Statistical Analysis Plan

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Protocol No:	20140111
PRA Project Id:	AMG710RA-710RAX
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1.0 Approvals

Sponsor

Sponsor Name: Amgen Inc.

Representative/ Title: PPD / Clinical Research Medical Director, Amgen Inc.

Signature /Date: PPD 6-6-2018

Representative/ Title: PPD / Biostatistics Sr. Manager, Amgen Inc.

Signature /Date: PPD 06 Jun 2018

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Project Manager/Title: PPD /Project Director

Signature /Date: PPD 6 JUNE 2018

Biostatistician / Title (Owner): PPD / Senior Biostatistician

Signature /Date: PPD 6 JUNE 2018

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2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Amgen Inc. Protocol 20140111.

3.0 Scope

This plan is a living document that will be created during the trial start-up. SAP1 will be drafted within three months of final case report form (CRF) and maintained throughout the primary analysis of the trial. The Statistical Analysis Plan 2 will be finalized prior to database lock for the primary analysis. SAP1 and SAP2 will require sign off from the Project Manager and the sponsor.

The Statistical Analysis Plan outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, concomitant medications, adverse events handling, laboratory data, pharmacokinetics (PK) concentration data, anti-drug antibody (ADA) data and physical examinations

4.0 Introduction

This statistical analysis plan describes the statistical methods to be used during the reporting and analyses of data collected under Amgen Inc. Protocol 20140111.

This SAP should be read in conjunction with the study protocol and CRF. This version of the plan has been developed using the protocol dated 17MAR2017 and CRF 4.0 dated 18JUL2017. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The SAP is to be developed in two stages. The purpose is to “finalize” a SAP so that we can start programming earlier in the process. Versions of the SAP up to initial Amgen approval will be known as SAP1. Changes following approval of SAP1 will be tracked in the SAP Change Log and a final version of the SAP, known as SAP2, will be issued for Amgen’s approval prior to unblinding for the primary analysis.

5.0 Study Objectives

5.1 Primary Objective

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

5.2 Secondary Objectives

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

6.0 Study Design

This is a randomized, double-blinded, active-controlled study in adult subjects with moderate to severe rheumatoid arthritis (RA) who have inadequate response to methotrexate (MTX). Approximately 550 subjects (275 per treatment group) will be enrolled. Randomization will be stratified based on prior biologic use for RA (yes vs. no) and geographic region (Asia Pacific, Europe, North America).

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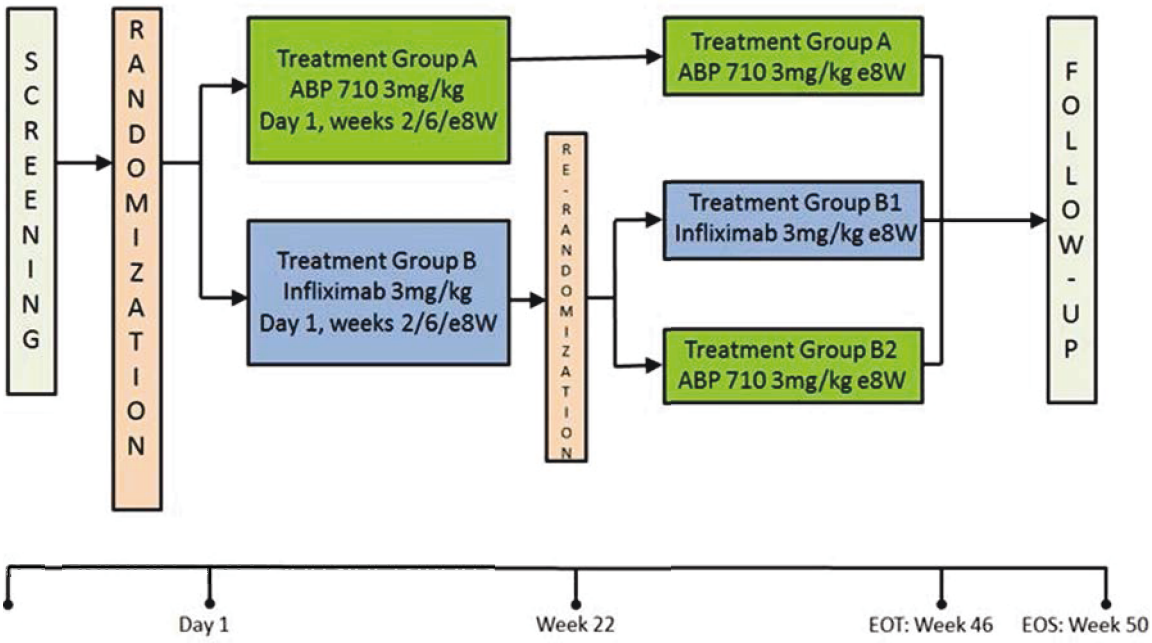
The subjects will be randomized in a 1:1 ratio to receive either ABP 710 (treatment group A) 3 mg/kg infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter, or infliximab (treatment group B) 3 mg/kg infusion on day 1, at weeks 2 and 6, and every 8 weeks thereafter until week 22. The primary endpoints will be evaluated at week 22.

At week 22, subjects initially randomized to the infliximab group (treatment group B) will be re-randomized in a 1:1 ratio to either continue receiving infliximab infusion every 8 weeks (treatment group B1), or switch to ABP 710 (treatment group B2) every 8 weeks. Subjects initially randomized to ABP 710 (treatment group A) will continue on the same treatment. Re-randomization will be managed to ensure that the blind is maintained. Subjects will continue on treatment until week 46, when the subjects will receive the last dose of investigational product (IP). Subjects will be considered study completers when they finish the week 50 end-of-study assessments. An independent data monitoring committee will evaluate the safety data throughout the study. Figure 1 below is a summary of the study design.

Figure1. Study Diagram



t a 0.05 significance level on the primary endpoint, response difference (RD) of at least 20% improvement in ACR core set measurements (ACR20) at week 22 between ABP 710 and infliximab, with an equivalence margin of (-15%, 15%), assuming an expected ACR20 rate for both ABP 710 and infliximab of 52% at week 22. This sample size will also achieve approximately 85% power to demonstrate equivalence on the RD of ACR20 between ABP 710 and infliximab with an equivalence margin of (-12%, 15%) at a significance level of 0.05 at week 22.

6.2 Randomization

At the initial randomization, approximately 550 subjects will be randomized in a 1:1 ratio to receive either ABP 710 (treatment group A) or infliximab (treatment group B) via an Interactive Voice or Web Response System (IXRS), stratified by geographic region and prior biologic use for RA (with prior biologic use capped at 30% of the study population).

Re-randomization will occur at week 22 such that subjects initially randomized to ABP 710 (treatment group A) will continue on the same treatment and subjects initially randomized to infliximab (treatment group B) will be re-randomized (1:1) to receive either infliximab (treatment group B1) or ABP 710

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(treatment group B2) stratified by geographic region and prior biologic use for RA. Treatment assignments will be managed to ensure that the blind is maintained. Subjects unable to complete the week 22 visit within the allowed visit window will not be re-randomized and will be discontinued from the study.

Assignment to the treatment arms will be based on a computer-generated randomization schedule created before the start of the study. The randomization schedule will be prepared by a statistician not otherwise involved the conduct of the study.

A third party vendor, ALMAC Clinical Technologies, will be responsible for generating the randomization and re-randomization schemes and managing the randomization activities of this study.

7.0 Study Variables and Covariates

7.1 Primary Variable

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

7.2 Secondary Variables

7.2.1 Efficacy

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

7.2.2 Safety

- Treatment-emergent adverse events, serious adverse events, and adverse events of special interest
- Clinically significant changes in laboratory values and vital signs
- Incidence of anti-drug antibodies

7.3 Exploratory Variable

- CCI [redacted]

7.4 Predetermined Covariates and Prognostic Factors

Unless stated otherwise, the following stratification factors will be adjusted as covariates in the model or be used to examine treatment effect in subgroups:

- Geographic region (Asia Pacific, Europe, North America).
- Prior biologic use for RA (Yes vs. No).

In addition, the following covariates may be used for further exploration in subgroups or as covariates:

- Age (< 65 years vs. ≥ 65 years),
- Race (White vs. Non-White),
- Gender,

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- Disease Duration (< 5 years vs. ≥ 5 years),
- Neutralizing ADA status (defined as a negative when neutralizing ADA is negative at all post baseline visits through week 22 and negative or no result at baseline, vs. positive when neutralizing ADA is positive at any post baseline visit through week 22 and negative or no result at baseline),
- Binding ADA status (defined as a negative when binding ADA is negative at all post baseline visits through week 22 and negative or no result at baseline, vs. positive when binding ADA is positive at any post baseline visit through week 22 and negative or no result at baseline)

Covariate values may be discordant if collected via eCRF and IXRS. Analyses that are intended to evaluate the treatment effect and include stratification variables as covariates in the model will be based on the eCRF stratification values, regardless of the subject's IXRS stratification values, to provide unbiased estimates of the effects of treatment and stratification variables without loss of efficiency (Ke et al, 2017).

For subgroup analyses where the subgroup factor is a stratification variable, an analysis similar to the primary analysis (except the inclusion of the subgroup factor) should be done for each subgroup defined by the eCRF values of the subgroup factor.

8.0 Definitions

8.1 General

Actual Treatment Received

The actual treatment received is the IP treatment the subject actually received, regardless of what the subject was randomized to. In cases where a subject received both ABP 710 and Infliximab through the first 22 weeks, the actual treatment received will be based on the majority of the IP treatment the subject received during the first 22 weeks. Similarly, in the weeks post week 22, if a subject received both ABP 710 and Infliximab, the actual treatment received will be based on the majority of the IP treatment the subject received post week 22. In the case of a tie, the actual treatment received will be assigned to ABP 710.

Baseline

Unless stated otherwise, for the endpoint of interest, the baseline is defined as the last non-missing assessment taken prior to the first dose of study IP. In cases where baseline assessments are taken on the same day as the first dose of IP, and either no times are reported or the IP and assessment times are the same, it will be assumed that these assessments are taken prior to IP being administered. For subjects who are randomized but not dosed after the randomization, the baseline is defined as the last non-missing assessment prior to or on the date of randomization.

Change from Baseline

Change from baseline is defined as (value at post-baseline visit – value at baseline).

Concomitant and Prior Medication

Prior medications are defined as medications with a stop date prior to first dose of study IP. Concomitant medications are defined as any medications ongoing at the start of IP treatment or with a start date on or after the first dose date.

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Total IP Exposure Duration

The total IP exposure duration in days through entire study is derived as:

(the minimum of (the last dose date +28, end of study date) - first dose date +1);

The total IP exposure duration in days through week 22 is calculated as:

- For subjects who were not re-randomized or were re-randomized but not dosed:
  (the minimum of (the last dose date prior to week 22 Re-randomization+28, end of study date)
  - first dose date + 1);

- For subjects who were dosed after re-randomization:
  (the first dose date after week 22 Re-randomization - 1) - first dose date + 1;

The total IP exposure duration in days post week 22 re-randomization is calculated as:

(the minimum of (the last dose date after week 22 Re-randomization+28, end of study date)
- first dose date after week 22 Re-randomization + 1)

End of Study Date

The end of study (EOS) date is the date recorded on the End of Study page of the eCRF for a randomized subject.

First Dose Date

The date on which a subject is administered the first dose of study IP. This date is also referred to as Study Day 1.

Last Dose Date

The date on which a subject is administered the last dose of study investigational product.

Last observation carried forward (LOCF)

A method of imputation where missing post-baseline data will be imputed by carrying forward the last non-missing post-baseline value for that endpoint. Baseline values will not be carried forward.

Non Responder Imputation

A method of imputation where missing post-baseline binary ACR response data will be imputed as non-responder, that is, not met ACR criteria, regardless of the reasons for missing data.

Percent Improvement from Baseline

For endpoints where higher scores indicate greater severity, the percent improvement from baseline is: (value at baseline – value at post-baseline visit) X 100 / (value at baseline).

For endpoints where lower scores indicate greater severity, the percent improvement from baseline is: (value at post-baseline visit – value at baseline) X 100 / (value at baseline).

If the baseline value is 0 and the post-baseline value is also 0, then the percent improvement from baseline is set to 0. If the baseline value is 0 and the post-baseline value is non-zero, then the percent improvement from baseline is set to “missing” (or ‘.’).

RA Disease Duration

The RA disease duration is the number of years from the date of diagnosis of RA to the date of randomization, which will be derived based on the table below. No imputation will be done for disease diagnosis date, but to avoid disease duration of zero, 1 month (or 1/12 years) may be added.

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Table 1. Calculation of the Duration of RA

Observed portion	Missing portion	Formula to Calculate Duration
Year, Month, Day		(Date of Randomization – Date of RA Diagnosis + 1)/365.25
Year, Month	Day	[Year(Date of Randomization)-Year(Date of RA Diagnosis)]+ [Month(Date of Randomization)-Month(Date of RA Diagnosis)]/12*
Year	Month, Day	[Year(Date of Randomization)-Year(Date of RA Diagnosis)] *

*if the duration equals 0, add 1 month or 1/12 years.

Re-Randomization

Re-randomization is defined at week 22 when subjects initially randomized to infliximab (treatment group B) are re-randomized (1:1) to receive either infliximab (treatment group B1) or ABP 710 (treatment group B2) via the IXRS system. Subjects initially randomized to ABP 710 (treatment group A) will continue on the same treatment. Re-randomization will be managed to ensure that the blind is maintained.

Study Day 1

The first day of investigational product administrated. For subjects who are randomized but not dosed after randomization, study day 1 is defined as the date of randomization.

Study Day

Study day is defined as the number of days from Study Day 1.

- Before Study Day 1: Study Day = (Date of Interest – Date of Study Day 1)
- On or After Study Day 1: Study Day = (Date of Interest – Date of Study Day 1) + 1

Therefore the day prior to Study Day 1 is -1.

Study Randomization

Study randomization is defined as when subject initially receives a random treatment allocation via the IXRS system.

Study Period

- Through week 22:

Defined as the first 22 weeks of the study from initial randomization to the 1st dose post week 22 for re-randomized subjects and to end of study for subjects not re-randomized. Subjects are classified according to their initial treatment: ABP 710 or Infliximab.

- Post Week 22

Defined as the time period post subjects' re-randomization starting from the 1st dose post week 22. Subjects are classified according to their full treatment arm: ABP 710/ABP 710, Infliximab/Infliximab, or Infliximab/ABP 710.

- Entire Study

Defined as the time period throughout the study from initial randomization to the end of study. Subjects are classified according to their full treatment arm: Non Re-randomized (ABP 710 and Infliximab) and Re-randomized (ABP 710/ABP 710, Infliximab/Infliximab, or Infliximab/ABP 710).

Study Visit

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study analysis visit as follows. Note that the following analytical visit windows for

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statistical analysis are different from the ones defined in Section 18.0 of the IXRS Business Requirement. The actual visit date is allowed to fall within specified interval of the target day; this avoids the existence of gaps between weeks.

For efficacy, safety (including laboratory[a]), PK:

Study Analysis Visit	Target Day	Study Day	Interval (days)
Baseline[b]	1	≤1	NA
Week 2	15	2 - 29	28
Week 6	43	30 – 71	42
Week 14	99	72 – 127	56
Week 22	155	128 – 183	56
Week 30	211	184 – 225	42
Week 34	239	226 - 253	28
Week 38	267	254 - 295	42
Week 46	323	296 - 337	42
Week 50	351	≥338	NA

[a] Laboratory parameters will only be included at the visits where it is scheduled for assessment in the output tables.

[b] If a subject has laboratory measurements on the same day as the first dose date but at a time after the first dose of IP is administered, the lab measurements will not be defined as baseline, but as week 2 measurements.

If more than one actual visit (including the unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the latest visit with non-missing data will be considered for analysis.

The rules above for selecting a visit from multiple ones within the same visit window are not applicable to retest values of lab data. If the lab measurement is a retest, the retest value will be chosen.

8.2 Efficacy

ACR20/50/70

The ACR composite score evaluates clinical improvement relative to an initial assessment for clinical trials in subjects with RA. The response difference of ACR20 will be considered the primary efficacy endpoint of the study.

The ACR20 response is defined as at least 20% improvement compared to baseline for both swollen and tender joint counts (66/68 joint counts), as well as for at least 3 out of the following 5 additional parameters:

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

Subjects with assessments meet the ACR20 response criteria described above will be classified as responders.

Secondary efficacy endpoints of ACR50 and ACR70 are defined in a similar fashion to ACR20 but require at least 50 and 70 percent improvement respectively.

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ACR/EULAR Remission

The ACR and the European League Against Rheumatism (EULAR) provide two definitions of remission in RA clinical trials as defined below.

Boolean-based definition:

At any time point, subject must satisfy all of the following:

Tender joint count ≤1†

Swollen joint count ≤1†

C-reactive protein ≤1 mg/dL

Subject's global health assessment ≤1 (on a 0–10 scale, SGH divided by 10)

Index-based definition:

At any time point, subject must have a

Simplified Disease Activity Index score (SDAI) of ≤3.3§

† For tender and swollen joint counts, use of a 28-joint count may miss actively involved joints, especially in the feet and ankles, and it is preferable to include feet and ankles also when evaluating remission.

§ **SDAI** is defined as the simple sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), subject's global health assessment (0–10 scale, SGH divided by 10), investigator's global health assessment (0–10 scale, IGH divided by 10), and C-reactive protein level (mg/dL).

Clinical Disease Activity Index (CDAI)

The CDAI is a clinical composite score for subjects with rheumatoid arthritis. The CDAI is defined as:

CDAI= TJC28 +SJC28 + SGH + IGH

Where TJC28 is the tender joint count of the 28 joints in the DAS, SJC28 is the swollen joint count of the 28 joints in the DAS, SGH is the subject's global health assessment score (on a 0 to 10 scale, SGH divided by 10), and IGH is the investigator's global health assessment (on a 0 to 10 scale, IGH divided by 10). A CDAI ≤ 2.8 is associated with remission, a CDAI > 2.8 and ≤ 10 is associated with low disease activity, a CDAI > 10 and ≤ 22 is associated with moderate disease activity, and a CDAI of > 22 is associated with high disease activity. In addition, a CDAI reduction of at least 6.5 represents moderate improvement.

DAS28-CRP

The DAS28-CRP is a composite measure of disease activity in RA. It is a continuous measure based on 28 DAS joints from the ACR, the Subject's Global Health Assessment score (as a score of 0 to 100), and CRP, as follows:

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

where TJC28 is the tender joint count of the 28 joints in the DAS, SJC28 is the swollen joint count of the 28 joints in the DAS, CRP is in mg/L, and SGH is the subject's global health Assessment in 0 to 100 scale.

If the CRP is at a non-detectable level, then replace it with the minimum undetectable level.

DAS28-CRP Remission

A subject will be considered to have achieved DAS28-CRP remission if the subject has a DAS28-CRP score less than 2.6.

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EULAR Response Based on DAS28-CRP

The definition of EULAR response based on DAS28-CRP is defined in Table below.

	DAS28-CRP improvement from Baseline		
Current DAS28-CRP	>1.2	0.6< improvement ≤1.2	≤0.6
≤ 3.2	Good response	Moderate response	No response
3.2<DAS28-CRP≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

Health Assessment Questionnaire – Disability Index (HAQ-DI)

The HAQ-DI score is defined as the average of the scores from eight sub-domains (dressing / grooming, arising, eating, walking, hygiene, reach, grip, and activities). The detailed score algorithm is described in Appendix 5.

Swollen Joint Count

The swollen joint count will be the number of joints that are assessed as swollen among the 66 joints specified in Section 17.3 of the protocol and the corresponding Joint Assessment CRF page. Method for handling missing joint assessments (including those due to artificial/fused joint or intra-articular corticosteroid injection) is defined in Appendix 4.

Tender Joint Count

The tender joint count will be the number of joints that are assessed as Pain/Tenderness among the 68 joints specified in Section 17.3 of the protocol and the corresponding Joint Assessment CRF page. Method for handling missing joint assessments (including those due to artificial/fused joint or intra-articular corticosteroid injection) is defined in Appendix 4.

8.3 Safety

AE Leading to Discontinuation from IP/Study

AEs leading to discontinuation from IP/study are those with an action taken with Investigational Medicinal Product of “Dose Discontinued” or those with other action taken of “Discontinued from Study”. If an AE leads to multiple actions taken with IP, only the last action will be captured in the eCRF.

Event of Interest (EOI)

An EOI is defined as a noteworthy event for a particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals (Council for International Organizations of Medical Sciences [CIOMS] VI, 2005). The EOIs for this study will include:

- Infusion reactions (Including Anaphylaxis, Hypersensitivity)
- Congestive heart failure
- Serious infections
- Opportunistic infections
- Malignancies
- Demyelinating disorders

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- Hepatitis B reaction
- Autoimmunity (Systemic lupus erythematosus (SLE) and Sarcoid)
- Hepatotoxicity
- Hematological reactions

AE preferred terms that are potentially representative of EOIs will be retrieved for review and analysis using the current version of MedDRA Queries (SMQs) at the time of the primary analysis if available. If no SMQ is available for use as a search tool for a given EOI (eg, infusion reactions), a customized search strategy developed at Amgen or medical review will be used. The detailed search strategy for the EOIs is provided in appendix 2.

Exposure Adjusted Incidence Rate

The exposure adjusted incidence rate is defined as the number of subjects with a particular AE divided by the total exposure-time among subjects in the respective treatment group at risk of an initial occurrence of the event. Specifically, exposure adjusted incidence rate will be calculated for each AE and treatment as follows:

Exposure Adjusted Incidence Rate = $\frac{n}{T} = \frac{n}{\sum t_i}$ where

n = the number of subjects with an AE event for the treatment group,
t_i = a subject's exposure time until the 1st AE event, or total exposure time if no AE event occurred, for the treatment group, and
T = the total exposure time for all subjects in the treatment group.

The subject's exposure time t_i is determined for all subjects whether they experience the AE or not, and is calculated within each treatment as follows:

- If the subject has 1 or more of the same AE event during a given treatment, t_i is the time from the first dose date of the respective treatment to the onset of the first AE event (date of first AE onset – first dose date for respective treatment + 1).
- If the subject had no AE event during a treatment, t_i is total exposure for that treatment (see definition of Total IP Exposure Duration for calculation)

Subject Incidence Rate

For adverse event summaries, subject incidence rate for a given event is defined as the number of subjects with at least 1 reported occurrence of the event divided by the number of subjects that received the given treatment or total subjects for the total column. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

Treatment-emergent Adverse Event

A treatment-emergent AE (TEAE) is defined as an AE that begins or increases in severity or frequency on or after the first study IP administration through EOS. If the AE starts on the same day as the first dose of IP then the flag indicating whether the AE started prior to the first dose on the adverse event CRF page will be used.

Treatment-related Adverse Event

Treatment-related AE is defined as an event which answers the question "is there a reasonable possibility that the event may have been caused by the Investigational Medicinal Product" as yes.

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9.0 Analysis Sets

The primary analysis will be performed using the intention-to-treat analysis set (ITT) based on the randomized treatment. The per-protocol (PP) analysis set will be used for sensitivity analyses of the key efficacy endpoints based on the actual treatment received. For safety endpoints, the Safety Analysis Set will be analyzed based on the actual treatment received.

9.1 Intention-to-Treat

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

9.2 Per Protocol

The per-protocol analysis set includes all subjects randomized in the study who have completed the specified treatment period, and did not experience a protocol deviation that affected their evaluation for the primary objective of the study. Analyses will be based on actual treatment received. Per-protocol analysis sets will be determined for the data through week 22 (PP22). The protocol deviations that affect evaluation of the primary objective will be determined based on a blinded data review prior to database lock for the primary analysis and final analysis.

9.3 Safety

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

10.0 Interim Analyses

No interim analyses are planned for this study.

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

The DMC will review unblinded safety data at regular intervals, as outlined in the DMC charter (approximately twice yearly; the start date will depend on subject accrual rates).

In addition, the DMC will communicate major safety concerns and recommendations regarding study modification or termination to Amgen management at any time during the conduct of the study.

Details regarding the DMC will be provided in the DMC charter and DMC analysis plan.

11.0 Data Review

11.1 Data Handling and Transfer

Data will be entered and exported as SAS® version 9.4 or higher datasets. Converted datasets will be created using SAS® and following standard Clinical Data Interchange Standards Consortium Standard Data Tabulation Model (CDISC SDTM, version 1.4, Implementation Guide version v3.2) conventions. Analysis datasets will be created using SAS® and following CDISC Analysis Data Model (ADaM, version 2.1, Implementation Guide 1.1) standards.

Medical history and AEs will be coded using the current version of MedDRA at the time of the primary analysis to assign a system organ class (SOC) and preferred term (PT) to each event. Adverse events and abnormal laboratory results considered as AEs are assigned a toxicity grade according to National Cancer Institute (NCI-US) Common Terminology Criteria for Adverse Events (CTCAE). Prior and

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concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary (WHO-DD) at the time of the primary analysis.

Additional details can be found in the PRA Data Management Plan and the Data Quality Plan for this study.

11.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures and listings (TFL) provides additional data screening as described below.

Review of a dry run of TFLs and a post-freeze TFL run on the frozen database allow for further data screening prior to database lock. The dry run will be discussed with Amgen in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and Amgen Data Management must approve database lock.

12.0 Statistical Methods

All statistical analyses will be performed using SAS® (Version 9.4 or higher).

The primary analysis (PA) will be performed after all subjects have completed their week 34 visit (or early terminated from the study prior to week 34). The data cut will happen when all subjects complete the week 34 visit or withdraw. All data collected by the time of data cut will be included in the primary analysis. An independent unblinded team who are not involved in the operations of the study after PA database lock will perform the PA. The final statistical analysis (FA) will be performed at the end of study after all subjects have completed their end of study visit (or early terminated from the study).

Unless otherwise specified, descriptive data summaries will be tabulated by treatment for all endpoints. Categorical data will be summarized using number of subjects (n), frequency and percentages of subjects falling into each category, with the denominator for percentages being the number of subjects in the study population for each treatment group, unless otherwise noted. Percentages will be rounded to one decimal place except for 100%, which will have no decimal place.

All continuous variables will be summarized using mean, standard deviation, median, minimum, maximum, 25th percentile (Q1), 75th percentile (Q3), and number of subjects with observations. The mean, median, Q1, and Q3 will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

For any of the summaries that are to be done by visit, the derived analytical study visit as defined in section 5.1 will be used for analysis unless otherwise noted.

12.1 Subject Disposition

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

- Number of subjects randomized at the initial randomization (2 treatment groups) and re-randomization (3 treatment groups) will be tabulated by geographic region, country, and center based on all initial randomized and re-randomized subjects, respectively.
- Subject disposition at week 22 and at end of study (including number of subjects who were randomized, treated with ABP 710/infliximab before and after week 22, completed treatment, discontinued treatment with reason of discontinuation, completed study and discontinued study with reason of discontinuation).
- Number of subjects in each analysis population by initial treatment, and reasons for exclusion from the per protocol analysis set through week 22.
- Important protocol deviation

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- Randomization list of subjects and their actual versus randomized treatment group for all randomized and re-randomized subjects.

12.2 Important Protocol Deviations

Per PRA processes, important protocol deviations (IPD) data will be entered into our Clinical Trials Management System (CTMS). The study team and Amgen will conduct on-going blinded reviews of the deviation data from CTMS. The per-protocol analysis set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock for the primary analysis and again prior to database lock for the final analysis of the entire study.

Based on the protocol deviation (PD) data entered into CTMS, a summary of incidence of IPDs will be tabulated using number and percentage of subjects by deviation type and initial randomized treatment through week 22 and by initial/re-randomized treatment through entire study. In addition, a summary of incidence of any eligibility related PDs (regardless of important or not important) will be tabulated using number and percentage of subjects by deviation type and initial randomized treatment. A listing of subjects with IPDs will be provided (with a flag indicating whether the deviation leads to exclusion from the per protocol analysis sets). A listing of subjects with eligibility criteria deviations will also be provided.

12.3 Treatments

12.3.1 Extent of Study Drug Exposure

For the IP (ABP 710 or infliximab), summary statistics will be provided for the total number of doses administered, total dose received, total weight-adjusted dose received, and total duration of IP exposure by initial treatment through week 22 (exclusive), by initial/re-randomized treatment from week 22 (inclusive) through the end of the study, and by initial/re-randomized treatment through entire study (from day 1 through the end of the study). An IP administration summary will also be provided by the reported visit for each dosing instance with number and percentage of subjects receiving a full or partial dose and dose delays/not administered with the associated reasons from day 1 until week 22 (exclusive) and by initial/re-randomized treatment from week 22 (inclusive) through the end of the study and for the entire study period. The percentages for the IP administration summary will be based on the number of subjects with the given visit. The summary will be performed using the Safety Analysis Set according to the actual treatment received.

Total weight-adjusted dose received (mg/kg) =total dose received (mg)/weight (kg)

A subject listing of each administered lot number(s) for IP and a listing of unique manufacturing lot numbers used in the study will be provided.

12.3.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the latest available World Health Organization-Drug Dictionary (WHO-DD) and will be summarized by preferred name. The prior medications will be summarized by initial treatment and initial/re-randomized treatment received. The concomitant medications will be summarized from first dose of IP through week 22 by initial treatment received and from first dose through the entire study by initial/re-randomized treatment received. The analysis will be performed using the Safety Analysis Set according to the actual treatment received.

The number and percentage of subjects using each medication will be displayed by treatment arm. Subjects taking more than one medication in the same preferred name will be counted once for the number of subjects taking that preferred name.

12.4 Demographic and Baseline Characteristics

The following demographics and baseline characteristics will be summarized for the ITT analysis set and PP22 analysis set by the initial treatment and the ITT analysis set by initial/re-randomized treatment:

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- age (in years, at time of signing informed consent) and age category (< 65 vs ≥ 65),
- race,
- sex,
- ethnicity,
- height,
- weight,
- body mass index (BMI),
- geographic region,
- prior biologic use for RA,
- duration of RA (in years) and duration of RA category (< 5 years vs ≥ 5 years),
- DAS28-CRP,
- swollen joint count,
- tender joint count,
- subject's global health assessment,
- investigator's global health assessment,
- subject's assessment of disease-related pain,
- HAQ-DI,
- CRP,
- use of oral corticosteroid at baseline (Yes/No)
- use of non-steroidal anti-inflammatory drug (NSAID) at baseline (Yes/No)
- rheumatoid factor (RF) status at screening (Negative/Positive)
- anti-cyclic citrullinated peptide (CCP) status at screening (Negative/Positive)
- rheumatoid factor and anti-cyclic citrullinated peptide status at screening (RF negative and anti-CCP negative; RF negative and anti-CCP positive; RF positive and anti-CCP negative; RF positive and anti-CCP positive)
- baseline methotrexate dose.

In addition, the disease characteristics including DAS28-CRP, swollen joint count, tender joint count, subject's global health assessment, investigator's global health assessment, subject's assessment of disease-related pain, HAQ-DI, and CRP at week 22 will be summarized by the initial/re-randomized treatment for all re-randomized subjects.

12.5 Efficacy Analyses

All efficacy analyses will be performed using the ITT analysis set based on subject's randomized treatment. Sensitivity analysis of the key efficacy endpoints will also be performed using the PP analysis set based on the actual treatment the subject received.

12.5.1 Primary Variable

The primary efficacy endpoint is the response difference of ACR20 at week 22 and will primarily be analyzed using the ITT analysis set with non-responder imputation. Clinical equivalence for the primary

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endpoint will be sequentially evaluated: first by comparing the 2-sided 90% CI of the RD of ACR 20 between ABP 710 and infliximab with equivalence margin of (-15%, 15%). If the first equivalence is established, the primary endpoint, RD of ACR 20 at week 22 will be further evaluated by comparing the same 2-sided 90% CI between ABP 710 and infliximab with an equivalence margin of (-12%, 15%).

The 90% CI for RD (ABP 710 – Infliximab) will be estimated from the stratified Newcombe confidence limits for the common RD to adjust for stratification factors. A sample SAS code is displayed below:

CCI

In addition, the 95% CI of RD through week 22 will be estimated using the same model and reported as a descriptive summary.

The percent of subjects achieving ACR20 will be also plotted over time by initial treatment through week 22 for the ITT analysis set with non-responder imputation.

Sensitivity Analyses

To assess the robustness of the primary ACR20 results through week 22, the primary analyses will be repeated using the ITT analysis set based on observed cases, ITT analysis set with last observation carried forward (LOCF) imputation and PP analysis set.

For each subgroup of geographic region (Asia Pacific, Europe and North America), prior biologic use for RA (Yes and No), age (< 65 years and ≥ 65 years), race, gender, disease duration (< 5 years and ≥ 5 years), neutralizing ADA status, binding ADA status and baseline oral corticosteroid use, the RD for ACR20 will also be examined using the same model for the primary efficacy analysis for each subgroup. These additional explorations will be performed on the ITT analysis set with non-responder imputation. Forest plots will be created to summarize the variability in the RDs across the subgroups.

In addition, the 90% and 95% CIs for RD will be estimate with non-responder imputation using generalized linear model adjusted for the stratification factors as covariates. A sample SAS code for PROC GENMOD is displayed below:

CCI

Note: Depending on treatment assignment, the contrast (1 -1) in the estimate statement may need to be reversed.

ACR20 will also be analyzed based on a repeated measures analysis, where data from all post-baseline assessed time points through week 22 visit (inclusive) is included as observed. 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 assuming an identity link function and an AR(1) correlation structure. A sample SAS code for PROC GENMOD with the repeated statement is displayed below:

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Note: Depending on treatment assignment and order of treatment-by-visit interaction, the contrast in the estimate statement may need to be reversed for each visit week.

To explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing not-at-random assumptions), tipping point analyses will be performed for the efficacy endpoints of ACR20 at week 22 using ITT analysis set.

The analysis will be performed using a general three-step approach:

(1) Multiple imputed datasets will be generated using PROC MI to generate multiple (e.g. 10) imputed datasets by imputing missing data assuming monotone missing pattern and subjects with missing values have, on average, worse response compared to those with observed values. The assumed difference between subjects with missing values and subjects with observed values (refer to as shift) can vary independently for the different treatment groups.

(2) Each of these imputed datasets is analyzed using the similar SAS procedure (Mantel-Haenszel estimates) as described in section 12.5.1.

(3) Results from all imputed datasets are then combined for overall inference using PROC MIANALYZE.

More specifically, for ACR20 at week 22, five equally spaced shifts (-0.5 to 0 by 0.125) for the response rates in subjects with missing ACR20 data will be examined. For given shifts, a sample SAS code is as follows:

CCI

12.5.2 Methods for Handling Dropouts and Missing Data

For ACR, the determination of ACR20/50/70 response will be based on the data available at each visit (refer to Appendix 3 for handling missing ACR individual components), taking into account prorated tenderness and swollenness of joints.

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For the primary analysis based on ITT analysis set, missing values will be imputed using the non-responder imputation method. As sensitivity analyses, efficacy endpoints will also be analyzed for the ITT analysis set based on observed cases, ITT analysis set with LOCF imputation and PP analysis set. In addition, tipping point analyses will be performed to explore the sensitivity of the results.

Missing safety and PK endpoints will not be imputed.

Imputation for Partial or Missing Dates

If dates are missing or incomplete for an AE (including deaths) or concomitant medication, the following algorithm will be used for imputation:

Table 2. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		Missing
		<1st dose	≥1st dose	<1st dose yyyymm	≥1st dose yyyymm	<1st dose yyyy	≥1st dose yyyy	
Partial: yyyymm	= 1st dose yyyymm	2	1	n/a	1	n/a	1	1
	≠ 1st dose yyyymm		2	2	2	2	2	2
Partial: yyyy	= 1st dose yyyy	3	1	3	1	n/a	1	1
	≠ 1st dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute as the date of first dose

2 = Impute as the first of the month

3 = Impute as January 1 of the year

4 = Impute as January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then there is a data error and do not impute the start date.

Imputation rules for partial or missing stop dates:

1. Initial imputation
    a. For partial stop date “mmyyyy”, impute the last of the month.
    b. For partial stop date “yyyy”, impute December 31 of the year.
    c. For completely missing stop date, do not impute.
2. If the stop date imputation leads to a stop date that is after the death date, then impute the stop date as the death date.
3. If the stop date imputation leads to a stop date that is before the start date, then there is a data error and do not impute the stop date.

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Imputation rules for partial or missing death dates:

4. If death year and month are available but day is missing:
    a. If “mmyyyy” for last contact date = “mmyyyy” for death date, set death date to the day after the last contact date.
    b. If “mmyyyy” for last contact date < “mmyyyy” for death date, set death date to the first day of the death month.
    c. If “mmyyyy” for last contact date > “mmyyyy” for death date, data error and do not impute.
5. If both month and day are missing for death date or a death date is totally missing, set death date to the day after the last contact date.

The imputed dates will be used to assess whether AEs should be considered as treatment-emergent and if medications should be included in the safety summaries as prior or concomitant, however the original, partial dates will be included in data listings.

12.5.3 Multiplicity

Clinical equivalence for the primary endpoint, RD of ACR20 at week 22, will be sequentially tested to maintain the family-wise type I error rate at 0.05: first by comparing the 2-sided 90% CI of the RD of ACR20 between ABP 710 and infliximab with an equivalence margin of (-15%, 15%). If the first equivalence is established, the primary endpoint, RD of ACR20 at week 22 will be further evaluated by comparing the same 2-sided 90% CI between ABP 710 and infliximab with an equivalence margin of (-12%, 15%).

12.5.4 Pooling of Sites

All sites will be pooled together for the analyses.

12.5.5 Secondary Variables

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

12.5.5.1 ACR20 at other Time Points and ACR50 and ACR70

Response difference of ACR20 at weeks 2, 6, 14, 30, 34, 38, 46, 50 (through entire study) as well as 90% and 95% CIs will be estimated for re-randomized subjects using a similar model as described in section 12.5.1, where the comparison between treatment sequence ABP 710/ABP 710 and infliximab/infliximab and the comparison between treatment sequence infliximab/ABP 710 and infliximab/infliximab will be estimated separately for ITT analysis set with non-responder imputed data.

The number of subjects achieving ACR50 and ACR70 will be evaluated at weeks 2, 6, 14, and 22 by frequency and percentage by initial treatment for ITT analysis set with non-responder imputed data and PP analysis set. The 90% and 95% CIs for the RD between initial treatments will be estimated using a similar model described in section 12.5.1.

The number of subjects achieving ACR50 and ACR70 through entire study will also be summarized by frequency and percentage by initial/re-randomized treatment for the re-randomized subjects with non-responder imputed data. The 90% and 95% CIs of RD between treatment sequences through entire study will be estimated using the similar model as of planned for ACR 20.

The percent of subjects achieving ACR50 and ACR70 will be plotted against visit by initial treatment through week 22, separately by initial/re-randomization treatment through entire study based on the ITT analysis set with non-responder imputed data for re-randomized subjects. The percent of subjects achieving ACR20 will be plotted over time by initial/re-randomized treatment sequence through entire study for re-randomized subjects with non-responder imputed data.

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12.5.5.2 DAS28-CRP

Treatment differences across time points at which DAS28-CRP change from baseline was assessed will be evaluated and descriptively summarized.

The comparison between treatment groups ABP 710 and infliximab through week 22 for the ITT analysis set with observed data, as well as the comparisons between treatment sequences (treatment sequence ABP 710/ABP 710 vs infliximab/infliximab and treatment sequence infliximab/ABP 710 vs. infliximab/Infliximab) for all re-randomized subjects through the entire study will be evaluated by using an analysis covariance (ANCOVA) model adjusted with baseline DAS28-CRP and stratification factors (geographic region and prior biologic use for RA), and DAS28-CRP change from baseline as the response variable. A sample SAS code for ANCOVA model using PROC GLM is displayed below:

CCI

The analysis for the period through week 22 will have the 2 treatments groups (ABP 710 vs Infliximab) included in the model, while all three initial/re-randomized treatment sequences will be included in the model when reporting for the entire study.

The differences between means as well as their associated 90% and 95% confidence intervals (CIs) will be reported for each visit.

The analyses through week 22 will be also repeated for the PP analysis sets.

Additionally, for each subgroup of geographic region (Asia Pacific, Europe and North America), prior biologic use for RA (Yes and No), age (< 65 years and ≥ 65 years), race, gender, disease duration (< 5 years and ≥ 5 years), neutralizing ADA status, binding ADA status and baseline oral corticosteroid use, descriptive summaries will be provided for mean difference of DAS28-CRP change from baseline between ABP 710 and infliximab at each time point through week 22 in the subgroups using similar model. These additional explorations will be performed on the ITT analysis set with observed data.

The mean +/- standard error of DAS28-CRP change from baseline will be plotted over time (visit) by initial treatment through week 22 and separately by initial/re-randomized treatment through entire study for the ITT analysis set with observed.

To evaluate treatment differences of DAS28-CRP change from baseline across time points, repeated-measures analysis will be utilized using ITT analysis set with observed data. Data from all assessed time points post-baseline through week 22 visit will be included in the analysis. Besides stratification variables, baseline DAS28-CRP scores, visit week, treatment, and treatment-by-visit interaction will be included in the model, with visit as a categorical variable and unstructured type of variance-covariance structure. Example code for PROC MIXED is displayed below:

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The 90% and 95% CIs will be estimated and reported for mean difference of DAS28-CRP change from baseline between ABP 710 and infliximab at each time point through week 22.

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12.6 Safety Analyses

All safety analyses will be performed on the safety analysis set based on each subject's actual treatment received. Unless stated otherwise, safety analysis summaries will be provided separately as follows:

- from day 1 until week 22 will be performed for the initial randomized treatment groups: ABP 710 and infliximab
- post week 22 to the end of the study will be performed for the re-randomized treatment groups: infliximab/infliximab and infliximab/ABP 710, and ABP 710/ABP 710,
- from day 1 until the end of the study will be performed for subjects who discontinued before re-randomization (initial treatment groups: ABP 710 and infliximab) and for the re-randomized treatment groups: infliximab/infliximab and infliximab/ABP 710, and ABP 710/ABP 710,

12.6.1 Adverse Events

All reported AEs will be coded to the appropriate SOC and PT according to the most current version of MedDRA at the time of the primary analysis, and the severity of each AE will be graded by the investigator per CTCAE v4.03 criteria..

There will be separate summaries for each AE summary unless otherwise specified: 1) AEs occurring through week 22 (prior to first dose of re-randomization IP), 2) AEs occurring post week 22 (AEs that have a start date on or after the first dose of re-randomization IP), and 3) AEs occurring through the entire study.

Overall summary of treatment-emergent AEs will be tabulated by treatment groups, and by subgroup of age group, gender, race, region, prior biologic use for RA, disease duration (< 5 years vs ≥ 5 years), binding ADA status and neutralizing ADA status through week 22.

Subject incidence of the following AEs will be tabulated by treatment groups and by SOC, PT, and maximum severity grade per CTCAE v4.03:

- treatment-emergent AEs,

Subject incidence of the following AEs will be tabulated by treatment groups and by SOC and PT:

- treatment-emergent AEs.
- treatment-related AEs.

Subject incidence of the following AEs will be tabulated by treatment groups and preferred term in descending order of frequency in total column, unless stated otherwise:

- treatment-emergent AEs,
- grade 3 or higher treatment-emergent AEs,
- treatment-related AEs,
- treatment-emergent AEs leading to infusion delayed/not administered,
- treatment-emergent AEs leading to discontinuation from IP/study,
- treatment-emergent EOIs.

Exposure adjusted subject incidence rate (EAIR) of the following AEs will be tabulated by drug exposure and preferred term in descending order of frequency for the ABP 710 arm:

- treatment-emergent AEs,
- treatment-related AEs.
- treatment-emergent EOIs.

Summary of EAIR for each EOI will be reported through the entire study, where the ratio of incidence rate between ABP 710 and Infliximab as well as its associated 95% CI estimated using a Poisson regression (log-linear) model, will be performed as shown below:

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An overall summary of treatment-emergent EOIs will be displayed by event of interest, maximum severity and treatment.

The risk difference and 95% CI of each EOI through week 22 and post week 22 will be calculated on the safety analysis set using Wald asymptotic confidence limits or exact confidence limits if the number of subjects for any treatment is less than 25. Sample SAS code is displayed below:

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Forest plots will be created to summarize the variability in risk difference across the EOIs.

Counting of AEs will be by subject, and subjects will be counted only once within each SOC or PT. For tables categorized by severity, subjects with multiple events within a particular SOC or preferred term will be counted under the category of their most severe event with that SOC or preferred term.

The following listings will be also provided: 1) subject listing of AEs; 2) subjects with TEAEs leading to discontinuation from IP/study.

12.6.2 Deaths and Serious Adverse Events

Subject incidence of the following will be tabulated by treatment group, SOC and PT:

- serious treatment-emergent AEs,
- serious treatment-related AEs.

Subject incidence of the following will be tabulated by treatment group and preferred term in descending order of frequency in total column:

- serious treatment-emergent AEs,
- serious treatment-related AEs,
- treatment-emergent fatal AEs.

Exposure adjusted subject incidence rate of the following AEs will be tabulated by treatment groups and preferred term in descending order of frequency for the ABP 710 arm: serious treatment-emergent AEs,

- serious treatment-related AEs.

A subject listing of SAEs will be also provided.

12.6.3 Laboratory Data

Laboratory test results are reported in International System of Units (SI) units.

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Laboratory values and change from baseline will be summarized using descriptive statistics at each analysis visit by initial treatment until week 22 (inclusive) and by initial/re-randomized treatment through entire study. Shift tables of the worst on-study laboratory toxicity based on CTCAE grading relative to baseline will be presented by treatment group through week 22 and separately for entire study.

The shift tables will take into account all post-baseline (schedule and unscheduled) laboratory results in the determination of the worst on-study laboratory toxicity. In addition, subject incidence tables and listings of grade ≥ 3 laboratory toxicities will be provided. Standard ranges will be used for the laboratory analysis.

Lab assessments will be grouped for summary as follows:

Hematology – white blood cell parameters: white blood cell count and differentials,

Hematology – red blood cell parameters: hemoglobin, packed cell volume or hematocrits, red blood cell count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration,

Hematology – other parameters: platelets,

Serum chemistry – hepatobiliary parameters: alanine aminotranferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, gamma glutamyltransferase,

Serum chemistry – general chemistry: sodium, potassium, albumin, total protein, non-fasting glucose,

Serum chemistry – renal function tests: urea, creatinine.

12.6.4 Vital Signs and Physical Examination

Observed and change from pre-infusion to end-of- infusion at each visit for each vital sign parameter will be summarized by parameter and initial treatment from study day 1 until week 22 and by initial/re-randomized treatment from study day 1 through entire study. Descriptive statistics will be shown for each visit/time point.

Clinically significant abnormal findings from physical examinations will be listed by subject.

12.6.5 Immunogenicity

The number and percentage of subjects developing binding ADA and those developing neutralizing ADA will be tabulated separately for three periods: 1) Through week 22 (day 1 until week 22 (inclusive)), 2) Post week 22 (from week 22 through the end of the study), and 3) Through Entire Study (from Day 1 through the entire study) for safety analysis set.

Pre-existing antibody through week 22 and through entire study is defined as the number of subjects with a positive antibody result on or before the first dose of IP. Developing antibody incidence at each visit, through week 22, and through entire study is defined as the number of subjects with a negative or no antibody result at baseline and a positive antibody result at a post-baseline time point divided by the number of subjects with a binding negative or no result at baseline and at least one post baseline result. A transient antibody result is defined as a positive post-baseline result with a negative result at the subject's last time point tested within the study period.

Pre-existing antibody by week 22 is defined as subjects with a positive antibody result on or before the first IP post-week 22 re-randomization. Developing antibody incidence post week 22 is defined as subjects with a negative result at week 22, and negative or no result before week 22, and a positive antibody result at a post-week 22 time point divided by the number of subjects with a binding negative result at week 22, and negative or no result before week 22, and at least one post-week 22 result.

The summary of ADA magnitude, where only subjects with positive binding ADA included for binding summary and only subjects with positive neutralizing ADA included for the neutralizing summary, will be descriptively provided by visit through week 22 and through entire study separately.

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12.7 Exploratory analyses

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[redacted]

13.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

The programming (including quality control) of the analysis datasets and TFLs will be conducted under PRA's standard processes PRS 050 and documented accordingly. The entire set of TFL will be checked for completeness and consistency prior to its delivery to the client by the lead statistician and a senior level statistician, or above, who is not a member of the project team.

The PRA validation process is repeated any time TFL are redelivered using different data. Execution of this validation process is documented through the study Table of Programs that is provided to the client at study conclusion.

14.0 References

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
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
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotranferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AR(1)	First-order autoregressive
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CCP	Anti-cyclic Citrullinated Peptide
CDAI	Clinical Disease Activity Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DAS	Disease Activity Score
DMC	Data Monitoring Committee
EAIR	Exposure adjusted incidence rate
eCRF	Electronic Case Report Form
EOI	Event of Interest
EOS	End of Study
GEE	Generalized Estimating Equation
GMR	Geometric mean ratio
HAQ-DI	Health Assessment Questionnaire Disability Index
IGH	Investigator's global health assessment (on a 0 to 10 scale).
IP	Investigational Product
IPD	Important protocol deviation

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ITT	Intention-to-treat
IXRS	Interactive Voice or Web Response System
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NCI-US	National Cancer Institute
NSAID	Non-steroidal Anti-inflammatory Drug
PD	Protocol deviation
PK	Pharmacokinetic
PP	Per Protocol
PP22	Per-protocol analysis sets through week 22
PT	Preferred Term
Q1	25th Percentile
Q3	75th Percentile
RA	Rheumatoid Arthritis
RD	Response difference
RF	Rheumatoid Factor
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SDAI	Simplified Disease Activity Index score
SDTM	Standard Data Tabulation Model
SGH	Subject's global health assessment score (on a 0 to 100 scale)
SI	International System of Units
SLE	Systemic lupus erythematosus
SJC28	Swollen Joint Count (28 Joints)
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TFL	Tables, Figures, and Listings
TJC28	Tender Joint Count (28 Joints)
VAS	Visual Analog Scale
WHO-DD	World Health Organization Drug Dictionary

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Appendix 2 Event of Interest Search Strategies [a]

Event of Interest	Category of EOI Query (SOC/SMQ/Amgen query)	Search Strategy	Additional Medical Evaluation for Determination of EOI
Infusion reactions including hypersensitivity	Infusion reactions (Amgen query)	Broad*- TEAE with start date same as, or one day after, IP administration date	No
	Hypersensitivity (SMQ)	Broad- TEAE with start date same as, or one day after, IP administration date	No
Congestive Heart Failure	Cardiac Failure (SMQ)	Broad	Yes
Serious Infections	Infections and Infestations (SOC)	CTCAE grade >= 3 or the serious TEAE	No
Opportunistic Infections	Infections and Infestations (SOC)		Yes
Malignancies	Malignancies (SMQ)	Narrow	Yes
Demyelinating disorders	Demyelination (SMQ)	Broad	Yes
Hepatitis B reactivation	Hepatitis B Infections (Amgen query)	Broad	Yes
Autoimmunity (SLE and Sarcoid)	Systemic Lupus Erthematosus (SMQ)	Broad	Yes
	Sarcoidosis (PT)		No
Hepatotoxicity	Drug Related Hepatic Disorders-comprehensive Search (SMQ)	Broad	No
Hematological reactions	Hematopoetic cytopenia (SMQ)	Broad	No

*Broad search strategy includes both narrow scope terms and broad scope terms.

[a] The pre-specified search strategies many times lead to direct medical concept of a certain EOI and support confirmation of the EOI. However, in many other cases, the search strategies aim to gather AE terms closely indicative of an EOI medical picture, capture signs and symptoms that could be existent in a certain medical condition, but cannot necessarily confirm a medical condition an EOI is meant to represent. For this latter scenario, an additional medical evaluation of the retrieved AE terms maybe required, for confirmation of an EOI that it truly is meant to represent.

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Appendix 3 Method for Missing individual components of ACR calculation

In the case of some ACR components are missing, the ACR composite scores will be based on the non-missing components. If a subject's non-missing components are not sufficient to identify ACR composite score, then that subject will be considered as missing ACR response. The corresponding algorithm is listed below (using ACR 20 as an example):

- If both Tender or Swollen Joint Counts are improved at least 20%, and
  - If three or more of the other five ACR components are improved at least 20%, the subject is an ACR 20 responder;
  - If three or more of the other five ACR components are not improved at least 20%, the subject is an ACR 20 non-responder;
  - If none of the above, the ACR response for the subject cannot be determined due to missing data and is therefore coded as missing.
- If either swollen or tender joint counts is not improved at least 20%, the subject is an ACR non-responder
- If either swollen or tender joint counts is missing and the other improved at least 20%, and
  - If three or more of the other five ACR components are not improved at least 20%, the subject is an ACR 20 non-responder;
  - Otherwise, the ACR response for the subject cannot be determined due to missing data and is therefore coded as missing

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Appendix 4 Method for missing individual joint assessments

A Pain/Tenderness or Swollen Joints may be coded as follows:

Joint Codes: 00 = None
01 = Positive
08 = Permanently inevaluable because of replaced, fused joint
09 = Not evaluated because of intra-articular corticosteroid injection
77 = Not Done

The missing individual joint assessments due to artificial/fused joint, intra-articular corticosteroid injection or not done for other reason are imputed as the followings:

For Joint Codes = 08,

- *At Screening*: Code as missing at current visit only
- *At Baseline:* Exclude the joint from the total joint counts for baseline and all subsequent visits.
- *Post-Baseline* (If a joint is coded as 08 at a post-baseline visit but not at baseline): Code as "01" (failed) beginning with the current visit and all visits subsequent to the current visit.

For Joint Codes = 09,

- *At Screening:* Code as "01" (failed) at current visit only
- *At Baseline:* Code as "01" (failed) for baseline and all subsequent visits.
- *Post-Baseline:* Code as "01" (failed) beginning with the current visit and all visits subsequent to the current visit.

For Joint Codes = 77,

- *At Baseline:* Code as missing and exclude the joint from the total joint counts for baseline.
- *Post-baseline:* Code as missing and exclude the joint from the total joint counts for the current visit.

If there are joints being excluded after above imputation, the Tender or Swollen Joint Counts will be prorated based on the algorithm described below.

Prorated Joint Counts

If at least half but not all joints are evaluable (14 joints for the DAS 28 joint counts, 34/33 for the 68/66 joint counts), then the observed prorated Tender or Swollen Joint Counts will be calculated. The prorated scores will be adjusted based upon the number of evaluable joints: the counted score will be multiplied by 28, 66, or 68 as applicable and divided by the number of joints evaluated. Otherwise, the Tender or Swollen Joint Counts is missing.

For example, if only 25 of the 28 DAS joints are assessed at a visit and 10 of those 25 are pain/tenderness and 8 of those 25 are swollen, the prorated joint counts are:

Tender Joint Counts: 10/25*28 = 11.20

Swollen Joint Counts: 8/25*28 = 8.96

That is, the values of 11.20 and 8.96 will be used in calculating the percent improvement, not the values of 10 and 8.

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Appendix 5 HAQ Scoring Algorithm

All language versions will use the following scoring system.

- There are four possible responses for each sub-category item, or component, within a category:

  0 = without ANY difficulty 2 = with MUCH difficulty

  1 = with SOME difficulty 3 = UNABLE to do

- Step 1: Calculate the maximum score for each of the 8 categories (7 of the categories are listed in the table below. The eighth category “Activities” is not listed in the table due to lack of questions regarding use of aids or device). At least one question in each category needs to be answered to compute the maximum score.
- If **an aid or device** is used or **help from another person** is needed, set the score for the associated category to the maximum score between 2 and the score in step 1.

Sub-domain	**Aids or devices**
Dressing&Grooming	Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
Arising	Special or built up chair
Eating	Built up or special utensils
Walking	Cane, Walker, Crutches, Wheelchair
Hygiene	Raised toilet seat, Bathtub seat, Bathtub bar, Long-handled appliances in bathroom
Reach	Long-handled appliances for reach
Grip	Jar opener (for jars previously opened)

If no more than 2 categories have missing scores, then the disability score is the mean of the non-missing category scores. Otherwise, the disability score is set to missing.

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Appendix 6 Tables, Figures, Listings, and Supportive SAS Output Appendices

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