively.

12.6.5 Pharmacodynamics

The PD similarity will be evaluated descriptively by calculating the 90% CI of complete CD19+ cell depletion rate difference between test-to-reference. The 95% CI will also be provided. The point estimate and CIs for rate difference will be estimated using a generalized linear model (specifically, a log-binomial regression model) with relevant baseline values and stratification factors as covariates using the FAS.

12.6.6 Efficacy

Clinical equivalence will be evaluated for DAS28-CRP at week 24 using the FAS consisting of all randomized subjects. **If PK similarity is established between rituximab (US) and rituximab (EU), the 2 arms will be combined into a single reference arm for the primary assessment of clinical equivalence between ABP 798 and rituximab. The results for ABP 798 vs. rituximab (EU) and ABP 798 vs. rituximab (US) will be provided for descriptive purposes. If PK similarity is not established, the ABP 798 arm will be compared to each of the individual rituximab arms separately to stablish clinical equivalence of ABP 798 to the individual reference arms.** The 95% CI for both the difference between ABP 798 and US-licensed rituximab or EU-authorized rituximab in DAS28-CRP change from baseline will also be provided.

With the planned sample size, there is **94% probability that the 90% CI of the difference between the ABP 798 arm and the pooled rituximab (rituximab [EU] and**

rituximab [US]) arm and 83% probability that the 90% CI of the difference between test (ABP 798) and reference (US-licensed rituximab or EU-authorized rituximab) in DAS28-CRP change from baseline at week 24 will fall into the equivalence margin of ± 0.6 (EULAR response criteria), assuming a standard deviation of 1.4 (Volkmann et al, 2010). **DAS28-CRP at other timepoints and ACR 20, 50 and 70 will be summarized descriptively.**

In addition, 90% and 95% CI for the risk ratio (RR) and risk difference (RD) of ACR20, **ACR50 and ACR70** at week 24 between ABP 798 and **rituximab (pooled US-**licensed **and EU-authorized** rituximab**,** US-licensed rituximab or EU-authorized rituximab) will also be provided and the outcome is descriptive. The CIs for the difference of DAS28-CRP change from baseline between the ABP 798 and rituximab arms will be estimated using repeated-measures analysis. Data from all assessed time points through week 24 visit will be included in the analysis. Besides stratification variables, visit (week), treatment, and treatment-by-visit interaction will be included in the model, with visit as a categorical variable. The CIs for RR and RD of ACR20**/50/70** between ABP 798 and rituximab arms will be estimated based on a repeated measures analysis where data from all assessed time points through week 24 visit are included. Besides stratification variables, visit week (as a categorical variable), treatment, and treatment-by-visit interaction will be included in the generalized estimating equation (GEE) model.

Other endpoints, RR and RD of ACR 20/**50/70** at weeks 8, 12, 40, and 48, and RR and RD of ACR50 and ACR70 at weeks 8, 12, 40, and 48 will be summarized descriptively by treatment. In addition, the difference of DAS28-CRP change from baseline between the ABP 798 and rituximab arms will be summarized descriptively by treatment at weeks 8, 12, 40, and 48.

12.6.7 Safety

All safety analyses will be performed using the Safety Analysis Set based on subject's actual treatment received. Safety analysis will include analyses of AEs, clinical laboratory tests, vital signs, ECGs, and antidrug antibodies. In general, summaries will be provided separately for day 1 up to the 1st infusion of the 2nd dose of investigational product by actual treatment groups, for the entire study by treatment groups defined by first dose, and for the day of the 1st infusion of the 2nd dose of investigational product up to the week 48/EOS visit with subjects grouped as receiving ABP 798 for both 1st and 2nd doses, receiving rituximab (US) for the 1st dose and ABP 798 for the 2nd dose, and receiving rituximab (EU) for both 1st and 2nd doses, unless otherwise specified.

12.6.7.1 Investigational Product Administration

For the investigational product (ABP 798, rituximab [US], or rituximab [EU]), summary statistics will be provided for the total number of doses.

12.6.7.2 Adverse Events

Safety analyses will focus on treatment-emergent AEs. Treatment-emergent events are those that begin or increase in severity or frequency at or after the time of first treatment up to the week 48/EOS visit (or within 28 days following the last dose of study treatment if subject discontinues study early). All treatment-emergent AEs will be summarized by treatment arm and according to the MedDRA system organ class (SOC) and preferred term. Summaries will be provided for the incidence of all treatment-emergent AEs and by severity and relatedness to investigational product. Additional summaries will be presented for SAEs.

All AE data will be listed by subject, and a separate listing will include all SAEs, including any deaths on study.

AEs of special interest (Section 11.3) will be summarized separately.

The exposure adjusted subject incidence rates of adverse events throughout the study may be tabulated for selected categories of adverse events.

12.6.7.3 Immunogenicity

The number and percentage of subjects developing antidrug antibodies and those developing neutralizing antibodies will be tabulated separately for day 1 to the 1st infusion of the 2nd dose of investigational product by actual treatment groups, and for day 1 of first infusion of second dose to 4 weeks after the 2nd infusion of the 2nd dose and for the entire study by treatment groups defined by first dose.

12.6.7.4 Concomitant Medications and Therapies

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

12.6.7.5 Clinical Laboratory Test

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 v4 grading, will be presented.

12.6.7.6 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, which will be included in the AE listings and summaries.

12.6.8 Interim Analysis

No formal interim analysis is planned for this study.

12.6.9 Data Monitoring Committee

A DMC external to Amgen and PRA will be formed with members consisting of individuals chosen for their expertise in rheumatology. 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 conduct an initial safety analysis after the first 18 subjects have received at least 1 dose of investigational product (ie, infusions on days 1 and 15) of either ABP 798, rituximab (US) or rituximab (EU).

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, in order to fulfill these obligations and to maintain current of study progress, Amgen monitors, or Amgen's designees, will visit the investigative sites 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 in order 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 AEs. 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 site 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 site 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 site 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 investigative sites, 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 site 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 other 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, etc).
- general condition and status remarks by the subject, including any *significant* medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE 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 Inc.

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 in order 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.

In order 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 investigative site and subject identity will remain confidential in all publications related to the study.

15 ADMINISTRATION PROCEDURES

15.1 Regulatory Approval

Amgen Inc., 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 of the protocol without agreement by the Sponsor and documented approval from the IRB/IECs 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/IECs 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, as appropriate, 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 798 or rituximab 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:

1. Investigator's Brochure
2. Current, signed version of the protocol and any previous versions of the protocol
3. Protocol amendments (if applicable)
4. Operations Manual (if applicable)
5. Current ICF (blank) and any previous versions of the ICF
6. 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 [IND] 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 the ICH GCP and by local or national regulations
7. Documentation of IRB/IEC approval of the protocol, the ICF, any protocol amendments, and any ICF revisions
8. All correspondence between the Investigator, IRB/IEC, and the Sponsor/CRO relating to study conduct

9. Lab certification(s)
10. Monitoring log
11. Investigational product invoices
12. Signature list of all staff completing eCRFs
13. Signature list of all staff completing drug accountability summaries

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17 APPENDICES

17.1 Appendix 1: Elements of Informed Consent

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 whom 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, et al. The American College of Rheumatology 1991 Revised Criteria for the Classification of Global Functional Status in Rheumatoid Arthritis. Arthritis & Rheumatism. 1992;35(5):498-502.

17.3 Appendix 3: DAS28 and ACR Core Set Measurements

DAS28 Core Set Measurements:

- tender joint count
- swollen joint count
- Subject's Global Health Assessment
- CRP

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 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 STUDY TO COMPARE PHARMACOKINETICS AND PHARMACODYNAMICS, EFFICACY AND SAFETY OF ABP 798 WITH RITUXIMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS

SUMMARY OF CHANGES

Test Drug: ABP 798

Protocol Number:	20130108	EudraCT number: 2013-005543-90
Study Phase:	1/3	
Date and Version:	20 March 2018, 4.0	

Sponsor:	Clinical Research Organization (CRO):
Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 US	PRA Health Sciences 4130 ParkLake Avenue Raleigh, NC 27612 US

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

Rationale:

This amendment is issued to make the following changes:

Update the Table of Contents to reflect the correct title of Appendix 3.

Delete the primary analysis as the revised regulatory filing strategy nullifies the need for it.

Clarify the ACR improvement description.

Added a secondary objective to demonstrate the PK similarity of rituximab (US) a rituximab (EU).

Update the sample size estimation and statistical methods language to clarify the efficacy analysis.

Clarify the efficacy measurements, procedures, and remove redundancies as needed.

Specify the statistical approach for the efficacy evaluation.

Update to clarify the dosing requirement for inclusion in the PK analysis population

Summary of Changes

Any changes in the synopsis that also appear in the body of the protocol will appear only once in this summary of changes document, under the section number. Additions are in bold and deletions are in strikethrough.

Section 2, Synopsis, Objectives
Section 7.2, Secondary Objectives
Add:

- **to demonstrate PK similarity between rituximab (US) and rituximab (EU) as assessed by AUC_{inf} and by C_{max} after second infusion of the first dose**

Section 2, Synopsis, Study Design and Methodology
Section 8.1, Overall Study Design and Plan
Remove:

The primary analysis will be conducted when all subjects have completed or have had the opportunity to complete the week 30 assessments.

Section 2, Synopsis, Study Evaluations, Secondary Criteria
Add:

- **ACR20, ACR50 and ACR70**

Section 2, Synopsis, Statistical Methods
Replace:

The PK similarity will be demonstrated by comparing the 90% confidence interval (CI) for the GMR of test (ABP 798)-to-reference (rituximab [US] or rituximab [EU]) for AUC_{inf} and C_{max} following the second infusion of the first dose with the bounds of 0.8 to 1.25, where α=0.05.

Clinical equivalence will be evaluated for DAS28-CRP at week 24 using the Full Analysis Set consisting of all randomized subjects. With the planned sample size, there is **83%** probability that the 90% CI of the difference between test (ABP 798) and reference (rituximab [US] or rituximab [EU]) in DAS28-CRP change from baseline will fall into the equivalence margin of ± 0.6 (EULAR response criteria), assuming a standard deviation of 1.4 (Volkmann, 2012). The 95% CI for both the difference between ABP 798 and US-licensed rituximab or EU authorized rituximab in DAS28 CRP change from baseline will also be provided.

With:

The PK similarity will be demonstrated by comparing the 90**%** confidence interval (CI) for the GMR of test (ABP 798)-to-reference (rituximab [US] or rituximab [EU]) **and rituximab [US] to rituximab [EU]** for AUC_{inf} and **for** C_{max} following the second infusion of the first dose with the bounds of 0.8 to 1.25, where α=0.05.

Clinical equivalence will be evaluated for DAS28-CRP at week 24 using the Full Analysis Set consisting of all randomized subjects. **If PK similarity is established between**

rituximab (US) and rituximab (EU), the 2 arms will be combined into a single reference arm for the primary assessment of clinical equivalence between ABP 798 and rituximab. The results for ABP 798 vs. rituximab (EU) and ABP 798 vs. rituximab (US) will be provided for descriptive purposes. If PK similarity is not established, the ABP 798 arm will be compared to each of the individual rituximab arms separately to establish clinical equivalence of ABP 798 to the individual reference arms.

With the planned sample size, there is **94% probability that the 90% CI of the difference between the ABP 798 arm and the pooled rituximab (rituximab[EU] and rituximab[US]) arm and** 83% probability that the 90% CI of the difference between test (ABP 798) and reference (US-licensed rituximab or EU-authorized rituximab) in DAS28-CRP change from baseline **at week 24** will fall into the equivalence margin of ± 0.6 (EULAR response criteria), assuming a standard deviation of 1.4 (Volkmann et al, 2010). **DAS28-CRP at other timepoints and ACR20, 50 and 70 will be summarized descriptively.**

Section 8.6.1.2.1, Efficacy Criteria
Replace:

ACR~~20~~

To achieve ACR20 response, at least 20% improvement compared to baseline is required for both swollen and tender joint counts (66/68 joint counts; Section **Error! Reference source not found.**), as well as for 3 out of the following 5 additional parameters:

With:

ACR

Improvement compared to baseline is required for both swollen and tender joint counts (66/68 joint counts; Section **Error! Reference source not found.**), as well as for 3 out of the following 5 additional parameters:

Section 12.5.4, Pharmacokinetic Analysis Set
Replace:

The PK Analysis Set includes all randomized subjects who received at least 1 infusion of investigational product and had an evaluable serum concentration-time profile. It will be analyzed according to actual treatment received.

With:
The PK Analysis Set includes all randomized subjects who received **the full protocol-specified dose on Day 1** and had an evaluable serum concentration-time profile. It will be analyzed according to actual treatment received.

Section 12.6, Statistical Methods
Replace:

The primary analysis will be performed after all subjects have completed or have had the opportunity to complete the week 30 assessments. Secondary analyses of long-term effects and safety will be performed after all subjects have had the opportunity to complete the week 48/EOS assessment.

With:

The final analysis will be performed after all subjects have completed or have had the opportunity to complete the week 48/EOS assessment. Secondary analyses of long-term effects and safety will be performed after all subjects have had the opportunity to complete the week 48/EOS assessment.

Section 12.6.1, Missing Data
Replace:
Imputation rules will be presented in the SAP before unblinding of the study for the primary analysis.

With:

Imputation rules will be presented in the SAP before unblinding of the study for the **final** analysis.

Section 12.6.4, Pharmacokinetics
Replace:

The PK similarity will be demonstrated by comparing the 90% confidence interval (CI) for the GMR of test (ABP 798)-to-reference (US-licensed rituximab or EU-authorized rituximab) for AUC_{inf} and for AUC_{inf} after first and second infusions and C_{max} after second infusion of the first dose with the bounds of 0.8 to 1.25, where α=0.05.

With:
The PK similarity will be demonstrated by comparing the 90**%** confidence interval (CI) for the GMR of test (ABP 798)-to-reference (rituximab [US] or rituximab [EU]) **and rituximab [US] to rituximab [EU]** for AUC_{inf} **and for C_{max} following the second** infusion of the first dose with the bounds of 0.8 to 1.25, where α=0.05.

Section 12.6.6, Efficacy
Replace:

Clinical equivalence will be evaluated for DAS28-CRP at week 24 using the FAS consisting of all randomized subjects. With the planned sample size, there is 83% probability that the 90% CI of the difference between test (ABP 798) and reference (US licensed rituximab or EU-authorized rituximab) in DAS28-CRP change from baseline will

fall into the equivalence margin of ± 0.6 (EULAR response criteria), assuming a standard deviation of 1.4 (Volkmann et al, 2010). The 95% CI for both the difference between ABP 798 and US-licensed rituximab or EU-authorized rituximab in DAS28-CRP change from baseline will also be provided. In addition, 90% and 95% CI for the risk ratio (RR) and risk difference (RD) of ACR20 at week 24 between ABP 798 and US licensed rituximab or EU-authorized rituximab will also be provided, and the outcome is descriptive. The CIS for the difference of DAS28-CRP change from baseline between the ABP 798 and rituximab arms will be estimated using repeated-measures analysis. Data from all assessed time points through week 24 visit will be included in the analysis. Besides stratification variables, visit (week), treatment, and treatment-by-visit interaction will be included in the model, with visit as a categorical variable. The CIs for RR and RD of ACR20 between ABP 798 and rituximab arms will be estimated based on a repeated measures analysis where data from all assessed time points through week 24 visit are included. Besides stratification variables, visit week (as a categorical variable), treatment, and treatment-by-visit interaction will be included in the generalized estimating equation (GEE) model.–Other endpoints, RR and RD of ACR20 at weeks 8, 12, 40, and 48, and RR and RD of ACR50 and ACR70 at weeks 8, 12, 24, 40, and 48 will be summarized descriptively by treatment. In addition, the difference of DAS28-CRP change from baseline between the ABP 798 and rituximab arms will be summarized descriptively by treatment at weeks 8, 12, 40, and 48.

With:
Clinical equivalence will be evaluated for DAS28-CRP at week 24 using the FAS consisting of all randomized subjects. **If PK similarity is established between rituximab (US) and rituximab (EU), the 2 arms will be combined into a single reference arm for the primary assessment of clinical equivalence between ABP 798 and rituximab. The results for ABP 798 vs. rituximab (EU) and ABP 798 vs. rituximab (US) will be provided for descriptive purposes. If PK similarity is not established, the ABP 798 arm will be compared to each of the individual rituximab arms separately to stablish clinical equivalence of ABP 798 to the individual reference arms.** The 95% CI for both the difference between ABP 798 and US-licensed rituximab or EU-authorized rituximab in DAS28-CRP change from baseline will also be provided.

With the planned sample size, there is **94% probability that the 90% CI of the difference between the ABP 798 arm and the pooled rituximab (rituximab [EU] and rituximab [US]) arm and** 83% probability that the 90% CI of the difference between test (ABP 798) and reference (US-licensed rituximab or EU authorized rituximab) in DAS28 CRP change from baseline at week 24 will fall into the equivalence margin of ± 0.6 (EULAR response criteria), assuming a standard deviation of 1.4 (Volkmann et al, 2010). **DAS28-CRP at other timepoints and ACR20, 50 and 70 will be summarized descriptively.**

In addition, 90% and 95% CI for the risk ratio (RR) and risk difference (RD) of ACR20, **ACR50 and ACR70** at week 24 between ABP 798 and **rituximab (pooled US-licensed and EU-authorized rituximab,** US-licensed rituximab or EU-authorized rituximab) will also be provided and the outcome is descriptive.

Other endpoints, RR and RD of ACR20**/50/70** at weeks 8, 12, 40, and 48, and RR and RD of ACR50 and ACR70 at weeks 8, 12, 40, and 48 will be summarized descriptively by treatment.

Section 3: Table of Contents Appendix 3 Title
Replace:

ACR Core Set Measurements

With:
DAS28 and ACR Core Set Measurements

A RANDOMIZED, DOUBLE-BLIND STUDY TO COMPARE PHARMACOKINETICS AND PHARMACODYNAMICS, EFFICACY AND SAFETY OF ABP 798 WITH RITUXIMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS

SUMMARY OF CHANGES

Test Drug: ABP 798

Protocol Number: 20130108 **EudraCT number:** 2013-005543-90

Study Phase: 1/3

Date and Version: **16 October 2017; Version 3.0**

Sponsor:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 US

Clinical Research Organization (CRO):
PRA Health Sciences
4130 ParkLake Avenue, Suite 400
Raleigh, NC 27612 US

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Rationale:

This amendment is issued to make the following changes:

- To make minor, non-substantive grammatical and typographic corrections (changes not detailed in this summary)
- To adjust the language regarding study treatment accountability logs to indicate a single log as opposed to logs for each subject
- To remove ACR20 from secondary efficacy endpoints
- To correct multiplicity adjustments and error rates for statistical analysis of pharmacokinetic variables
- To add the DAS28 core set measurements to Appendix 2

A RANDOMIZED, DOUBLE-BLIND STUDY TO COMPARE PHARMACOKINETICS AND PHARMACODYNAMICS, EFFICACY AND SAFETY OF ABP 798 WITH RITUXIMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS

SUMMARY OF CHANGES

Test Drug: ABP 798

Protocol Number: 20130108 **EudraCT number:** 2013-005543-90

Study Phase: 1/3

Date and Version: **01 December 2016; Version 2.0**

Sponsor:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 US

Clinical Research Organization (CRO):
PRA
4130 ParkLake Avenue, Suite 400
Raleigh, NC 27612 US

CONFIDENTIAL

Rationale:

This amendment is issued to make the following changes:

- To make minor, non-substantive grammatical and typographic corrections (changes not detailed in this summary)
- To update Medical Monitor contact information
- To update International Council for Harmonisation (ICH) terminology
- To update pharmacokinetics terminology for consistency with the Statistical Analysis Plan
- To clarify the end of study period
- To clarify the end of trial date
- To modify the Inclusion Criteria as follows:
    1. To specify subjects must have had intolerance or an inadequate response to one or more TNF inhibitor therapies
    2. To specify that subjects must have completed at least 4 weeks of a TB prophylaxis regimen prior to enrollment
- To modify the Exclusion Criteria as follows:
    1. To allow subjects with a positive hepatitis B surface antigen or hepatitis B core antibody result to enroll provided documentation of hepatitis B virus immunization is provided
    2. To add adalimumab to the list of biologic therapies not allowed within 3 months prior to first dose of investigational product
    3. To add ocrelizumab to the list of prohibited prior treatments
- To change terminology from “local practice” to “local guidance” to ensure investigators follow general treatment guidelines
- To add citations for the administration of investigational product intravenously
- To add visits to the list of rescue medication administration guidelines
- To specify the format of unique subject identifiers
- To specify randomization stratification in regards to prior biologic therapies used to treat rheumatoid arthritis
- To clarify the day pharmacokinetic sampling timeframes
- To specify and clarify visit windows
- To specify that creatinine clearance will only be assessed at screening
- To clarify that C-reactive protein results will be blinded to study sites
- To correct terminology related to visual analog scales

- To specify the timeframe for performing screening assessments and procedures
- To clarify treatment versus infusion terminology
- To add that differential was added to hematology tests
- To add additional pharmacokinetic parameters as outlined in the Statistical Analysis Plan