Statistical Analysis Plan

A Randomized, Double-Blind Study to Compare Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of ABP 798 with Rituximab in Subjects with Moderate to Severe Rheumatoid Arthritis

Sponsor:	Amgen Inc.
Protocol No:	20130108 – Date 20-March-2018 – Version 4.0
PRA Project Id:	AMGRA798-798RAX
Version Date:	10-December-2018
Version Number:	2.0

APPROVALS

Sponsor Name:	Amgen Inc.
Name of Sponsor Representative/Title:	PPD / Clinical Research Medical Director, Amgen Inc.
Signature of Sponsor Representative /Date:	PPD 10 DEC 2018
Name of Sponsor Representative/Title:	PPD / Biostatistics Sr. Manager, Amgen Inc.
Signature of Sponsor Representative /Date:	PPD 10 Dec 2018
Name of Project Manager/Title:	PPD / Project Manager
Signature of Project Manager/Date:	PPD 10 Dec 2018
Name of Biostatistician /Title:	PPD / Principal Biostatistician
Signature of Biostatistician /Date:	PPD 10 Dec 2018 FOR PPD

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Amgen Inc. Protocol 20130108, titled "A Randomized, Double-Blind Study to Compare Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of ABP 798 with Rituximab in Subjects with Moderate to Severe Rheumatoid Arthritis."

This SAP should be read in conjunction with the study protocol and electronic Case Report Forms (eCRFs). This version of the plan has been developed using the protocol version 4.0 dated 20 March 2018 and eCRFs version 5.0 dated 17 November 2016. Any further changes to the protocol or eCRFs may necessitate updates to the SAP.

The SAP is to be developed in two stages. The purpose is to "finalize" a SAP in order to start programming earlier in the process. Versions of the SAP up to initial sponsor approval will be known as SAP1. Changes following approval of SAP1will 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 final analysis.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

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

2.2 SECONDARY OBJECTIVES

The secondary objectives are:

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

3. STUDY DESIGN

This is a randomized, double-blind, active-controlled 3-arm study in adult subjects with moderate to severe Rheumatoid Arthritis (RA) who have an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs), which must include intolerance or inadequate response to one or more tumor necrosis factor (TNF) inhibitor therapies.

Approximately 300 subjects (100 per treatment group) will be enrolled. The subjects will be randomized to receive either 2 IV infusions of ABP 798, 1000 mg each, given 2 weeks apart (treatment group A), or 2 IV infusions of rituximab (US) 1000 mg each, given 2 weeks apart (treatment group B) or 2 IV infusions of rituximab (EU), 1000 mg each, given 2 weeks apart (treatment group C) in a double blind fashion. A total of 2 doses will be administered during the study; each dose consists of 2 infusions, 2 weeks apart.

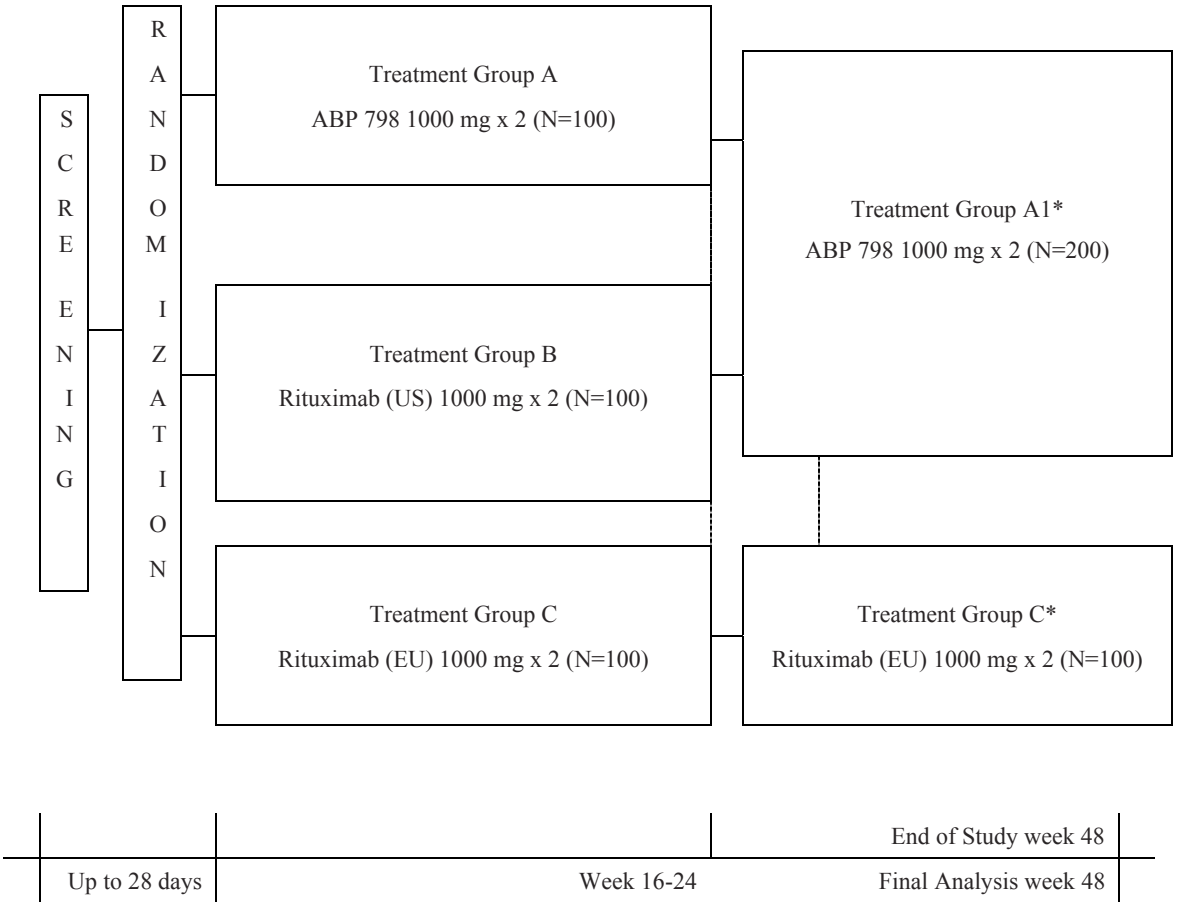
An independent data monitoring committee (DMC) will evaluate the safety data throughout the study, including an initial safety analysis after the first 18 subjects have received the first dose (1000 mg x 2 infusions of either ABP 798 or rituximab (EU) or rituximab (US)).

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

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

See Figure 1 below for a summary of the study design.

Figure 1 Study Diagram



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

3.1 SAMPLE SIZE CONSIDERATIONS

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

be tested between ABP 798 versus rituximab (US) and ABP 798 versus rituximab (EU), each with a significance level of 0.05. The similarity between rituximab (US) and rituximab (EU) will be evaluated as well.

With the planned sample size, there is 94% probability that the 90% CI of the difference between the ABP 798 arm and the pooled rituximab (rituximab [EU] and rituximab [US]) arm and 83% probability that the 90% CI of the difference between test (ABP 798) and reference (rituximab [EU] or rituximab [US]) in DAS28-CRP change from baseline at week 24 will fall into the equivalence margin of ± 0.6 (EULAR response criteria), assuming a standard deviation of 1.4 (Volkmann et al, 2010) and true mean difference of 0.

3.2 RANDOMIZATION

Approximately 300 subjects will be randomized in a 1:1:1 ratio to receive either ABP 798, rituximab (US), or rituximab (EU) via an Interactive Voice or Web Response System (IXRS), stratified by geographic region (North America, Eastern Europe, and Western Europe), seropositivity (RF-positive and/or CCP-positive vs. RF-negative and CCP-negative), and number of prior biologic therapies used for RA (1 vs. >1).

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 involved in the conduct of the study.

A third party vendor, PPD [redacted], will be responsible for generating the randomization scheme and managing the randomization activities of this study.

4. STUDY VARIABLES AND COVARIATES

4.1 PRIMARY VARIABLE

- The primary PK endpoints are the AUC_{inf} and C_{max} following the 2nd infusion of 1st dose.

4.2 SECONDARY VARIABLES

4.2.1 Pharmacokinetic

The secondary PK endpoints will include:

- AUC from time 0 on day 1 prior to the 1st infusion of the 1st dose to 14 days postdose ($AUC_{0\text{-}14\ day}$)
- AUC from time 0 on day 1 prior to the 1st infusion of the 1st dose to week 12 ($AUC_{0\text{-}12\ wk}$)
- C_{max} following the 1st infusion of the 1st dose.

- Additional PK endpoints including the time of C_{max} (t_{max}), last measurable serum concentration after the second infusion up to week 12 (C_{last}),terminal elimination half-life ($t_{1/2}$), the terminal elimination rate constant (λ_z), clearance (CL), mean residence time (MRT), percent of AUC extrapolation (%AUC_{extrap}), and $AUC_{0\text{-}12\ wk}/AUC_{inf}$.

4.2.2 Efficacy

The efficacy endpoints include:

Primary efficacy endpoint:

- Disease activity score (DAS) 28-CRP change from baseline at week 24.

Secondary efficacy endpoints:

- DAS 28-CRP change from baseline at week 8, 12, 40 and 48.
- ACR20, ACR50 and ACR70 at weeks 8, 12, 24, 40 and 48.
- Hybrid ACR at weeks 8, 12, 24, 40 and 48.

4.2.3 Pharmacodynamic

Pharmacodynamic (PD) endpoints will include the percent of subjects with complete depletion in CD19+ cell count from day 1 to day 3 and duration of CD19+ B-cell complete depletion.

4.2.4 Safety

Safety endpoints include the following:

- Treatment-emergent adverse events (TEAE) and serious adverse events (SAE).
- Clinically significant changes in laboratory values.
- Changes in vital signs.
- Incidence of anti-drug antibodies.

4.3 PREDETERMINED COVARIATES AND PROGNOSTIC FACTORS

For the PK analyses, geographic region and weight will be used as covariates in the model for the primary statistical analysis. The following covariates may be used for further exploration in subgroups:

- Negative binding anti-drug antibodies (ADA) during first dose period
- Negative neutralizing ADA during first dose period

For efficacy analyses, unless stated otherwise, the following stratification factors will be included as covariates in the model or be used to examine treatment effect in subgroups:

- Geographic region (North America vs. Eastern Europe vs. Western Europe)

- Seropositivity (RF-positive and/or CCP-positive vs. RF-negative and CCP-negative)
- Prior biologic use for RA (1 vs >1)

In case the analysis model doesn't converge, the strata with least number of subjects may be combined to address the convergence issues.

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

- Age Group (<65 years vs ≥65 years)
- Race (Caucasian vs Non-Caucasian)
- Gender
- Binding ADA status during first dose period (negative vs positive)
- Neutralizing ADA status during first dose period (negative vs positive)
- Oral Corticosteroid use at baseline (Yes vs No)

Additional baseline demographic and disease characteristics in Section 9.4 may also be considered as covariates in the model for assessing DAS28-CRP change from baseline at week 24.

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 statistical analysis (except the inclusion of the subgroup factor) should be done for each subgroup defined by the eCRF values of the subgroup factor.

5. DEFINITIONS

5.1 GENERAL

Actual Treatment Received

The actual treatment received is the investigational product (IP) treatment the subject actually received, regardless of what the subject was randomized to. In cases where a subject received more than 1 IP during a dose, the actual treatment received for that dose will be based on the first IP infusion of the dose the subject received. The actual treatment received for the entire study will be based on the combination of the actual treatment received for the first infusion of the two doses. In cases where a subject received only the 1st dose of IP, the actual treatment received for the entire study will be determined by the actual treatment of the 1st IP dose and the intended treatment of the 2nd

dose per protocol. The actual treatment for the study will be unplanned if the sequence of the actual treatment of each dose are not described in the protocol.

Specifically, by design for each subject, 2 doses will be administered during the study where each dose consists of 2 infusions, and each infusion consists of 2 boxes. In the cases where a subject receives mismatched boxes (differing IP) among the 2 possible boxes within an infusion, if either box is ABP 798 then the actual treatment for the infusion will be ABP 798.

Baseline

For the endpoint of interest, the baseline is defined as the last non-missing assessment taken prior to the first infusion of the first dose of study IP. In cases where baseline assessments are taken on the same day as the first infusion of 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.

For the ADA analysis following the 1st infusion of the 2nd dose, the baseline is defined as last non-missing assessment prior to the 1st infusion of the 2nd dose.

Binding and Neutralizing ADA status During First Dose Period

Subjects will be considered to have negative binding ADA status during first dose period if subjects had negative binding ADA

- from baseline up to 1st infusion of 2nd dose for subjects who received 2nd dose, or
- from baseline up to week 24 (day 175) or EOS (whichever is earlier) for subjects who didn't receive 2nd dose.

Subjects will be considered to have positive binding ADA status during first dose period if subjects had positive binding ADA status at any time point

- up to the 1st infusion of the 2nd dose for subjects who received 2nd dose, or
- up to week 24 (day 175) or EOS (whichever is earlier) for subjects who didn't receive 2nd dose.

The same definition applies to subjects' neutralizing ADA status. Subjects with a binding negative or no result at baseline and at least one post baseline will be included in this derivation.

Change from Baseline

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

Completed Study

A subject is considered to have completed the study if they indicated they completed study on the EOS eCRF.

Concomitant and Prior Medication

Prior medications are defined as medications with a stop date prior to the first infusion of the 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.

Duration of IP Exposure

For subjects who received 2nd dose of IP, the duration of IP exposure will be derived as min (EOS date, analysis data cutoff date) minus date of first IP exposure + 1 day.

For subjects who didn't receive 2nd dose of IP, the duration of IP exposure will be derived as min (EOS date, week 24 [day 175], analysis data cutoff date) minus date of first IP exposure + 1 day.

Early Retreatment

If 1st infusion of 2nd dose is administered prior to Study Day 162, subjects are considered as receiving early retreatment.

End of Study Date

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 infusion of first dose of study IP. This date is also referred to as Study Day 1.

Infusion delay

If an IP administration form for a visit is entered with an infusion administered of NONE and a reason for delay/not administered, and also there is infusion information entered on a subsequent IP form, that subject is considered having an infusion delay.

There is one exception. If the second infusion of the 1st dose is delayed for such a large extended period that it falls at week 16 or after, the infusion will be entered in the week 24 folder. In this case, the Day 15 IP infusion will be considered missing instead of delayed.

Infusion missed

When a subject with an IP administration form entering an infusion administered of NONE and a reason for delay/not administered but there is no subsequent IP form with infusion information, the subject is considered to have missed an infusion at that visit.

In addition, if the second infusion of the 1st dose is delayed for such a large extended period that it falls at week 16 or after, the infusion will be entered in the week 24 folder. In this case, the Day 15 IP infusion will be considered missing.

Last Dose Date

The date on which a subject is administered the last infusion of the last dose of study IP.

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 a disease duration of zero, 1 month (or 1/12 years) may be added.

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.

Seropositivity

For seropositivity summary at baseline, a normal or negative baseline result for RF would be <12 IU/mL and for CCP3 would be <20 Units based on the laboratory assay maker's guidance.

Study Day 1

Study Day 1 is defined as the first day of IP administration. For subjects who are randomized but not dosed after the 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 receives a random treatment allocation via the IXRS system.

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 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.
In general, 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. For Week 24, only actual visits that occur before or on same date as first infusion of second dose should be considered.

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.

PK concentration will be summarized by the scheduled sample visit in the protocol. For PK concentration collected in the unscheduled visits or in the early discontinuation study visit, the associated scheduled sample visit is defined as below. If multiple records are assigned to the same visit, the one closest to the reference date/time will be selected into the summary.

FOR PK ANALYSES:

Scheduled Sample Visit	Window Mapping
Day 1 Pre-dose	Prior to the 1st IP infusion of 1st dose start time but on the same day
Day 1 End of infusion	within 10 minutes of 1st infusion of 1st dose stop date/time
Day 1 3 hours	3 hr ± 10 minutes after 1st IP infusion of 1st dose stop date/time
Day 1 6 hours	6 hours ± 10 minutes after 1st IP infusion of 1st dose stop date/time

Day 2 24 hours post-dose	24 hr ± 3 hours after 1st IP infusion of 1st dose stop date/time
Day 3 48 hours post-dose	48 hr ± 3 hours after 1st IP infusion of 1st dose stop date/time
Day 15 Pre-dose	Prior to the 2nd IP infusion of 1st dose start time but on the same day
Day 15 End of infusion	within 10 minutes of 2nd infusion of 1st dose stop date/time
Day 15 3 hours	3hr ± 10 minutes after 2nd IP infusion of 1st dose stop date/time
Day 15 6 hours	6hr ± 10 minutes after 2nd IP infusion of 1st dose stop date/time
Day 16 24 hours post-dose	24 hr ± 3 hours after 2nd IP infusion of 1st dose stop date/time
Day 17 48 hours post-dose	48hr ± 3 hours after 2nd IP infusion of 1st dose stop date/time
Week 4	2 wks (14 days) ± 2 days after the 2nd infusion of 1st dose stop date
Week 8	6 wks (14 days) ± 2 days after the 2nd infusion of 1st dose stop date
Week 12	10 wks (14 days) ± 2 days after the 2nd infusion of 1st dose stop date
Week 24 Pre-dose	Prior to the 1st IP infusion of 2nd dose start time but on the same day
Week 26 Pre-dose	Prior to the 2nd IP infusion of 2nd dose start time but on the same day
Week 30	4 wks (28 days) ± 2 days from the 2nd infusion of 2nd dose stop date
Week 48	22 wks (154 days) ± 2 days from the 2nd infusion of 2nd dose stop date

FOR EFFICACY ANALYSES:

Study Analysis Visit	Target Day	Study Day	Interval (days)
Baseline	1	≤1	NA
Week 8	57	2 – 70	69
Week 12	85	71 – 105	42
Week 24	169	106 – 210	98
Week 40	281	211– 308	98
Week 48	337	≥309	NA

FOR SAFETY (HEMATOLOGY AND CHEMISTRY) ANALYSES:

Study Analysis Visit[a]	Target Day	Study Day	Interval (days)
Baseline[b]	1	≤1	NA
Week 2	15	2 – 16	15
Day 17	17	17	1
Week 4	29	18 – 42	25
Week 8	57	43 – 105	70
Week 24	169	106 – 175	63
Week 26	183	176 – 196	21
Week 30	211	197 – 245	49
Week 40	281	246 – 308	63
Week 48	337	≥309	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 lab measurements on the same day as the first infusion date of first dose but at a time after the first infusion of first dose is administered, the lab measurements will not be defined as baseline, but as Week 2 measurements.

FOR CD19+, IGA, IGM AND IGG ANALYSIS:

Study Analysis Visit[a]	Target Day	Study Day	Interval (days)
Baseline[b]	1	≤1	NA
Day 2	2	2	1
Day 3	3	3	1
Week 4	29	15 – 42	28
Week 24	169	106 – 210	98
Week 48	337	≥309	NA

[a] IgG and IgA will not be collected at Day 2 and Day 3
[b] If a subject has measurements on the same day as the first infusion date of first dose but at a time after the first infusion of first dose is administered, the measurements will not be defined as baseline, but as Day 2 measurement.

FOR VITAL SIGNS ANALYSES:

Study Analysis Visit[a]	Target Day	Study Day[b]	Interval (days)
Baseline	NA	Day 1 prior to infusion	NA
Day 1 end of infusion (EOI)	NA	Day 1 after infusion	NA
Day 1 3 hours	NA	Day 1 3 hours after EOI	NA
Day 1 6 hours	NA	Day 1 6 hours after EOI	NA
Week 2	NA	Day 15 prior to infusion	14

Day 15 EOI	NA	Day 15 after infusion	NA
Day 15 3 hours	NA	Day 15 3 hours after EOI	NA
Day 15 6 hours	NA	Day 15 6 hours after EOI	NA
Week 24	169	106 – 175	63
Week 26	183	176 – 196	21
Week 30	211	197 – 245	49
Week 48	337	≥309	NA

[a]If a visit date with multiple records, the highest value per parameter will be selected for analysis.
[b]Day 1 and Day 15 visit/timepoint are directly associated with infusion date/time.

FOR ADA ANALYSES:

Study Analysis Visit	Target Day	Study Day	Interval (days)
Baseline[a]	1	≤1	NA
Week 2	15	2 – 16	15
Week 24	169	106 – 175	63
Week 30	211	197 – 245	49
Week 48	337	≥309	NA

[a] If a subject has ADA assessments on the same day as the first infusion date of first dose but at a time after the first infusion of first dose is administered, the ADA assessments will not be defined as baseline, but as Week 2 assessments.

5.2 PHARMACOKINETIC

Pharmacokinetic parameters will be calculated from serum concentration-time data using noncompartmental analysis (NCA) methods using Phoenix WinNonLin® Version 6.4 or higher (Pharsight Corp, St. Louis, MO). The following PK parameters will be reported for serum rituximab and ABP 798, using actual elapsed sampling times:

Variable	Definition
C_{max1}	Maximum observed serum concentration following Dose 1 Infusion 1
C_{max2}	Maximum observed serum concentration following Dose 1 Infusion 2
t_{max1}	Time to which the maximum serum concentration was observed following Dose 1 Infusion 1
t_{max2}	Time to which the maximum serum concentration was observed following Dose 1 Infusion 2
TLST1	Time of last quantifiable concentration following Dose 1 Infusion 1

CLST1	Last quantifiable concentration following Dose 1 Infusion 1 over first 14 days postdose (day 15)
$AUC_{0\text{-}14\ day}$	Area under the serum concentration-time curve from time 0 on day 1 prior to the first infusion of the first dose to last quantifiable concentration associated with Dose 1 Infusion 1 over the first 14 days postdose (day 15)
TLST2	Time of last quantifiable concentration associated with Dose 1 Infusion 2
CLST2	Last quantifiable concentration after Dose 1 Infusion 2
$AUC_{0\text{-}12\ wk}$	Area under the serum concentration-time curve from time 0 on day 1 prior to the first infusion of the first dose to last quantifiable concentration over 12-week profile
AUC_{inf}	Area under the serum concentration-time curve from time 0 on day 1 prior to the first infusion of the first dose extrapolated to infinity; calculated as $AUC_{last} + CLST2/\lambda_z$, where AUC_{last} is the AUC from time 0 to the last quantifiable concentration up to week 12 (i.e. $AUC_{0\text{-}12\ wk}$)
$t_{1/2}$	Terminal elimination half-life determined from time 0 to Week 12 profile; calculated as $\ln(2)/\lambda_z$
λ_z	Terminal elimination rate constant
CL	Clearance
AUMC	Area under the first moment curve
MRT	Mean residence time; calculated as $AUMC_{inf}/AUC_{inf} - TI/2$, where TI represents infusion duration and $AUMC_{inf}$ is the area under the moment curve from the time of first dosing extrapolated to infinity.
$AUC_{0\text{-}12\ wk}/AUC_{inf}$	calculated as $AUC_{0\text{-}12\ wk}/AUC_{inf}$
$AUC_{\%extrap}$	Percent of AUC extrapolated to infinity in AUC_{inf}

Following administration, $C_{max.}$ t_{max}, CLST and TLST will be obtained directly from the experimental observations. If multiple maxima occur at equal concentrations after an infusion, the first temporal value will be used.

$AUC_{0\text{-}14\ day}$, $AUC_{0\text{-}12\ wk}$ and AUC_{inf} will be estimated using the linear trapezoidal rule.

Values of $AUC_{0\text{-}14\ day}$ and C_{max} associated with Dose 1 Infusion 2 will be listed but excluded from descriptive statistics and statistical analysis if the time of the last concentration following Dose 1 Infusion 1 is outside ± 2 day window around Day 15.

Values of $AUC_{0\text{-}12\ wk}$ will be listed but excluded from descriptive statistics and statistical analysis if the time of the last concentration following Dose 1 Infusion 2 is outside ± 2 week window around Week 12.
The terminal half-life, $t_{1/2}$, where determined, will be calculated as $\ln(2)/\lambda_z$. The number of data points included in the regression will be determined by visual inspection, but a minimum of three data points in the terminal phase, excluding C_{max}, will be required to estimate λ_z. λ_z values (and consequently $t_{1/2}$ and AUC_{inf} values) will be considered unreliable estimates if the time period over which an individual λ_z was required is less than twice the resultant $t_{1/2}$ or the adjusted coefficient of determination 'Rsq' is less than or equal to 0.8. Additional exclusions of PK parameters, if any, will be described in the CSR.

5.3 EFFICACY

ACR20/50/70

The ACR composite score evaluates clinical improvement relative to an initial assessment for clinical trials in subjects with RA.

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
- Investigator's Global Health Assessment
- Subject's assessment of pain
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- C-Reactive Protein (CRP)

ACR50 and ACR70 are defined in a similar fashion to ACR20 but require at least 50 and 70 percent improvement respectively. Method for handling missing data is described in the appendice 2.

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, and CRP, as follows:

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

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 detectable 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.

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 4.

Hybrid ACR Response

Hybrid ACR response is a continuous score of the mean improvement in the core set measures combining the ACR20, ACR50, and ACR70 response rates.

The hybrid ACR can be calculated when all 7 components are available following the table below (American College of Rheumatology Committee to Reevaluate Improvement Criteria, 2007):

	Mean % change in all 7 core set measures			
ACR Status	<20	>=20, <50	>=50, <70	>=70
Not ACR20	Mean % change	19.99	19.99	19.99
ACR20 but not ACR50	20	Mean % change	49.99	49.99
ACR50 but not ACR70	50	50	Mean % change	69.99
ACR70	70	70	70	Mean % change

If a core set measure worsens by > 100% , the percentage change will be limited to 100%.

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 3.

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 3.

5.4 SAFETY

Adverse Event of Interest (AEOI)

An AEOI is defined as a noteworthy TEAE 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 AEOIs for this study will include:

- infusion reactions including hypersensitivity,
- cardiac disorders,
- serious infections,
- progressive multifocal leukoencephalopathy,
- hematological reactions,
- hepatitis B reaction,
- opportunistic infections
- hypogammaglobulinemia.
- severe mucocutaneous reactions,
- gastrointestinal perforation

Events of interest were identified using the latest versions of pre-specified Standardised MeDRA query (SMQ) where 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 where SMQ is not available. Appendix 5 provides the search strategy used to retrieve the events of interest. The preferred terms used in the searches are stored in a central PRA server location for analyses.

Exposure Adjusted Incidence Rate (EAIR) for Adverse Events and Adverse Event of Interest

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 $= \frac{n}{T} = \frac{n}{\sum ti}$,

where n is the number of subjects with events, ti is a subject's exposure time under a given unit and T is the total exposure time under a given time unit of the subjects in the group. If a subject has multiple events, the ti is the time from the first dose date of the respective treatment to the onset of the first event. For those subjects who crossed over from one IP treatment during the 1st dose to another IP treatment during the 2nd dose, the exposure time following each of the doses will be counted in the respective treatment

group. For a subject with no event, the *ti* is set to the total exposure time duration of IP exposure (as defined in Section 5.1) for that subject.

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 at 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.

5.5 PHARMACODYNAMICS

Complete depletion of CD19+ cell count

Complete depletion of CD19+ cell count at any post-dose time is defined as CD19+ cell counts < 20 cell/uL (0.02 x10^9 cell/L). Subjects with missing CD19+ cell count at baseline or subjects with CD19+ cell count < 20 cell/uL at baseline will be excluded from the derivation of complete depletion of CD19+ cell count.

Duration of CD19+ B-cell complete depletion

This variable will be defined only for subjects who had a CD19+ B-cell complete depletion for at least one post-dose time. It is defined as time from the first incidence of complete depletion of CD19+ cell count to when CD 19+ cell count first increases to >=20 cell/uL. Subjects whose CD 19+ cell count doesn't increase to >=20 cell/uL will be censored at the last CD19 assessment date.

6. ANALYSIS SETS

The primary statistical analysis for the PK endpoints will be based on the PK parameter analysis set. Sensitivity analysis for the PK endpoints will be based on the per-protocol (PP) PK parameter analysis set. The primary statistical analysis for the PD endpoint and efficacy endpoints will be performed using the full analysis set (FAS). The Per-protocol analysis set will be used for sensitivity analyses of the key efficacy endpoints. The analysis of safety endpoints will be based on the safety analysis set. The immunogenicity analysis will be based on anti-drug antibody analysis set.

6.1 FULL ANALYSIS SET

The FAS includes all subjects randomized in the study, with treatment assignment based on treatment the subject is randomized to (regardless of actual treatment received).

6.2 PER-PROTOCOL ANALYSIS SET

The per-protocol (PP) analysis set includes all randomized subjects who have had two full infusions for the 1st dose (drug compliance of 90%-110%), have completed the week 24 disease assessment (complete DAS28-CRP assessment in the week 24 window of day 106-210 and before the 1st infusion of the 2nd dose), and did not experience a protocol deviation up to week 24 that affects their evaluation for the secondary objectives of the study to assess clinical efficacy. The protocol deviations that affect evaluation of the secondary objectives will be determined based on a blinded data review prior to database lock. Analyses for the per-protocol analysis set will be based on actual treatment received.

6.3 SAFETY ANALYSIS SET

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

6.4 PHARMACOKINETIC CONCENTRATION ANALYSIS SET

The PK concentration analysis set is defined as the subset of subjects in the safety analysis set who received the full protocol-specified dose on Day 1 and had at least one evaluable serum concentration (including results below the quantifiable limit) of ABP 798 or rituximab. Pharmacokinetic concentration data from subjects will be analyzed according to the actual treatment received. Subjects to be excluded from the PK concentration analysis set will be determined based on a blinded data review prior to database lock.

6.5 PHARMACOKINETIC PARAMETER ANALYSIS SET

The PK parameter analysis set is defined as the subset of subjects in the safety analysis set who received the full protocol-specified dose on Day 1 and had an evaluable ABP 798 or rituximab serum concentration time profile. The PK parameter analysis set will be used for the primary statistical analysis of PK endpoints. Pharmacokinetic parameter data from subjects will be analyzed according to the actual treatment received. Subjects to be excluded from the PK parameter analysis set will be determined based on a blinded data review prior to database lock.

6.6 PER-PROTOCOL PHARMACOKINETIC PARAMETER ANALYSIS SET

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

6.7 ANTI-DRUG ANTIBODY ANALYSIS SET

Anti-drug antibody analysis set is defined as the subset of subjects in the safety analysis set who had at least 1 evaluable antibody test. Immunogenicity data from subjects will be analyzed according to the actual treatment received.

7. INTERIM ANALYSES

No interim analyses are planned for this study.

A Data Monitoring Committee (DMC) external to Amgen and PRA will be formed with members consisting of individuals chosen for their expertise in inflammatory disorders. 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). The DMC will also review an initial safety analysis after the first 18 subjects have received the first dose.

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.

8. DATA REVIEW

8.1 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 1.3, Implementation Guide version v3.1.3) conventions. Analysis datasets will be created using SAS® and following CDISC Analysis Data Model (ADaM, version 2.1, Implementation Guide 1.0) standards.

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

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

8.2 DATA SCREENING

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

Review of a post-freeze dry run of TFLs allows for further data screening prior to final database lock for the entire study. This dry run will be discussed with the sponsor in data review meetings to identify any final data issues and seek corrections prior to the final database lock for the entire study. The PRA statistician and the sponsor must approve database lock.

9. STATISTICAL METHODS

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

The final analysis will be performed after all subjects have completed or have had the opportunity to complete the week 48/EOS assessment.

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. Confidence intervals will be provided where specified.

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. Confience intervals will be provided where specified.

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.

9.1 SUBJECT DISPOSITION

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

- Number of subjects randomized will be tabulated by region, country and center based on the FAS.
- Number of subjects randomized will be tabulated by stratification factors based on the FAS.
- Subject disposition (including number randomized, treated with ABP 798/rituximab (US)/rituximab (EU), completed treatment, discontinued treatment with reason of discontinuation, completed study, and discontinued study with reason of discontinuation) using each of the analysis sets defined in Section 6.

- Summaries of analysis sets with reason for exclusion for all screened subjects.
- Randomization list of subjects and their actual versus randomized treatment group for all randomized subjects.

9.2 PROTOCOL DEVIATIONS

Protocol deviation (PD) data will be entered into the Clinical Trials Management System (CTMS). The study team will conduct on-going reviews of the PD data from CTMS. The per-protocol analysis set and per protocol PK parameter analysis set must be finalized at the post-freeze data review meeting (or earlier), prior to the database lock.

Based on the PD data entered into CTMS, a summary of important PDs will be tabulated using number and percentage of subjects with important PD by deviation type and randomized treatment arm. A listing of subjects with important PDs will be provided (with a flag indicating whether the deviation leads to exclusion from the per-protocol and per-protocol pharmacokinetic analysis sets). A summary table and listing of eligibility criteria deviations will also be tabulated showing the violations of the inclusion/exclusion criteria for each subject.

9.3 TREATMENTS

9.3.1 Extent of IP Exposure

For the IP (ABP 798, rituximab (US) or rituximab (EU)), summary statistics will be provided for the total number of doses administered, total dose received, total duration of IP exposure, number of subjects with four full infusions and number of subjects with at least one partial infusion (including missed infusion), number of subjects with at least one infusion delay, number of subjects with at least one infusion missed, and number of subjects with at least one infusion interruption by treatment group. An IP administration summary will also be provided by the reported visit for each dosing/infusion instance, with summaries of the number of subjects receiving a full or partial infusion, infusion delay, infusion missed and infusion interruption as well as reasons, and reasons for ending IP by treatment group. The percentages for the IP administration summary will be based on the number of subjects with the given visit. The analysis will be performed using the safety analysis set according to the actual treatment received.

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.

9.3.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded by WHO-DD and will be summarized by preferred name and treatment group. The prior medications and concomitant medications will be summarized by treatment groups. 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.

9.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following demographics and baseline characteristics will be summarized by treatment for each of the analysis sets defined in Section 6.

- age (in years, at time of signing informed consent) and age category (<65 vs ≥65),
- race,
- sex,
- ethnicity,
- height,
- weight,
- body mass index (BMI),
- BSA,
- geographic region (North America, Eastern Europe, and Western Europe),
- Number of prior biologic use for RA (1 vs. >1),
- Number of prior biologic use for RA (1, 2, 3, etc.),
- seropositivity (RF-positive and/or CCP-positive vs. RF-negative and CCP-negative),
- Duration of RA (in years) and duration of RA category (<5, ≥5 years),
- DAS28-CRP,
- swollen joint count(66 and 28 counts)
- tender joint count, (68 and 28 counts)
- 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),
- baseline methotrexate dose.

Medical conditions at screening and the status of the medical condition at randomization (continuing versus resolved) will be summarized by SOC and PT and tabulated by treatment groups ABP 798/ABP 798, rituximab (US)/ABP 798, rituximab

(EU)/rituximab (EU) and total. The analysis will be performed using the safety analysis set according to the actual treatment received.

9.5 PHARMACOKINETIC ANALYSES

9.5.1 Pharmacokinetic Concentrations

Serum rituximab and ABP 798 concentrations will be summarized descriptively by treatment and nominal sampling time point for the PK concentration analysis set. The following descriptive statistics will be calculated at each of the sampling times: arithmetic mean (mean), coefficient of variation (CV), SD, Q1, Q3, Geometric mean, Geometric CV, minimum, median, maximum and the number of measurements. For calculation of summary concentrations, values below the quantifiable limit (BQL) will be set to zero.

In the event that a subject does not receive the full protocol-specified infusion, subsequent PK samples may be considered not evaluable and excluded from the descriptive statistics and mean concentration-time profiles. In addition, if samples are collected with a substantial deviation from nominal time that impacts the presentation of PK data, they will be excluded from the PK concentration vs nominal time profile. The samples excluded from the PK concentration analysis will be determined based on a blinded data review prior to unblinding for the final analysis.

Individual and mean (±SD) serum concentration-time profiles of rituximab and ABP 798 will be presented graphically using nominal time by treatment on a semi-logarithmic and a linear scale.

9.5.2 Pharmacokinetic Parameters

PK parameters for ABP 798 and rituximab will be estimated using noncompartmental analysis methods with Phoenix WinNonlin® Version 6.4 or higher (Pharsight Corp., St. Louis, MO).

In the event that a subject does not receive the full protocol-specified infusion, subsequent PK samples may be considered not evaluable and thus certain PK parameters may not be reportable. In addition, if the full protocol-specified dose was given but there was a long dose interruption or unusually long infusion duration that was deemed to impact PK, the PK profile may be considered not evaluable. The subject exclusion from the PK parameter analysis set will be determined based on a blinded data review prior to unblinding for the final analysis. Any such exclusion will be clearly listed in the CSR along with justification for exclusion.

Pharmacokinetic parameters will be listed by subject and summarized descriptively by treatment for the PK parameter analysis set. The following descriptive statistics will be provided: n, arithmetic mean, SD, Q1, Q3, minimum, median and maximum. Only n, median, Q1, Q3, minimum and maximum will be reported for t_{max}. In addition, geometric mean, and geometric CV will be calculated for AUC_{inf}, $AUC_{0\text{-}14\ day}$, $AUC_{0\text{-}12\ wk}$, C_{max} , CLST2 , $t_{1/2,}$ λz , CL, MRT, AUC%extrap and $AUC_{last}/AUC_{inf.}$

The serum PK parameters will be estimated from the individual concentration data for all subjects in the PK parameter analysis set. In estimating the PK parameters, BQL values at

the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Actual sampling times will be used in all computations.

PRIMARY STATISTICAL ANALYSIS

The PK similarity will be demonstrated by comparing the 90% CI for the GMR of test (ABP 798)-to-reference (US-licensed rituximab or EU-authorized rituximab) and rituximab [US] to rituximab [EU] for AUC_{inf} and for C_{max} following the second infusion of the first dose with the bounds of 0.8 to 1.25. Point estimates and CIs for the GMR will be estimated from an analysis of covariance model using the PK parameter analysis set.

For AUC_{inf} and C_{max} after second infusion of the first dose, the point estimates and 90% CIs for the GMR for will be estimated using an analysis of covariance model adjusted for weight and geographic region. A sample SAS code for PROC MIXED is displayed below:

CCI

The geometric least square means for each treatment will be presented. The ratios of the geometric means for the comparison of the test treatment to the reference treatment will be obtained by exponentiating the difference of the means on the natural log scale. The CIs will be obtained by exponentiating the CI for the difference between the means on the log scale. Plots of the ratio of geometric means and 90% CI will be displayed.

Additionally, the similarity between PK endpoints of rituximab (US) and rituximab (EU) will be evaluated as well. The GMRs and 90% CIs will be generated for other PK endpoints: $AUC_{0\text{-}14\ day}$, $AUC_{0\text{-}12\ wk}$, and C_{max} after the first infusion of the first dose by using the same methods as stated above.

SENSITIVITY ANALYSES

A sensitivity analysis of all PK parameters will be analyzed similarly to the primary statistical analysis using the PP PK parameter analysis set.

In addition, the following sensitivity analyses will be performed on the PK parameter analysis set:

- The point estimates and CIs for the GMR will be estimated using a model similar to the primary statistical analysis model but excluding all covariates.
- The point estimates and CIs for the GMR will be estimated using the primary statistical analysis model for the subgroups of subjects with negative binding ADA status and negative neutralizing ADA status during first dose period.

9.6 PHARMACODYNAMICS ANALYSES

All pharmacodynamics analyses will be performed using the FAS according to randomized treatment.

9.6.1 **CD19**

The pharmacodynamics similarity will be evaluated descriptively for the difference in percent of subjects with complete CD19+ cell depletion between test (ABP 798) and reference (US-licensed rituximab or EU-authorized rituximab) from day 1 to day 3. Subjects with baseline value less than 20 cell/uL or missing will not be evaluable for CD19+ depletion analyses. The point estimate, the 90% CI and the 95% CI will be provided for rate difference and will be estimated using a generalized linear model (specifically, a log-binomial regression model) with stratification factors as covariates. A sample SAS code for PROC GENMOD is displayed below:

CCI

Note: The contrasts in the estimate statement may need to be changed depending on the order of the treatments.

Descriptive statistics for CD19+ counts as well as change from baseline will be provided at day 2 and day 3.

In addition, for duration of CD19 complete depletion, KM estimates and 90% CIs will be calculated by randomized treatment group for event time quartiles.

9.6.2 **IgA, IgG and IgM**

The total IgA, IgG and IgM levels as well as change from baseline will be summarized descriptively by treatment and visit.

9.7 EFFICACY ANALYSES

All efficacy analysis will be performed using the FAS based on subject's randomized treatment. Sensitivity analysis of DAS28 at week 24 will also be performed using the per-protocol analysis set based on the actual treatment the subject received.

Analyses will be performed for two different time periods:

1. From day 1 until week 24 (efficacy analysis visit weeks 8, 12 and 24), only including results prior to 1st infusion of 2nd dose. Subjects who had the 1st infusion of 2nd dose prior to week 24 will have their efficacy endpoints data censored at the timing of 1st infusion of 2nd dose. For example, if disease

assessment is done at day 1 of week 16 and 1st infusion of 2nd dose is done on the same day, then the disease assessment on day 1 of week 16 will be included in modeling, but any disease assessment after that day will not be included.

2. Day 1 through EOS (efficacy analysis visit weeks 8, 12, 24, 40 and 48). Analyses will be performed separately for all subjects and the subgroup of subjects who received the 1st infusion of the 2nd dose at week 24 (i.e., excluding early retreatment subjects as defined in section 5.1).

If PK similarity is established between rituximab (US) and rituximab (EU), the 2 arms will be combined into a single reference arm for the primary assessment of clinical equivalence of DAS28-CRP change from baseline at week 24 between ABP 798 and rituximab. The results for ABP 798 vs. rituximab (EU) and ABP 798 vs. rituximab (US) will be provided for descriptive purposes. If PK similarity is not established, the ABP 798 arm will be compared to each of the individual rituximab arms separately to establish clinical equivalence of ABP 798 to the individual reference arms.

The pooling of the reference arms for ACR20/50/70 and hybrid ACR analyses will be conducted similarly.

9.7.1 DAS28-CRP

PRIMARY STATISTICAL ANALYSIS

DAS28-CRP at Week 24

The analyses will be performed on the FAS based on the day 1 through week 24 time period described above, with observed data. Subjects with missing baseline DAS28-CRP will not be included in the analysis since no change from baseline can be calculated. Analyses will assess the hypothesis that there are no clinically meaningful differences between ABP 798 and rituximab arms in DAS28-CRP change from baseline at week 24. This primary efficacy endpoint will be tested by comparing the 2-sided 90% CI of the change from baseline at week 24 of DAS28-CRP between ABP 798 and rituximab arms with an equivalence margin of (-0.6, 0.6).

To evaluate treatment differences across time points at which DAS28-CRP was assessed, repeated-measures analysis will be utilized for the day 1 through week 24 time period described above. Data from all assessed postbaseline time points will be included in the analysis. Besides stratification variables, baseline DAS28-CRP value, visit (week), treatment, and treatment-by-visit interaction will be included in the models, with visit as a categorical variable. The adjusted mean with 95% CI for each arm and 90% and 95% CIs for the mean difference will be constructed for mean difference of DAS28-CRP change from baseline between ABP 798 and rituximab arms at each time point.

The mixed model repeated measures analysis will be implemented using PROC MIXED in SAS. Because the time points at which measurements occur are not equally spaced (8, 12, and 24 weeks) and because measurements over time are expected to be correlated, with correlation coefficients being greater for time points that are closer together, a

spatial covariance structure denoted SP(POW) in SAS will be used. However, before implementing this structure, its appropriateness will be checked by choosing the smaller Akaike's information criterion when comparing the SP(POW) covariance structure with unstructured covariance structure. Example code for PROC MIXED with three treatment groups is displayed below:

CCI

Note: The contrasts in the lsmestimate statement may need to be changed depending on the order of the treatments. Only the individual arm comparison SAS code is presented.

DAS28-CRP at Other Time Points

For time period from Day 1 to EOS, the treatment difference and its confidence intervals will be estimated using an ANCOVA model with baseline DAS28-CRP measurement and stratification factors as covariates at each visit window. A sample SAS code for ANCOVA model using PROC MIXED is displayed below:

CCI

Note: The contrasts in the estimate statement may need to be changed depending on the order of the treatments. Only the individual arm comparison SAS code is presented.

SENSITIVITY ANALYSES

To assess the robustness of the DAS28-CRP at week 24 results, the repeated measures analysis described above will be repeated using the PP analysis set based on the day 1 through week 24 time period described above. In addition, DAS28-CRP change from

baseline at week 24 will be analyzed using ANCOVA adjusting for stratification factors and baseline DAS28-CRP results.

A sensitivity analysis will also be done to explore the impact of the baseline covariates in section 9.4 on DAS28-CRP at week 24 in addition to the stratification factors. A stepwise model selection (with <0.25 p-value to enter the model and <0.1 to stay in the model) will be fit using PROC GLM and will be used to determine if any of the covariates have significant impact on the outcome variable. The final repeated measures model will be fit using PROC MIXED and will maintain treatment, the stratification factors, baseline DAS28-CRP, visit and visit by treatment regardless and the covariates identified by the stepwise model and the same covariance structure selected in the primary statistical analysis regardless. This additional exploration will be performed on the FAS based on the day 1 through week 24 time period described above.

Additional sensitivity analysis considering the drop-out and missing value will be described in the section 9.7.4.

In addition, for each subgroup (described in section 4.4) the DAS28-CRP at week 24 will also be examined in the subgroups. These additional explorations will be performed on the FAS based on the day 1 through week 24 time period described above by using the repeated measures analysis with the same covariance structure chosen in the primary statistical analysis. The 90% CI and 95% CIs of difference in mean change from baseline of DAS28-CRP will be displayed.

The DAS28-CRP change from baseline will be plotted by treatment and visit for the FAS with adjusted mean and 95% CI.

9.7.2 ACR 20/50/70

The analyses of ACR20/50/70 are descriptive. The RR of ACR20/50/70 at week 8, week 12 and week 24 (refers to the analysis visit) will be analyzed based on the day 1 through week 24 time period using a repeated measures analysis, where data are included as observed for both FAS and PP, unless otherwise specified. 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 a log link and an AR (1) correlation structure. Both 90% CI and 95% CI will be provided.

A sample SAS code for PROC GENMOD with the repeated statement is displayed below:

CCI

CCI

Note: The contrasts in the estimate statement may need to be changed depending on the order of the treatments. Only the individual arm comparison SAS code is presented.

The risk difference (RD) of ACR20 at week 8, week 12 and week 24 between ABP 798 and rituximab arms and corresponding 90% and 95% CIs will be displayed based on a GEE model similar to the above model with the link function changed to 'link=identity' and without the exponential transformation option under LSMESTIMATE and LSMEANS statement.

From Day 1 to EOS, the RR of ACR20/50/70 between ABP 798 and rituximab arms and their corresponding CIs will be estimated at each visit (weeks 8, 12, 24, 40 and 48) using generalized linear model (specifically, a log-binomial regression model) adjusted for the stratification factors as covariates with observed data. A sample SAS code for PROC GENMOD is displayed below:

CCI

Note: The contrasts in the estimate statement may need to be changed depending on the order of the treatments. Only the individual arm comparison SAS code is presented.

The RD of ACR20 between ABP and rituximab arms and their corresponding CIs will be obtained, based on a similar generalized linear model with link function changed to 'link=identity' and without the exponential transformation option under LSMESTIMATE and LSMEANS statements.

The adjusted percent of subjects achieving ACR20/50/70 will be plotted by treatment and week for the FAS accordingly.

9.7.3 Hybrid ACR

The analyses of hybrid ACR are descriptive. The mean difference of hybrid ACR score at week 8, week 12 and week 24 (refers to the analysis visit) will be analyzed using a repeated measures analysis described in section 9.7.1. From Day 1 to EOS, the mean difference and its confidence intervals will be estimated using an ANOVA model with stratification factors as covariates at each visit window. A similar sample SAS code for it is displayed in section 9.7.1.

9.7.4 Methods for Handling Dropouts and Missing Data for Efficacy

For ACR, the determination of ACR20/50/70 response will be based on the data available at each visit (refer to Appendix 2 for handling missing ACR individual components), taking into account prorated tenderness and swollenness of joints.

For the primary DAS28-CRP analysis, the primary repeated measures model will be fit to the observed data. The rate of missing DAS28-CRP at week 24 will be tabulated with reasons, such as missing baseline, incomplete week 24 assessment (missing up to 3 of 4 components), outside of the defined week 24 analysis time frame, missing week 24 component assessments (missing all 4 components), and discontinued from the study early prior to week 24 (day 210).

Tipping point analyses will be performed for the efficacy endpoints of DAS28-CRP change from baseline at week 24 based on ANCOVA model using FAS analysis set to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing not-at-random assumptions). Assumptions (tipping point) under which the 90% CI no longer rules out unacceptable differences in efficacy as determined by DAS28-CRP change from baseline at week 24 between ABP 798 and reference (Rituximab (US) and Rituximab (EU)) will be identified.

In this analysis, all the observed data will be included as non-missing, regardless of adherence to treatment or use of prohibited medication. The analysis will be performed using a general three-step approach:

(1) Multiple imputation will be done using PROC MI to generate multiple (e.g., 10) imputed datasets by imputing missing data assuming monotone missing pattern and that subjects with missing data have, on average, worse or better efficacy compared to those who have values. The mean difference between the (unobserved) missing values and observed values (refer to as shift) can vary independently for the different treatment groups. For this analysis, the shifts for Rituximab(EU) and Rituximab(US) are assumed to be the same.

(2) Each of these imputed datasets (which contains identical values of non-missing data but different values imputed for missing data) is analyzed using standard SAS procedure, e.g., PROC GLM, PROC GENMOD, etc.

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

For DAS28-CRP change from baseline at week 24, seven equally spaced shifts (-0.9 to 0.9 by 0.3) for the DAS28-CRP change from baseline for subjects with missing data will be explored. A sample SAS code for given shifts is given as follows:

CCI

CCI

Note: Only the individual arm comparison SAS code is presented.

9.7.5 Multiplicity

No multiplicity adjustment will be done for efficacy endpoints.

9.7.6 Pooling of Sites

All sites will be pooled together for all analyses.

9.8 SAFETY ANALYSES

All safety analyses will be performed on the Safety analysis set based on subject's actual treatment received. In general, summaries will be provided separately for (1) day 1 to 1st infusion of the 2nd dose of IP (exclusive) for subjects who received 2nd dose or to week 24 (day 175) or EOS (whichever is earlier) for subjects who didn't receive 2nd dose and (2) entire study, unless otherwise specified.

9.8.1 Adverse Events

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

Only TEAE will be tabulated.

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

Subject incidence of the following AEs will be tabulated by preferred term in descending order of frequency in the ABP798 column:

- treatment-emergent AEs
- grade 3 or higher treatment-emergent AEs
- treatment-emergent AEs leading to discontinuation of IP/study
- treatment-emergent AEs leading to infusion delay/infusion not given
- treatment-emergent AEOIs

For treatment-emergent AEOIs, the point estimate and 95% CI for RD of the subject incidence between ABP and the reference product are provided.

Exposure adjusted subject incidence rate (EAIR) of the following AEs will be tabulated by preferred term in descending order of frequency in the ABP798 column for the entire study:

- treatment-emergent AEs
- treatment-emergent AEOIs

The point estimate and 95% CI for RR of the EAIR between ABP and the reference product are also provided.

AEs leading to discontinuation of 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 subjects have an AE for action taken with Investigational Medicinal Product of "dose delayed/not administered" checked, that AE leads to the infusion delay/infusion not given. If an AE leads to multiple actions taken with IP, only the last action will be captured in the eCRF.

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.

An overall summary table of treatment-emergent AEOIs will be displayed, providing the number and percent of subjects that are within each AEOI category. In addition, infusion reaction EOIs will also be summarized by PT and maximum CTCAE grade and also by infusion and PT.

A subject listing of AEs leading to discontinuation of IP/ study will be provided.

9.8.2 Deaths and Serious Adverse Events

Subject incidence of the following will be tabulated by SOC, PT and maximum severity grade per CTCAT V4.03:

- serious treatment-emergent AEs

Subject incidence of the following will be tabulated by preferred term in descending order of frequency of the ABP798 arm:

- serious treatment-emergent AEs
- treatment-emergent fatal AEs

A subject listing of SAEs and AEs with fatal outcome will be also provided.

9.8.3 Laboratory Data

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

Laboratory values and change from baseline will be summarized using descriptive statistics at each analysis visit by treatment. Shift tables of the worst on-study laboratory toxicity based on CTCAE v4.03 grading relative to baseline will be presented by treatment group. The shift tables will take into account all post-baseline (schedule and unscheduled) laboratory results for determination of worst on-study laboratory toxicity within the two summary timeframes listed previously. For labs with toxicity grading in two directions, for toxicity due to decreased value, the maximum grade is corresponding to the minimum post-baseline value. For toxicity due to increase value, the maximum grade is corresponding to the maximum post-baseline value. In addition, subject incidence tables and listings of grade ≥ 3 laboratory toxicities will be provided based on all post-baseline (scheduled and unscheduled) laboratory results for each of the two reporting periods. 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 differential
- Hematology – red blood cell parameters: hemoglobin, packed cell volume or hematocrit, red blood cell count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration
- Hematology – other parameters: platelets
- Serum chemistry – hepatobiliary parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, gamma glutamyl transferase
- Serum chemistry – general chemistry: sodium, potassium, albumin, total protein, non-fasting glucose
- Serum chemistry – renal function tests: urea, creatinine

9.8.4 Vital Signs and Physical Examination

Observed and change from baseline in vital signs will be summarized by parameter and treatment. Descriptive statistics will be shown for baseline, each post-baseline time point up to EOS, and the change from baseline to each post-baseline time point.

9.8.5 Immunogenicity

The number and percentage of subjects developing binding and neutralizing ADA will be tabulated by treatment .

Pre-existing antibody incidence and developing antibody incidence will be summarized. Pre-existing antibody is defined as a positive antibody result at baseline (see Section 5.1 for definition of baseline). Developing antibody incidence is defined as a negative or no binding antibody result at baseline and a positive antibody result at a post-baseline time point. 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.

In addition, the frequency and percent of subjects with positive binding or neutralizing ADA results will be tabulated by visit and treatment.

9.8.6 Methods for Handling Missing Data for Safety

Missing safety 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* <1st dose	Stop Date: Complete: *yyyymmdd* ≥1st dose	Stop Date: Partial: *yyyymm* <1st dose *yyyymm*	Stop Date: Partial: *yyyymm* ≥1st dose *yyyymm*	Stop Date: Partial: *yyyy* <1st dose *yyyy*	Stop Date: Partial: *yyyy* ≥1st dose *yyyy*	Stop Date: Missing
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.

Imputation rules for partial or missing death dates:

1. 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.
2. 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.

9.9 EXPLORATORY ANALYSES

9.9.1 DAS28-CRP Individual Components

The DAS28-CRP individual components of swollen (28) and tender joint counts (28), subject's global health assessment, and CRP will be summarized as change from baseline descriptively by treatment and visit using the FAS as observed.

9.9.2 ACR Individual Components

The ACR individual components of swollen (66) and tender joint counts (68), subject's global health assessment, investigator's global assessment, subject's assessment of disease-related pain, HAQ-DI and CRP will be summarized descriptively by treatment and visit using the FAS as observed.

10. CHANGE FROM PROTOCOL SPECIFIED ANALYSIS

Druing the development of this document, pharmacokinetic concentration analysis set was defined in the SAP to better describe the analysis population criteria which will be the population set in the PK serum concentration TFLs. Additionally, the definition of per protocol and per protocol pharmacokinetic parameter analysis sets were modified to include "important protocol deviation" instead of "protocol deviation" to properly reflect the population included in this analysis set.

Furthemore, per protocol analysis set criteria also includes the condition of 2 full infusion of the first dose, meaning that the drug compliance of 90%-110% of the first dose, additionally to ensure this analysis set follows the protocol requirements.

11. VALIDATION

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.

12. REFERENCES

Ke C, Wang J, Zhang C, Jiang Q, Snapinn S. On errors in stratified randomization. Statistics in Biopharmaceutical Research 2017; 9 (2): 225-33.

Volkmann ER, Agrawal H, Maranian P, Furst DE. Rituximab for rheumatoid arthritis: A meta-analysis and systematic review. Clin Med Insights: Therapeutics 2010:2 749-760.

American College of Rheumatology Committee to Reevaluate Improvement Criteria, 2007, A 286 Proposed Revision to the ACR20: The Hybrid Measure of American College of Rheumatology Response, Arthritis Rheum., Mar 15;57(2):193-202

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
AEOI	Adverse Event of Interest
AE	Adverse Event
ALT	Alanine Aminotranferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
BQL	Below Quantifiable Limit
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
CL	clearance
C_{last}	Last measurable Concentration
C_{max}	Maximum Concentration
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DAS	Disease Activity Score
DMARDs	Disease-modifying Anti-rheumatic Drugs
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EOI	End of Infusion
EOS	End of Study
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
GEE	Generalized Estimating Equation
GH	General Health

GMR	Geometric Mean Ratio
HAQ-DI	Health Assessment Questionnaire Disability Index
IP	Investigational Product
IPD	Important protocol deviation
IXRS	Interactive Voice or Web Response System
IV	Intravenous
KM	Kaplan-meier
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
NCA	Noncompartmental techniques
NCI-US	National Cancer Institute
NSAID	Non-steroidal Anti-inflammatory Drug
PD	Pharmacodynamic
PD	Protocol Deviations
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
Q1	25^{th} Percentile
Q3	75^{th} Percentile
RA	Rheumatoid Arthritis
RD	Risk Difference
RF	Rheumatoid Factor
RR	Risk Ratio
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SDAI	Simplified Disease Activity Index score
SDTM	Standard Data Tabulation Model
SI	International System of Units
SJC28	Swollen Joint Count (28 Joints)
SMQ	Standardised MedDRA Query
SOC	System Organ Class
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent Adverse Event
TFL	Tables, Figures, and Listings
T_{max}	Time to which the maximum serum concentration was observed
TJC28	Tender Joint Count (28 Joints)
TNF	Tumor Necrosis Factor

VAS	Visual Analog Scale
WHO-DD	World Health Organization Drug Dictionary
λz	Terminal elimination rate constant

APPENDIX 2 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

APPENDIX 3 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 DAS28 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.

APPENDIX 4 HAQ-DI SCORING ALGORTIHM

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.

APPENDIX 5 LIST OF EVENTS OF INTEREST AND THE ASSOCIATED SMQ AND EOI SEARCHING STRATEGIES

Event of Interest	Category of EOI query (SMQ, Amgen query, or SOC)	Search Strategy	Additional Medical Review of the SMQ or SOC dataset for confirmation of the 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
Cardiac disorders	Cardiac disorders (SOC)		No
Serious infections	Infections and Infestations (SOC)	CTCAE grade >=3 or the serious TEAE	No
Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy (Amgen query)	Broad	Yes
Hematological reactions	Hematopoietic cytopenia (SMQ)	Broad	No
Hepatitis B reactivation	Hepatitis B Infection (Amgen query)	Broad	Yes
Opportunistic infections	Infections and infestations (SOC)		Yes
Hypogammaglobulinemia	Immune mediated events associated with oncologic immune therapies (Amgen query)	Broad	Yes

Severe mucocutaneous reactions	Severe cutaneous adverse reactions (SMQ)	CTCAE grade >=3 or the serious TEAE, Broad search	No
Gastrointestinal perforation	Gastrointestinal perforation(SMQ)	Narrow	No

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

APPENDIX 6 LIST OF POST-TEXT TABLES, FIGURES, LISTINGS, AND SUPPORTIVE SAS OUTPUT APPENDICES

Table Number	Table Title
14.1	**Disposition and Analyzed Dataset Tables**
Table 14.1.1	Subject Analysis Sets by Treatment (All Screened Subjects)
Table 14-1.2.1.	Randomization by Region, Country and Center (Full Analysis Set)
Table 14-1.2.2.	Randomization by Stratification Factors (Full Analysis Set)
Table 14-1.3.1.	Subject Study Disposition by Treatment (Full Analysis Set)
Table 14-1.3.2.	Subject Study Disposition by Treatment (Safety Analysis Set)
Table 14-1.3.3.	Subject Study Disposition by Treatment (Pharmacokinetic Concentration Analysis Set)
Table 14-1.3.4.	Subject Study Disposition by Treatment (Pharmacokinetic Parameter Analysis Set)
Table 14-1.3.5.	Subject Study Disposition by Treatment (Per Protocol Analysis Set)
Table 14-1.3.6.	Subject Study Disposition by Treatment (Per Protocol Pharmacokinetic Parameter Analysis Set)
Table 14-1.3.7.	Subject Study Disposition by Treatment (Anti-drug Antibody Analysis Set)
14.2	**Demographic and Baseline Characteristics Data Tables**
Table 14-2.1.	Demographic and Baseline Characteristics by Treatment (Full Analysis Set)
Table 14-2.2.	Demographic and Baseline Characteristics by Treatment (Safety Analysis Set)
Table 14-2.3.	Demographic and Baseline Characteristics by Treatment (Pharmacokinetic Concentration Analysis Set)
Table 14-2.4.	Demographic and Baseline Characteristics by Treatment (Pharmacokinetic Parameter Analysis Set)
Table 14-2.5.	Demographic and Baseline Characteristics by Treatment (Per Protocol Analysis Set)

Table 14-4.8.8.	Summary of Swollen Joint Counts by Visit – DAS28-CRP Component (Full Analysis Set)
Table 14-4.8.9.	Summary of Tender Joint Counts by Visit – DAS28-CRP Component (Full Analysis Set)
Table 14-4.8.10.	Summary of Subject's Global Health Assessment by Visit – DAS28-CRP Component (Full Analysis Set)
Table 14-4.8.11.	Summary of CRP by Visit – DAS28-CRP Component (Full Analysis Set)
Table 14-4.10.1.1.	Repeated Measures Analysis of DAS28-CRP Change From Baseline at Week 24 Comparing ABP 798 with Pooled Rituximab (Full Analysis Set)
Table 14-4.10.1.2.	Analysis of DAS28-CRP Change From Baseline (ANCOVA) at Week 24 Comparing ABP 798 with Pooled Rituximab (Full Analysis Set)
Table 14-4.10.1.3.1.	Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 ThroughWeek 24 (Full Analysis Set)
Table 14-4.10.1.3.2.	Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through Week 24 (Per Protocol Analysis Set)
Table 14-4.10.1.4.1.	Analysis of DAS28-CRP Change From Baseline (ANCOVA) Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through End of Study (Full Analysis Set)
Table 14-4.10.1.4.2.	Analysis of DAS28-CRP Change From Baseline (ANCOVA) Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through End of Study (Per Protocol Set)
Table 14-4.10.1.6.	Tipping Point Analysis Results for Mean Difference of DAS28-CRP Change From Baseline at Week 24 for ABP 798 vs Pooled Rituximab with 90% Confidence Interval (Full Analysis Set)
Table 14-4.10.1.7.	Repeated Measures Analysis with Additional Selective Covariates for DAS28-CRP Change From Baseline at Week 24 Comparing ABP 798 with Pooled Rituximab (Full Analysis Set)
Table 14-4.10.5.1	Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing ABP 798 with Pooled Rituximab by Age Subgroup - Day 1 Through Week 24 (Full Analysis Set)
Table 14-4.10.5.2	Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing ABP 798 with Pooled Rituximab by Race Subgroup – Day 1 Through Week 24 (Full Analysis Set)

Table 14-6.1.2.	Overall Summary of Treatment-emergent Adverse Events by Treatment –Day 1 Through End of Study (Safety Analysis Set)
Table 14-6.2.1.1.	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment – Day 1 Until 1st Infusion of 2nd Dose (Safety Analysis Set)
Table 14-6.2.1.2.	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Treatment – Day 1 Through End of Study (Safety Analysis Set)
Table 14-6.2.2.1.	Treatment-emergent Adverse Events by Preferred Term and Treatment – Day 1 Until 1st Infusion of 2nd Dose (Safety Analysis Set)
Table 14-6.2.2.2.	Treatment-emergent Adverse Events by Preferred Term and Treatment – Day 1 Through End of Study (Safety Analysis Set)
Table 14-6.2.2.3.	Treatment-emergent Adverse Events by Age Subgroup, Preferred Term and Treatment – Day 1 Until 1st Infusion of 2nd Dose (Safety Analysis Set)
Table 14-6.2.2.4.	Treatment-emergent Adverse Events by Age Subgroup, Preferred Term and Treatment – Day 1 Through End of Study (Safety Analysis Set)
Table 14-6.2.3.1.	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, Maximum CTCAE Grade, and Treatment – Day 1 Until 1st Infusion of 2nd Dose (Safety Analysis Set)
Table 14-6.2.3.2.	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, Maximum CTCAE Grade, and Treatment – Day 1 Through End of Study (Safety Analysis Set)
Table 14-6.2.4.1.	Grade ≥3 Treatment-emergent Adverse Events by Preferred Term and Treatment - Day 1 Until 1st Infusion of 2nd Dose (Safety Analysis Set)
Table 14-6.2.4.2.	Grade ≥3 Treatment-emergent Adverse Events by Preferred Term and Treatment – Day 1 Through End of Study (Safety Analysis Set)
Table 14-6.3.1.1.	Treatment-emergent Adverse Events Leading to Discontinuation of IP/Study by Preferred Term and Treatment – Day 1 Until 1st Infusion of 2nd Dose (Safety Analysis Set)
Table 14-6.3.1.2.	Treatment-emergent Adverse Events Leading to Discontinuation of IP/Study by Preferred Term and Treatment – Day 1 Through End of Study (Safety Analysis Set)

Listing 16-2.7.3.	Subjects Who Experienced Serious Treatment-emergent Adverse Events (Safety Analysis Set)
Listing 16-2.8.1.	Subjects Who Experienced a Grade ≥3 Hematology Result (Safety Analysis Set)
Listing 16-2.8.2.	Subjects Who Experienced a Grade≥3 Serum Chemistry Result (Safety Analysis Set)
Listing 16-2.8.3.	Subject Binding and Neutralizing Antibody Classification – Through Entire Study (ADA Analysis Set)
Listing 16-2-8.4.	On-study Procedure (Safety Analysis Set)

SUPPORTIVE SAS OUTPUT APPENDICES

Appendix 1	Statistical Output of Table 14-4.1.1: Repeated Measures Analysis of DAS28-CRP Change From Baseline at Week 24 – Primary Analysis (Full Analysis Set)
Appendix 2	Statistical Output of Table 14-4.1.2: Analysis of DAS28-CRP Change From Baseline at Week 24 – Sensitivity Analysis (Full Analysis Set)
Appendix 3	Statistical Output of Table 14-4.1.3.1: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Visit – Day 1 Through Week 24 (Full Analysis Set)
Appendix 4	Statistical Output of Table 14-4.1.3.2: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Visit – Day 1 Through Week 24 (Per Protocol Analysis Set)
Appendix 5	Statistical Output of Table 14-4.1.4.1: Analysis of DAS28-CRP Change From Baseline by Visit – Day 1 Through End of Study (Full Analysis Set)
Appendix 6	Statistical Output of Table 14-4.1.4.2: Analysis of DAS28-CRP Change From Baseline by Visit – Day 1 Through End of Study (Full Analysis Set – Subgroup who received the 1st infusion of the 2nd dose at week 24)
Appendix 7	Statistical Output of Table 14-4.1.6: Tipping Point Analysis Results for Mean Difference of DAS28-CRP Change From Baseline at Week 24 for ABP 798 vs Rituximab with 90% Confidence Interval (Full Analysis Set)
Appendix 8	Statistical Output of Table 14-4.1.7: Repeated Measures Analysis with Additional Selective Covariates for DAS28-CRP Change From Baseline at Week 24 (Full Analysis Set)

Appendix 9	Statistical Output of Table 14-4.2.1: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Age Subgroup - Day 1 Through Week 24 (Full Analysis Set)
Appendix 10	Statistical Output of Table 14-4.2.2: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Race Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 11	Statistical Output of Table 14-4.2.3: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Gender Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 12	Statistical Output of Table 14-4.2.5: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Binding Anti-drug Antibodies Status Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 13	Statistical Output of Table 14-4.2.6: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Neutralizing Anti-drug Antibodies Status Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 14	Statistical Output of Table 14-4.2.7: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Baseline Oral Corticosteroid Use Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 15	Statistical Output of Table 14-4.3.1: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Geographic Region Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 16	Statistical Output of Table 14-4.3.2: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Seropositivity Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 17	Statistical Output of Table 14-4.3.3: Repeated Measures Analysis of DAS28-CRP Change From Baseline by Prior Biologics Use Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 18	Statistical Output of Table 14-4.5.1.1: Repeated Measures Analysis of ACR20 by Visit – Day 1 Through Week 24 (Full Analysis Set)
Appendix 19	Statistical Output of Table 14-4.5.1.2: Repeated Measures Analysis of ACR20 by Visit – Day 1 Through Week 24 (Per Protocol Analysis Set)

Appendix 20	Statistical Output of Table 14-4.5.2.1: Analysis of ACR20 by Visit – Day 1 Through End of Study (Full Analysis Set)
Appendix 21	Statistical Output of Table 14-4.5.2.2: Analysis of ACR20 by Visit – Day 1 Through End of Study (Full Analysis Set – Subgroup who received the 1st infusion of the 2nd dose at week 24)
Appendix 22	Statistical Output of Table 14-4.5.3.1: Repeated Measures Analysis of Hybrid ACR by Visit – Day 1 Through Week 24 (Full Analysis Set)
Appendix 23	Statistical Output of Table 14-4.5.3.2: Repeated Measures Analysis of Hybrid ACR by Visit – Day 1 Through Week 24 (Per Protocol Set)
Appendix 24	Statistical Output of Table 14-4.5.3.3: Analysis of Hybrid ACR by Visit – Day 1 Through End of Study (Full Analysis Set)
Appendix 25	Statistical Output of Table 14-4.5.3.4: Analysis of Hybrid ACR by Visit – Day 1 Through End of Study (Full Analysis Set – Subgroup who received the 1st infusion of the 2nd dose at week 24)
Appendix 26	Statistical Output of Table 14-4.6.1: Repeated Measures Analysis of ACR50 by Visit – Day 1 Through Week 24 (Full Analysis Set)
Appendix 27	Statistical Output of Table 14-4.6.2.1: Analysis of ACR50 by Visit – Day 1 Through End of Study (Full Analysis Set)
Appendix 28	Statistical Output of Table 14-4.6.2.2: Analysis of ACR50 by Visit – Day 1 Through End of Study (Full Analysis Set – Subgroup who received the 1st infusion of the 2nd dose at week 24)
Appendix 29	Statistical Output of Table 14-4.7.1: Repeated Measures Analysis of ACR70 by Visit – Day 1 Through Week 24 (Full Analysis Set)
Appendix 30	Statistical Output of Table 14-4.7.2.1: Analysis of ACR70 by Visit – Day 1 Through End of Study (Full Analysis Set)
Appendix 31	Statistical Output of Table 14-4.7.2.2: Analysis of ACR70 by Visit – Day 1 Through End of Study (Full Analysis Set– Subgroup who received the 1st infusion of the 2nd dose at week 24)
Appendix 32	Statistical Output of Table 14-4.10.1.1: Repeated Measures Analysis of DAS28-CRP Change From Baseline at Week 24

	Comparing ABP 798 with Pooled Rituximab (Full Analysis Set)
Appendix 33	Statistical Output of Table 14-4.10.1.2: Analysis of DAS28-CRP Change From Baseline (ANCOVA) at Week 24 Comparing ABP 798 with Pooled Rituximab (Full Analysis Set)
Appendix 34	Statistical Output of Table 14-4.10.1.3.1: Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 ThroughWeek 24 (Full Analysis Set)
Appendix 35	Statistical Output of Table 14-4.10.1.3.2: Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through Week 24 (Per Protocol Analysis Set)
Appendix 36	Statistical Output of Table 14-4.10.1.4.1: Analysis of DAS28-CRP Change From Baseline (ANCOVA) Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through End of Study (Full Analysis Set)
Appendix 37	Statistical Output of Table 14-4.10.1.4.2: Analysis of DAS28-CRP Change From Baseline (ANCOVA) Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through End of Study (Per Protocol Set)
Appendix 38	Statistical Output of Table 14-4.10.1.6: Tipping Point Analysis Results for Mean Difference of DAS28-CRP Change From Baseline at Week 24 for ABP 798 vs Pooled Rituximab with 90% Confidence Interval (Full Analysis Set)
Appendix 39	Statistical Output of Table 14-4.10.1.7: Repeated Measures Analysis with Additional Selective Covariates for DAS28-CRP Change From Baseline at Week 24 Comparing ABP 798 with Pooled Rituximab (Full Analysis Set)
Appendix 40	Statistical Output of Table 14-4.10.5.1: Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing ABP 798 with Pooled Rituximab by Age Subgroup - Day 1 Through Week 24 (Full Analysis Set)
Appendix 41	Statistical Output of Table 14-4.10.5.2: Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing ABP 798 with Pooled Rituximab by Race Subgroup – Day 1 Through Week 24 (Full Analysis Set)
Appendix 42	Statistical Output of Table 14-4.10.5.3: Repeated Measures Analysis of DAS28-CRP Change From Baseline Comparing

Appendix 52	Statistical Output of Table 14-4.12.1.2: Repeated Measures Analysis of Hybrid ACR Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through Week 24 (Per Protocol Analysis Set)
Appendix 53	Statistical Output of Table 14-4.13.1: Repeated Measures Analysis of ACR50 Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through Week 24 (Full Analysis Set)
Appendix 54	Statistical Output of Table 14-4.14.1: Repeated Measures Analysis of ACR70 Comparing ABP 798 with Pooled Rituximab by Visit – Day 1 Through Week 24 (Full Analysis Set)
Appendix 55	Statistical Output of Table 14-6.5.1.1: Overall Events of Interest Treatment-emergent Adverse Events by Treatment – Day 1 Until 1st Infusion of 2nd Dose (Safety Analysis Set)
Appendix 56	Statistical Output of Table 14-6.7.1: Exposure Adjusted Incidence Rate for Treatment-emergent Adverse Events by Preferred Term and Treatment - Day 1 Through End of Study (Safety Analysis Set)
Appendix 57	Statistical Output of Table 14-6.7.2: Exposure Adjusted Incidence Rate for Treatment-emergent Adverse Events of Interest by Treatment – Day 1 Through End of Study (Safety Analysis Set)
Appendix 58	Statistical Output of Table 14-9.3.1.1: Summary of Statistical Assessment of PK Parameters (PK Parameter Analysis Set)
Appendix 59	Statistical Output of Table 14-9.3.1.2: Summary of Statistical Assessment of PK Parameters for Negative Binding ADA Status Subgroup (PK Parameter Analysis Set)
Appendix 60	Statistical Output of Table 14-9.3.1.3: Summary of Statistical Assessment of PK Parameters for Negative Neutralizing ADA Status Subgroup (PK Parameter Analysis Set)
Appendix 61	Statistical Output of Table 14-9.3.1.4: Summary of Statistical Assessment of PK Parameters without Covariates (PK Parameter Analysis Set)
Appendix 62	Statistical Output of Table 14-9.3.2: Summary of Statistical Assessment of PK Parameters (Per Protocol PK Parameter Analysis Set)

APPENDIX 7 SHELLS FOR POST-TEXT TABLES, FIGURES, AND LISTINGS

See associated TFL shell document.