1 TITLE PAGE

A RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY OF ABP 501 EFFICACY AND SAFETY COMPARED TO ADALIMUMAB IN SUBJECTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS

Test Drug: ABP 501

Protocol Number: 20120262 **EudraCT number:** 2013-000525-31

Study Phase: 3

[redacted]

[redacted]

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.

[redacted]

2 SYNOPSIS

NAME OF SPONSOR: Amgen	**PROTOCOL No.:** 20120262
NAME OF STUDY TREATMENT: ABP 501	
TITLE OF STUDY: A Randomized, Double-Blind, Phase 3 Study of ABP 501 Efficacy and Safety Compared to Adalimumab in Subjects with Moderate to Severe Rheumatoid Arthritis	
STUDY CENTERS: Approximately 150 sites in Europe, North America, and Latin America	
STUDY PERIOD: Approximately 500 subjects will be randomized in a 1:1 ratio to receive ABP 501 or adalimumab. The end of study (end of trial) will be the date when the last subject has their last study assessment.	**PHASE OF DEVELOPMENT:** Phase 3
PLANNED STUDY DATES: The study consists of a screening period of up to 4 weeks, a treatment period of 22 weeks, followed by a safety follow-up period through to week 26, for a total of up to 30 weeks. The expected enrollment duration is 12 months.	
OBJECTIVES: **Primary Objective:** The primary objective for this study is to assess the efficacy of ABP 501 compared with adalimumab. **Secondary Objective(s):** The secondary objectives are to assess the safety and immunogenicity of ABP 501 compared with adalimumab. **Exploratory Objective(s):** [redacted] to assess the trough serum concentration of ABP 501 compared with adalimumab	
STUDY DESIGN AND METHODOLOGY: This is a randomized, double-blind, active-controlled study in adult subjects with rheumatoid arthritis (RA) who have an inadequate response to methotrexate (MTX). Approximately 500 subjects (250 per treatment group) will be enrolled. The subjects will be randomized to receive either ABP 501 40 mg subcutaneous (SC) every 2 weeks or adalimumab 40 mg SC every 2 weeks in a blinded fashion until week 22. The assessment of the primary endpoint will be at week 24. Optional pharmacogenetic testing will be performed on subjects who consent to a pharmacogenetic substudy.	
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 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 3 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 > 1.0 mg/dL 6. Positive rheumatoid factor or anti-cyclic citrullinated peptide (CCP) at screening 7. Subjects must be taking MTX for ≥ 12 consecutive weeks and on a stable dose of 7.5 to 25 mg/week for ≥ 8 weeks prior to receiving the study drug and be willing to remain on stable dose throughout the study 8. For subjects on nonsteroidal anti-inflammatory drugs (NSAIDs) or low potency analgesics such as tramadol, soma compounds, fioricet, fiorinal, dose should be stable for ≥ 2 weeks prior to screening	

9. For subjects on oral corticosteroids, (≤ 10 mg prednisone or equivalent), doses should be stable 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 adequate prophylaxis initiation prior to receiving study drug in accordance with local recommendations
    - 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 (IP)

Exclusion Criteria:

Rheumatoid Arthritis related

1. Class IV RA (Hochberg 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 28 days prior to first dose of IP
    - a serious infection, defined as requiring hospitalization or intravenous (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 C virus (HCV) antibody positivity at screening
8. Uncontrolled, clinically significant systemic disease such as diabetes mellitus, cardiovascular disease including moderate to severe heart failure (New York Heart Association [NYHA] class III/IV), renal disease, liver disease or hypertension
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 disease-modifying antirheumatic drugs (DMARDs) 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 IP initiation
    - 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
    - Janus kinase (JAK) inhibitor eg, tofacitinib excluded within 28 days prior to first dose of IP
16. Prior use of 2 or more biologic therapies for RA
17. 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 within 3 months prior to first dose of IP
    - Other experimental or commercially available biologic therapies for rheumatoid arthritis within 3 months or 5 half-lives (whichever is longer) prior to first dose of IP
    - Rituximab within 9 months prior to IP along with evidence of B cell recovery
18. Live vaccines within 3 months prior to the first dose of IP
19. Chronic use of high potency narcotic analgesics such as morphine or morphine derived medications, fentanyl, codeine, hydromorphone, levorphanol, meperidine, methadone, oxycodone or hydrocodone at screening
20. Subjects that have taken any of the above agents in the past must have recovered from all drug-related adverse events (AEs)
21. Previous receipt of Humira® (adalimumab) or a biosimilar of adalimumab
22. 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 drug study(s) including vaccines, or subject is receiving other investigational agent(s)

General

23. For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 5 months after the last dose of investigational product
24. 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 5 months after the last dose of study drug. Male subjects must agree not to donate sperm during study and for 5 months following treatment with test article or until the scheduled end of the study (whichever is longer)
25. Known sensitivity to mammalian cell derived drug products or hypersensitivity to the active substance or to any of the excipients of ABP 501 or adalimumab
26. 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
27. Any disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures
28. Active substance abuse (within 24 weeks of screening)

NUMBER OF SUBJECTS: Approximately 500 subjects will be randomized in a 1:1 ratio to receive ABP 501 or adalimumab. The sample size is chosen to achieve > 90% power to demonstrate equivalence at a 2-sided significance level of 0.05 on the primary efficacy endpoint risk ratio (RR) of ACR20 (20% improvement in ACR core set measurements) at week 24 (assuming an expected ACR20 response for both ABP 501 and adalimumab of 63% at week 24) between ABP 501 and adalimumab, with an equivalence margin of (0.738, 1/0.738) and assuming a 15% dropout by week 24. Randomization will be stratified by geographic region and prior biologic use for RA (with prior biologic use capped at 40% of the study population).

STUDY TREATMENT(S):
Test Product, Dose and Mode of Administration:
ABP 501 40 mg SC (Treatment A), every 2 weeks
Reference Therapy, Dose and Mode of Administration:
Adalimumab 40 mg SC (Treatment B), every 2 weeks

DURATION OF TREATMENT: Subject will receive IP for 22 weeks, plus a screening period of up to 4 weeks, efficacy analysis at week 24 followed by safety follow-up period to week 26, for a total of up to 30 weeks.

STUDY EVALUATIONS:

Primary Efficacy Criterion:
- RR of ACR20 at week 24

Secondary Efficacy Criteria:
- Disease Activity Score (DAS) 28-CRP change from baseline at weeks 2, 4, 8, 12, 18, and 24
- RR of ACR20 at weeks 2 and 8
- Risk ratio of ACR50 (50% improvement in ACR core set measurements) and ACR70 (70% improvement in ACR core set measurements) responses at week 24

Safety Criteria:
- Treatment-emergent AEs and serious adverse events
- Clinically significant changes in laboratory values and vital signs
- Incidence of antidrug antibodies

Exploratory Criterion:
- [redacted]
- Trough serum concentrations of ABP 501 and adalimumab on weeks 2, 4, 12, 24, and end of study

STATISTICAL METHODS:
Clinical equivalence for the primary endpoint, RR of ACR20 at week 24, will be evaluated by comparing the 2-sided 90% confidence interval (CI) of the RR of ABP 501 and adalimumab with an equivalence margin of (0.738, 1/0.738). The 90% CI will be estimated using generalized linear model (specifically, a log-binomial regression model), with relevant baseline values and stratification factors as covariates.

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 with observations. Safety endpoints will be summarized descriptively as well. Subgroup analyses (by age, race, sex and stratification factors as appropriate) will be presented if deemed necessary.

The full analysis set (FAS) including all subjects randomized in the study will be used to perform the efficacy analysis based on subjects' actual treatment received. The per-protocol analysis set, which is a subset of the FAS including subjects who have completed the treatment period and did not experience a protocol deviation that affects their evaluation for the primary objective of the study will be used for sensitivity analyses of the key efficacy endpoints. For safety endpoints, all randomized subjects who received at least 1 dose of investigational product (ie, Safety Analysis Set) will be analyzed based on the actual treatment received.

[redacted]

3 TABLE OF CONTENTS

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LIST OF FIGURES

[redacted]

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
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{360}	AUC from 0 to 360 hours
CCP	Cyclic citrullinated peptide
CDC	Complement-mediated cytotoxicity
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum observed concentration
COX-2	Cyclooxygenase-2
CRO	Clinical research organization
CRP	C-reactive protein
DAS	Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ESR	Erythrocyte sedimentation rate

[redacted]

EULAR	European League Against Rheumatism
FAS	Full analysis set
FcγRIII	Fc gamma receptor Type III
FcRn	Fc neonatal receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCG	Human chorionic gonadotrophin
HUVEC	Human umbilical vein endothelial cells
IA	Intra-articular
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IM	Intramuscular
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IXRS	Interactive voice and web response system
JAK	Janus kinase
Kd	Dissociation equilibrium binding constant
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteinase
MTX	Methotrexate

NSAID	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
PIN	Personal Identification Number
PK	Pharmacokinetic
PPD	Purified protein derivative
QTc	Corrected QT interval
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor-κB ligand
RR	Risk ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SUSAR	Suspected unexpected serious adverse reactions
TIMP	Tissue inhibitor of metalloproteinase
TNF	Tumor necrosis factor
TNFR1	Tumor necrosis factor receptor 1
VAS	Visual analogue scale
WHO	World Health Organization

[redacted]

5 ETHICS

5.1 Ethics Committee

This study will be conducted in compliance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and International Conference on 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.

[redacted]

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 guidelines indicated in the Declaration of Helsinki and all applicable regulatory requirements.

[redacted]

[redacted]

7 STUDY OBJECTIVES

7.1 Primary Study Objective

The primary objective for this study is to assess the efficacy of ABP 501 compared with adalimumab.

7.2 Secondary Study Objectives

The secondary objectives are to assess the safety and immunogenicity of ABP 501 compared with adalimumab.

7.3 Exploratory Objectives

[redacted]

- the trough serum concentration for ABP 501 compared with adalimumab.

[redacted]

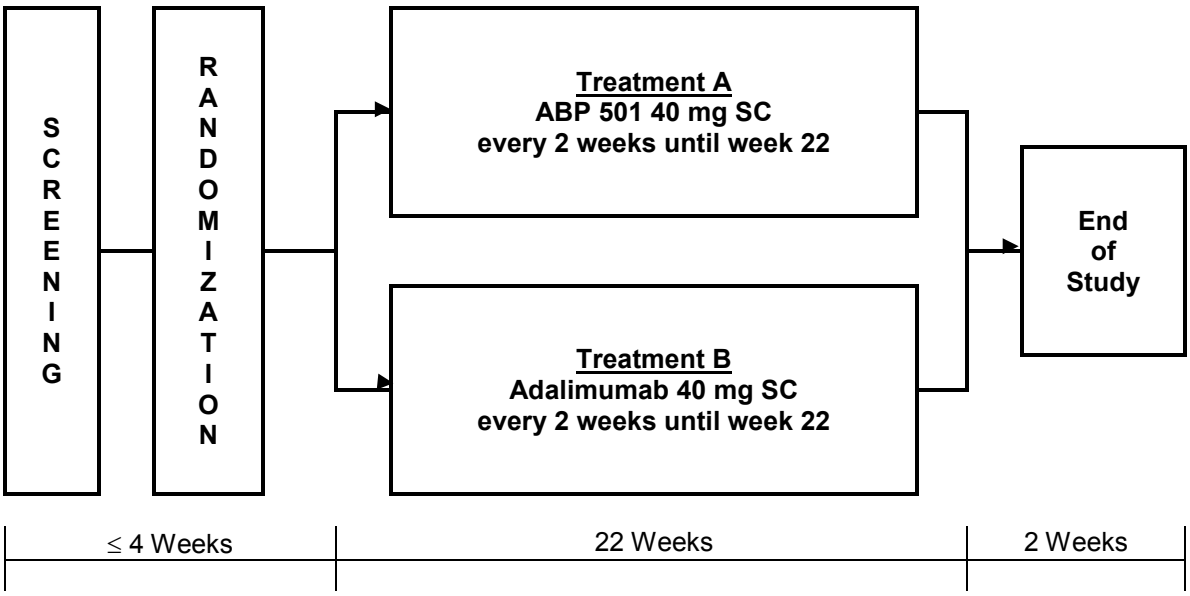
8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a randomized, double-blind, active-controlled study in adult subjects with RA who have an inadequate response to methotrexate (MTX). Approximately 500 subjects (250 per treatment group) will be enrolled. The subjects will be randomized to receive either ABP 501 40 mg SC every 2 weeks or adalimumab 40 mg SC every 2 weeks in a blinded fashion until week 22. The assessment of the primary endpoint will be at week 24. Figure 1 is a summary of the study design.

[redacted]

Figure 1. Study Diagram



SC = subcutaneous

[redacted]

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 ICF before any study specific procedures
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 3 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. Positive rheumatoid factor or anti-cyclic citrullinated peptide (CCP) at screening
7. Subjects must be taking MTX for ≥ 12 consecutive weeks and on a stable dose of 7.5 to 25 mg/week for ≥ 8 weeks prior to receiving the study drug and be willing to remain on stable dose throughout the study
8. For subjects on nonsteroidal anti-inflammatory drugs (NSAIDs) or low potency analgesics such as tramadol, soma compounds, fioricet, fiorinal, dose should be stable for ≥ 2 weeks prior to screening
9. For subjects on oral corticosteroids, (≤ 10 mg prednisone or equivalent), 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 adequate prophylaxis initiation prior to receiving study drug in accordance with local recommendations
    - 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

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[16] 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 28 days prior to first dose of IP

- a serious infection, defined as requiring hospitalization or intravenous (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 C virus (HCV) antibody positivity at screening
8. Uncontrolled, clinically significant systemic disease such as diabetes mellitus, cardiovascular disease including moderate to severe heart failure (New York Heart Association [NYHA] class III/IV), renal disease, liver disease or hypertension
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 disease-modifying antirheumatic drugs (DMARDs) 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 IP initiation
    - 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
- Janus kinase (JAK) inhibitor eg, tofacitinib excluded within 28 days prior to first dose of IP

16. Prior use of 2 or more biologic therapies for RA

17. 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 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
    - Rituximab within 9 months prior to IP along with evidence of B cell recovery
18. Live vaccines within 3 months prior to the first dose of IP
19. Chronic use of high potency narcotic analgesics such as morphine or morphine-derived medications, fentanyl, codeine, hydromorphone, levorphanol, meperidine, methadone, oxycodone or hydrocodone at screening
20. Subjects that have taken any of the above agents in the past must have recovered from all drug-related AEs
21. Previous receipt of Humira® (adalimumab) or a biosimilar of adalimumab
22. 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 drug study(s) including vaccines, or subject is receiving other investigational agent(s)

General

23. For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 5 months after the last dose of investigational product
24. 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 5 months after the last dose of study drug. Male subjects must agree not to donate sperm during study and for 5 months following treatment with test article or until the scheduled end of the study (whichever is longer)
25. Known sensitivity to mammalian cell derived drug products or hypersensitivity to the active substance or to any of the excipients of ABP 501 or adalimumab
26. 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
27. Any disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures
28. Active substance abuse (within 24 weeks of screening)

8.4.3 Withdrawal and Replacement of Subjects

8.4.3.1 Criteria for Subject Withdrawal

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

[redacted]

[redacted]

[redacted] Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The Investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

Reasons for removal from protocol-required investigational product(s) or procedural assessments might include:

- subject request to end investigational product(s) 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

[redacted]

[redacted]

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

[redacted]

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

- Treatment A: ABP 501 40 mg SC
- Treatment B: adalimumab 40 mg SC

In both treatment groups, doses will be administered on day 1 and every 2 weeks (± 3 days) until week 22 by site staff.

No dose reductions or changes are allowed.

ABP 501/adalimumab will be administered after all other procedures are completed for each visit. If the subject presents with an infection at the dosing visit(s), the administration of investigational product may be delayed (up to 3 days). If a dose is delayed or missed for any reason, subsequent doses should be administered at the original scheduled dosing dates in relation to the first dose date.

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

[redacted]

[redacted]

8.5.6 Dose Adjustments and Dose Escalation

No dose adjustments or escalations are planned for this study.

[redacted]

[redacted]

8.6 Efficacy and Safety Variables

8.6.1 Efficacy and Safety Measurements Assessed

[redacted]

8.6.1.1 Efficacy Measurements

8.6.1.1.1 Primary Efficacy Criterion

The primary efficacy endpoint is risk ratio (RR) of ACR20 (20% improvement in ACR core set measurements) at week 24. 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 17.3), as well as for 3 out of the following 5 additional parameters:

- Subject's Global Health Assessment (on a 0 to 10 horizontal scale; Section 17.4)
- Investigator's Global Health Assessment (on a 0 to 10 horizontal scale; Section 17.4)
- Subject's assessment of pain (on a 100-mm visual analogue scale (VAS); Section 17.4
- Health Assessment Questionnaire – Disability Index (HAQ-DI; Section 17.4)
- CRP

8.6.1.1.2 Secondary Efficacy Criteria

Secondary efficacy endpoints include change from baseline of DAS28-CRP at each time point (weeks 2, 4, 8, 12, 18, and 24), RR of ACR20 responses at weeks 2 and 8, and RR of ACR50 and ACR70 responses at week 24.

[redacted]

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 0 to 10 horizontal 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.[16]

ACR50/70

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

8.6.1.2 Safety Measurements

Safety endpoints include the following:

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

8.6.1.3 Exploratory Measurements

Exploratory endpoints include the following:

- [redacted].
- the trough serum concentration for ABP 501 compared with adalimumab on weeks 2, 4, 12, 24 and end of study.

[redacted]

9 STUDY EVALUATIONS BY VISIT

After signing the informed consent, there are 15 visits, including a screening visit, a day 1 visit (day of first treatment), treatment visits every 2 weeks until week 22, a disease assessment visit at week 24, and a follow-up safety visit at week 26.

9.1 Screening

After subjects have provided informed consent, the following assessments/procedures will be performed:

- targeted medical history, including history of all prior treatments for RA within the past 3 years and any prior biologic therapy for RA
- physical examination, including evaluation of body systems 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 screening is acceptable)
- screening joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- tuberculosis testing (PPD or Quantiferon test)
- clinical laboratory testing, including serology, serum chemistry, hematology, and CRP
- collection of samples for urinalysis
- serum pregnancy test for women of childbearing potential

[redacted]

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 therapy 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 prestudy MTX regimen during the screening period.

[redacted]

[redacted]

9.2 Baseline (Day 1, first day of treatment)

Day 1 will be defined as the first day of treatment. After subjects are confirmed to meet the entry criteria (Section 8.4), Investigator (or designee) will contact the IXRS to randomize the subject centrally to receive either ABP 501 or adalimumab. The following assessments/procedures will be performed before treatment:

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

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 501 or adalimumab, 40 mg, will be administered as an SC injection in a double-blinded fashion; IP will be assigned based on box numbers provided by the IXRS. The injection should not be given into areas where the skin is tender, bruised, red, or hard. 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. Subjects will continue on their stable MTX regimen.

The subjects will assess their level of injection pain using a 100-mm VAS, immediately (eg, within 5 minutes) following the injection.

9.3 Week 2 (± 3 days)

Two weeks (± 3 days) after the first treatment, the subject will return to the study center for treatment. The following assessments/procedures will be performed before treatment at week 2:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI,

Section 17.4); subjective assessments will be the first assessments performed at the visit
- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- clinical laboratory testing, including hematology and CRP
- collection of predose 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. SAEs will be reported as outlined in Section 11.2.2. After completion of pretreatment procedures, ABP 501 or adalimumab, 40 mg, will be administered as an SC injection in a double-blinded fashion; IP will be assigned based on box numbers provided by the IXRS. Injection sites should be rotated, and the injection should not be given into areas where the skin is tender, bruised, red, or hard.

9.4 Week 4 (± 3 days)

Four weeks (± 3 days) after the first treatment, the subject will return to the study center for treatment. The following assessments/procedures will be performed before treatment at week 4:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI, Section 17.4); subjective assessments will be the first assessments performed at the visit
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- clinical laboratory testing, including serum chemistry, hematology, urine pregnancy (for women of childbearing potential), and CRP
- collection of predose PK samples and antidrug antibody 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. After completion of pretreatment procedures, ABP 501 or adalimumab, 40 mg, will be administered as an SC injection in a double-blinded fashion; IP will be assigned based on box numbers provided by the IXRS. Injection sites should be rotated, and the injection should not be given into areas where the skin is tender, bruised, red, or hard.

The subjects will assess their level of injection pain using a 100-mm VAS, immediately (eg, within 5 minutes) following the injection.

9.5 Weeks 6, 8, and 10 (± 3 days)

Six weeks (± 3 days), 8 weeks (± 3 days), and 10 weeks (± 3 days) after the first treatment, the subject will return to the study center for treatment. The following assessments/procedures will be performed before treatment at weeks 6, 8, and 10:

- at week 8 only - subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI, Section 17.4); subjective assessments will be the first assessments performed at the visit
- at week 8 only - joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- at week 8 only - clinical laboratory testing, including hematology, urine pregnancy (for women of childbearing potential), and CRP

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. After completion of pretreatment procedures, ABP 501 or adalimumab, 40 mg, will be administered as an SC injection in a double-blinded fashion; IP will be assigned based on box numbers provided by the IXRS. Injection sites should be rotated, and the injection should not be given into areas where the skin is tender, bruised, red, or hard.

At week 8 only, the subjects will assess their level of injection pain using a 100-mm VAS, immediately (eg, within 5 minutes) following the injection.

9.6 Week 12 (± 3 days)

Twelve weeks (± 3 days) after the first treatment, the subject will return to the study center for treatment. The following assessments/procedures will be performed before treatment at week 12:

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

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 501 or adalimumab, 40 mg, will be administered as an SC injection in a double-blinded fashion; IP will be assigned based on box numbers provided by the IXRS. Injection sites should be rotated, and the injection should not be given into areas where the skin is tender, bruised, red, or hard.

The subjects will assess their level of injection pain using a 100-mm VAS, immediately (eg, within 5 minutes) following the injection.

9.7 Weeks 14, 16, 18, 20, and 22 (± 3 days)

Fourteen weeks (± 3 days), 16 weeks (± 3 days), 18 weeks (± 3 days), 20 weeks (± 3 days), and 22 weeks (± 3 days) after the first treatment, the subject will return to the study center for treatment. The following assessments/procedures will be performed before treatment at weeks 14, 16, 18, 20, and 22:

- At weeks 16 and 20 only - clinical laboratory testing, including hematology and urine pregnancy (for women of childbearing potential)
- at week 18 only - subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI; Section 17.4); subjective assessments will be the first assessments performed at the visit
- at week 18 only - joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- at weeks 18 only - clinical laboratory testing CRP, only

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 501 or adalimumab, 40 mg, will be administered as an SC injection in a double-blinded fashion; IP will be assigned based on box numbers provided by the IXRS. Injection sites should be rotated, and the injection should not be given into areas where the skin is tender, bruised, red, or hard.

9.8 Week 24 (± 3 days)

Twenty-four weeks (± 3 days) after the first treatment, the subject will return to the study center. The following assessments/procedures will be performed before treatment at week 24:

- subjective assessments (Subject's Global Health Assessment, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI; Section 17.4); subjective assessments will be the first assessments performed at the visit

- physical examination, including evaluation of body systems
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- joint assessments (ACR and DAS tender/swollen joint counts; Section 17.3)
- clinical laboratory testing (CRP and 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.

9.9 Week 26 (end of study)

Twenty-six weeks (± 5 days) after the first treatment, the subject will return to the study center for a follow-up safety assessment. The following assessments/procedures will be performed at week 26/End of Study:

- physical examination, including evaluation of body systems
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- clinical laboratory testing, including serum chemistry, hematology, and urine pregnancy (for women of childbearing potential)
- collection of PK samples and antidrug antibody samples
- collection of samples for urinalysis
- [redacted]

All AEs, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF through 28 days after the last treatment with ABP 501/ adalimumab. SAEs will be reported as outlined in Section 11.2.2. Any SAEs ongoing at week 26 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, Investigator's Global Health Assessment, subject's assessment of pain, and HAQ-DI (Section 17.4) will be completed; these assessments should be the first assessments performed at the visits 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 66/68 joint set for ACR and the 28 joint count for DAS. All joint assessments will be performed by an experienced joint evaluator. The evaluator cannot be the treating physician and cannot interact with the subject on the study beyond the assessment of joints. The evaluator should not discuss the subject's clinical status nor should the evaluator have access to subject medical records or eCRFs including prior joint assessments. The same evaluator should perform joint assessments across all time points for a subject where possible.

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

The 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.

[redacted]

10.3 Pregnancy Test

Pregnancy will be determined by evaluation of 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.

10.4 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.

10.5 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, the 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.

10.6 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, QT, and corrected QT (QTc) intervals (msec) 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.

10.7 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.

10.8 Chest Radiography

Chest radiography will include anterior/posterior or posterior/anterior and lateral views. Historical films obtained or formal reports signed off by a radiologist in the 3 months prior to screening are acceptable.

10.9 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 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 platelet count.

Clinical chemistry: Sodium, potassium, urea, creatinine, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, gamma glutamyl transferase, nonfasting glucose. 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 baseline visit and onward will be blinded 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 [redacted]

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

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

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.

10.10 Blood Samples for Pharmacokinetic Analysis

During treatment, a series of serum samples will be taken according to the study flow chart. The exact times of blood sampling will be recorded.

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

[redacted]

12 [redacted] STATISTICAL ANALYSIS

[redacted]

12.1 [redacted]

[redacted]

12.2 Sample Size Estimation

Approximately 500 subjects will be randomized in a 1:1 ratio to receive ABP 501 or adalimumab. The sample size is chosen to achieve > 90% power to demonstrate equivalence at a 2-sided significance level of 0.05 on the primary efficacy endpoint RR of ACR20 at week 24 (assuming an expected ACR20 response for both ABP 501 and adalimumab of 63% at week 24) between ABP 501 and adalimumab, with an equivalence margin of (0.738, 1/0.738) and assuming a 15% dropout by week 24. This planned sample size will also provide > 90% power to demonstrate equivalence at a 2-sided significance level of 0.05 for secondary endpoint, DAS28-CRP change from baseline (common standard deviation of 1.7 assumed for both ABP 501 and adalimumab) between ABP 501 and adalimumab, with an equivalence margin of ± 0.6 (ref. 16). Randomization will be stratified by geographic region and prior biologic use for RA (with prior biologic use capped at 40% of the study population).

12.3 Statistical Analysis Plan

An 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 and prior biologic use for RA (with prior biologic use capped at 40% of the study population).

12.5 Analysis Populations

The primary analysis 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. For safety endpoints, the Safety Analysis Set will be analyzed based on the actual treatment received.

12.5.1 Full Analysis Population

The FAS includes all subjects randomized in the study, with treatment assignment based on actual treatment received.

12.5.2 Per-protocol Population

The per-protocol analysis set is a subset of the FAS which includes subjects who have completed the treatment period and did not experience a protocol deviation that affects their evaluation for primary objective of the study. The protocol deviations that affect evaluation of primary objective will be determined based on a blinded data review prior to database lock.

12.5.3 Safety Analysis Population

The safety analysis set includes all randomized subjects who received at least 1 dose of investigational product, with treatment assignment based on actual treatment received.

12.6 Statistical Methods

Clinical equivalence for the primary endpoint, RR of ACR20 at week 24, will be evaluated by comparing the 2-sided 90% CI of the RR of ABP 501 and adalimumab with an equivalence margin of (0.738, 1/0.738). The 90% CI for risk ratio will be estimated using generalized linear model (specifically, a log-binomial regression model) with relevant baseline values and stratification factors as covariates.

The primarily analysis will be performed at the end of study (end of trial) after all subjects have completed the week 24 disease assessments and the follow-up safety assessment at week 26 or terminated early.

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 with observations. Safety endpoints will be summarized descriptively as well. Subgroup analyses (by age, race, sex, and stratification factors as appropriate) will be presented if deemed necessary.

12.6.1 Missing Data

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

12.6.2 Demographic and Baseline Data

The following demographics 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 factors
- subject disposition (including number of subjects who were screened, randomized, treated with ABP 501/adalimumab, completed treatment, discontinued treatment with reason of discontinuation, completed study, and discontinued study with reason of 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 Efficacy

All efficacy analysis will be performed using the FAS based on subject's actual treatment received. As a sensitivity analysis, the equivalence test on primary endpoint, RR of ACR20 at week 24, will be also performed using the per-protocol analysis set. Analyses will assess the hypothesis that there are no clinically meaningful differences between ABP 501 and adalimumab in RR of ACR20 at week 24. The hypothesis will be tested by comparing the 2-sided 90% CI of the RR of ACR20 between ABP 501 and adalimumab estimated using a log-binomial regression model (Section 12.6) with an equivalence margin of (0.738, 1/0.738).

Inferential analyses will only be performed for the primary endpoint. To evaluate treatment differences across DAS28 assessed time points, repeated-measures analysis will be utilized. 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 90% CIs will be constructed for change from baseline at each time point. Analyses of changes scores from baseline will include baseline values as a covariate.

Other endpoints, RR of ACR20 at weeks 2 and 8, and risk ratio of ACR50 and ACR70 at week 24 will be summarized descriptively by treatment. For binary variables, the 90% CI for risk ratio will be estimated using generalized linear model (specifically, a log-binomial regression model) adjusted for stratification factors and other relevant covariates (Section 12.6).

12.6.5 Pharmacokinetics

Serum ABP 501 and adalimumab concentrations will be summarized descriptively by treatment for each sampling time point.

12.6.6 Safety

All safety analyses will be performed using the safety analysis population based on subject's actual treatment received. Safety analysis will include analyses of AEs, clinical laboratory tests, vital signs, and antidrug antibodies.

12.6.6.1 Investigational Product Administration

For the investigational product (ABP 501 or adalimumab), summary statistics will be provided for the total number of doses and total duration of IP exposure throughout the treatment exposure period.

12.6.6.2 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 but on or within 28 days following the last dose of study treatment. 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 study drug. 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.

Adverse events of special interest (Section 11.3) will be listed and may be summarized separately.

12.6.6.3 Immunogenicity

The number and percentage of subjects developing antidrug antibodies and those developing neutralizing antibodies will be tabulated for each treatment.

[redacted]

12.6.6.5 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.

12.6.6.6 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.

12.6.7 Interim Analysis

No interim analyses are planned.

[redacted]

[redacted]

[redacted]

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 the protection of the subjects' interests. Amgen will not provide ABP 501 or adalimumab after termination of the trial or upon discontinuation of the study for the subject.

[redacted]

[redacted]

16 REFERENCE LIST

[redacted]

[redacted]

16. 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. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum. 1998 Oct;41(10):1845-50.

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