Statistical Analysis Plan

A Randomized, Double-Blind Study Evaluating the Efficacy, Safety, and Immunogenicity of ABP 798 Compared with Rituximab in Subjects with CD20 Positive B-cell Non-Hodgkin Lymphoma (NHL)

Test Drug: ABP 798

Sponsor:	Amgen Inc.
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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 20130109, titled "A Randomized, Double-Blind Study Evaluating the Efficacy, Safety, and Immunogenictiy of ABP 798 Compared with Rituximab in Subjects with CD20 Positive B-cell Non-Hodgkin Lymphoma (NHL)."

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 dated 07 January 2016 version 3.0 and eCRFs dated 17 SEP 2014. 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 so that programming can start earlier in the process. Versions of the SAP up to initial sponsor approval will be known as SAP1. SAP1.1 is issued to reflect protocol version 3.0. Changes following approval of SAP1.1 will be tracked in the SAP Change Log and a final version of the SAP, known as SAP2, will be issued for Amgen's approval prior to database lock.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is to evaluate the efficacy of ABP 798 compared with rituximab.

2.2 SECONDARY OBJECTIVES

The secondary objective is to assess the pharmacokinetics (PK), pharmacodynamics, safety, tolerability, and immunogenicity of ABP 798 compared with rituximab.

3. STUDY DESIGN

This is a randomized, double-blind study in adult subjects with Grade 1 or 2 follicular B-cell non-Hodgkin lymphoma (NHL) and low tumor burden. Approximately 250 subjects (125 per treatment group) will be randomized (1:1) to receive investigational product (IP) (ABP 798 or rituximab) at a dose of 375 mg/m^2 administered as an intravenous (IV) infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20. Tumor assessment will be performed at baseline and weeks 12 and 28. Subjects will be stratified by geographic region and age (> 60 vs. ≤ 60 years).

The primary efficacy endpoint is the risk difference of the overall response rate by week 28. Response to treatment will be assessed according to 1999 IWG-NHL criteria (Cheson et al,

1999). Investigators will assess the status of each subject's follicular B-cell NHL at baseline and weeks 12 and 28. Assessment will include physical examination and radiographic examination. Copies of all scheduled and unscheduled screening and on-study computed tomography (CT) scans performed to monitor or diagnose NHL must be submitted to the central imaging vendor, Perceptive Informatics, Inc. See the Independent Review Charter for details on the independent review of the imaging and clinical data.

A subject will remain on study until week 28. Subjects who discontinue IP before week 20 will be followed for 8 weeks after the last dose of IP and then complete the end of study visit.

An independent data monitoring committee (DMC) will evaluate the safety data throughout the study, including an initial safety review after the first 12 subjects have received at least 2 doses of IP. No formal interim analysis is planned.

3.1 SAMPLE SIZE CONSIDERATIONS

Approximately 250 subjects will be randomized in a 1:1 ratio to receive ABP 798 or rituximab.

3.2 RANDOMIZATION

Approximately 250 subjects will be randomized in a 1:1 ratio via Interactive Voice or Web Response System (IXRS) to receive IP (either ABP 798 or rituximab).

Randomization will be stratified by geographic region (Eastern Europe, Western Europe/Other, North America, Japan) and age (> 60 vs. ≤ 60 years).

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 generated using a permuted block design within each stratum. IXRS data is integrated into the electronic data capture (EDC) system for subject enrollment. IXRS data is then imported for external data reconciliation.

A third party vendor, ALMAC Clinical Technologies, 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 endpoint of the study is the RD of ORR by week 28.

4.2 SECONDARY VARIABLES

4.2.1 Efficacy

The secondary efficacy endpoint is RD of ORR at week 12.

4.2.2 Pharmacokinetics

The PK endpoints are serum concentrations at predose and immediately after the end of infusion at week 12.

4.2.3 Pharmacodynamics

The pharmacodynamics endpoints include:

- Percent of subjects with complete depletion of CD19+ cell count from baseline to study day 8
- Total immunoglobulin G (IgG) and immunoglobulin M (IgM) levels.

4.2.4 Safety

The safety endpoints include the following:

- Treatment-emergent adverse events (AEs)
- Treatment-emergent serious adverse events (SAEs)
- Clinically significant changes in laboratory values and vital signs
- Incidence of anti-drug antibodies (ADA)
- On-study progression-free survival (PFS)
- On-study overall survival (OS)

4.3 TERTIARY VARIABLES

Other variables that will be summarized are:

- Exposure to IP
- Concomitant medications.

4.4 PREDETERMINED COVARIATES AND PROGNOSTIC FACTORS

Unless stated otherwise, the following stratification factors will be adjusted as covariates in the model, be used as stratification variables in stratified analysis, or be used to examine efficacy in subgroups:

- Geographic region (Eastern Europe vs. Western Europe/Other vs. North America vs. Japan),
- Age (> 60 vs. ≤ 60 years)

Primary analyses that are intended to evaluate the treatment effect will be based on the IXRS stratification values, regardless of the subject's eCRF stratification values. For subgroup analyses where the subgroup factor is a stratification variable, an analysis similar to the primary analysis (except the inclusion of the subgroup factor) should be done for each subgroup defined by the eCRF values of the subgroup factor.

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

- Follicular lymphoma international prognostic index (FLIPI) (low, intermediate, high)
- Presence of B symptoms (yes vs. no)

5. DEFINITIONS

5.1 GENERAL

Actual Treatment Received

Defined according to the majority of doses received.

Change From Baseline

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

Disease Duration

The disease duration is the number of months from the date of original diagnosis of NHL 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 may be added.

Table 1. Calculation for Disease Duration

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

*If the duration equals 0, add 1 month.

Dose Delay

A dose will be considered delayed when the IP administration eCRF indicates that a dose was given but a reason for dose delay is present.

Dose Withheld

A dose will be considered withheld when the IP administration eCRF indicates that no dose is given and a reason for dose delay is present.

Duration of IP exposure

Duration of IP exposure in weeks will be defined as (end of study date – date of first dose of IP + 1) / 7.

Follicular Lymphoma International Prognostic Index and Risk Categories

The follicular lymphoma international prognostic index (FLIPI) is based on the following 5 prognostic factors:

- Age (≥ 60 years)
- Ann Arbor Disease Stage (Stage III-IV, Stage III includes IIIE, IIIES, and IIIS)
- Hemoglobin level (<120 g/L)
- Serum lactate dehydrogenase level (> upper limit of normal)
- Number of nodal sites (> 4)

Subjects with 0-1 risk factors are defined as low risk, subjects with 2 risk factors are defined as intermediate risk, and subjects with 3 or more risk factors are defined as high risk.

Study Baseline

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

no times are reported, 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 efficacy endpoints, baseline is defined as the last non-missing assessment prior to or on the date of randomization.

Study Day

Study day 1 is defined as the first day that IP is administered to the subject. The day before study day 1 is referenced as study day –1. The study day of a given assessment is calculated as (date of assessment – first dose date of IP + 1).

Study Investigational Product

Study IP is referred to as ABP 798 or rituximab.

Study Randomization

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

5.2 EFFICACY

Evaluable Disease Assessment

A subject's disease assessment on a particular date will be considered evaluable if an overall response of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), CR/unconfirmed (CRu), or relapsed disease can be established by the central, independent, blinded radiologists' and oncologist's assessments per the 1999 IWG-HNL.

Overall Response Rate (ORR)

The overall response rate is defined as the percentage of subjects with a CR, CRu, or PR as defined by the 1999 IWG-NHL criteria (Cheson et al, 1999). All subjects that do not meet the criteria for response for a given analysis will be considered non-responders. The ORR will be calculated separately based on the central, independent, blinded radiologists' and oncologist's assessments and the investigator's assessment.

The primary endpoint is based on ORR by week 28. This is defined as the percentage of subjects who have achieved CR, CRu, or PR on or before week 28. To allow for a window around the scheduling of the week 28 visit, assessments done on or before week 30 (week 28 + 2 weeks) will be considered in this analysis.

For the secondary efficacy endpoint of RD of ORR at week 12, assessments done on or before week 14 (week 12 + 2 weeks) will be considered in the calculation of ORR.

Time-to-Event Endpoints

Time-to-event in days will be calculated as (event date – start date + 1). The duration in days may be converted to months as 12*(number of days / 365.25) or to weeks as number of days / 7.

5.3 PHARMACODYNAMICS

Complete depletion of CD19+ cell count

Complete depletion of CD19+ cell count is defined as CD19 cell count < 0.01 x 10^9/liter.

5.4 SAFETY

Event of Interest (EOI)

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

- infusion reactions
- tumor lysis syndrome
- cardiac disorders
- serious infections
- severe mucocutaneous reactions
- hematological toxicity
- progressive multifocal leukoencephalopathy
- GI perforation

AE preferred terms that are potentially representative of the EOI will be retrieved for review and analysis using the latest version of pre-specified Standardized MedDRA Queries (SMQs) if available.

Infusion reaction and tumor lysis syndrome EOIs will be summarized separately for:

- all events and
- events with onset day coincident with first IP infusion or the day after the first IP infusion.

If no SMQ is available for use as a search tool for a given EOI (e.g, infusion reactions) a customized search strategy will be developed and the preferred terms used in that search will be provided in an appendix to the SAP prior to the database lock.

Exposure-adjusted Incidence Rates of Adverse Events

Exposure-adjusted incidence rate is calculated as the number of subjects in a treatment group that experienced the event at least once divided by the total subject exposure times in the group. For subjects who experience the event, the exposure time is calculated as the time from the first dose date of IP to the onset of the first event. For subjects who do not experience the event, the exposure time is calculated as the time from the first dose of IP to the minimum of the end of study (EOS) visit date and death date.

Last Known Date Alive

The last known date alive will be the maximum of: end of study date, non-fatal AE start and stop dates, IP administration dates, serum chemistry and hematology sample collection dates, ADA sample collection dates, concomitant medication dates, vital sign dates, PK sample collection dates, and NHL lesion assessment dates.

Overall Survival (OS)

On-study OS is defined as the time from randomization to the date of death. Subjects who have not died before the week 28/EOS visit will be censored for OS at the last known date alive on or prior to EOS.

Progression-free Survival (PFS)

PFS is defined as the time from randomization until the first occurrence of disease progression per 1999 IWG-NHL criteria or death from any cause. For subjects alive and progression-free at the week 28/EOS visit, PFS will be censored at the date of the last disease evaluation demonstrating lack of progression. Subjects who have no post-baseline disease assessments will have their PFS times censored on the date of randomization. PFS will be calculated separately based on the central, independent, blinded radiologists' and oncologist's assessments and the investigator's assessment of progression.

Treatment-emergent Adverse Event

A treatment-emergent AE is defined as an AE that begins or increases in severity or frequency on or after the date of first IP and up to the EOS visit.

5.5 IMPUTATION FOR PARTIAL OR MISSING DATES

Partial or missing admission and discharge dates for hospitalizations will not be imputed.

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

	Stop Date			
Start Date	Complete: *yyyymmdd*	Partial: *yyyymm*	Partial: *yyyy*	missing

		<1st dose	≥1st dose	<1st dose *yyyymm*	≥1st dose *yyyymm*	<1st dose *yyyy*	≥1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then 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 (i.e. set the stop date as missing).

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 concomitant medications should be included in the safety summaries, however the original, partial dates will be included in data listings.

6. ANALYSIS SETS

6.1 FULL ANALYSIS SET

The full analysis set (FAS) includes all subjects randomized in the study. Analyses for the FAS will be based on randomized treatment assignment.

6.2 PER PROTOCOL SET

The per protocol (PP) analysis set is a subset of the FAS which includes subjects who have completed all 4 weekly IP doses or who permanently ended IP prior to completing 4 weekly IP doses due to reasons allowed per protocol (ie, disease progression, adverse events and death), had at least one post-baseline tumor assessment, and did not experience a protocol deviation that would affect their evaluation for the primary objective of the study. The protocol deviations that affect evaluation for the primary objective will be determined based on a blinded data review prior to database lock.

Analyses for the PP 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 dose of IP.

All safety analyses will be conducted on this analysis set according to actual treatment received.

7. INTERIM ANALYSES

A safety analysis will be performed by the DMC after the first 12 subjects have received at least 2 doses of IP.

No interim analyses of efficacy or pharmacodynamics are planned.

8. DATA REVIEW

8.1 DATA HANDLING AND TRANSFER

Data will be entered electronically into a database built with Medidata Rave and exported as SAS® version 9.1.3 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 Medical Dictionary for Regulatory Activities (MedDRA) 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) version 4.03. Prior and concomitant medications will be coded using the current version of World Health Organization Drug Dictionary (WHO-DD).

Additional details can be found in the PRA Clinical Informatics Plan for this study.

8.2 DATA SCREENING

Beyond the data screening built into the PRA Clinical Informatics Plan, the PRA programming of analysis datasets and Tables, Figures, and Listings (TFLs) provides additional data screening. Presumed data issues will be output into SAS® logs identified by the word "Problem" and extracted from the logs by a SAS® macro and sent to the Data Management team for review.

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

9. STATISTICAL METHODS

All statistical analyses will be performed using SAS® Version 9.1.3 or higher.

Unless otherwise specified, descriptive data summaries will be tabulated by treatment for all endpoints. For continuous outcomes, the descriptive statistics include number of subjects with observations (n), mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. 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.

Categorical outcomes will be summarized by number and percent of subjects falling into each category. Percentages will be rounded to one decimal place except for 100%, which will have no

decimal place. Kaplan-Meier (KM) estimates of quartiles will be provided for time-to-event endpoints.

9.1 SUBJECT DISPOSITION

The following information will be summarized for subject disposition and accountability for each of the analysis sets defined in Section 6, unless stated otherwise:

- Number of subjects randomized will be tabulated by region, country, and site (for the FAS)
- Subject disposition (including number of subjects who were treated with ABP 798/rituximab, completed all planned IP doses, discontinued IP early with reason for discontinuation, completed study, and discontinued study early with reason for discontinuation)
- Summary of analysis populations with reason for exclusion (for all screened subjects)
- Number and percent of subjects on study at each visit
- Randomization list of subjects and their actual versus randomized treatment group (for the FAS)

9.2 PROTOCOL DEVIATIONS AND VIOLATIONS

Protocol deviations and violations (PDV) data will be entered into the Clinical Trials Management System (CTMS). The study team will conduct on-going reviews of the PDV data from CTMS and the resulting set of subjects to be included in the PP analysis set throughout the study, adjusting the PDV criteria as seems appropriate. The subjects to be included in the PP analysis set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

Based on the PDV data entered into CTMS, the major protocol deviations, thought to potentially impact the statistical analyses or subject safety, will be listed and tabulated using incidence and percentages by deviation type, deviation, and randomized treatment group. A summary of inclusion/exclusion criteria deviations will also be provided. See the protocol deviation guidance document for details on specific deviation types and deviations.

9.3 TREATMENTS

All analyses in this section will be performed on the safety analysis set based on a subject's actual treatment received.

9.3.1 Extent of Study Drug Exposure

Summary statistics will be provided for the total number of IP doses administered and the total duration of IP exposure throughout the study. The overall incidence of IP dose delays, dose

interruptions, and withheld doses as well as the reasons will be tabulated. The numbers of subjects receiving a full or partial dose and subjects with a dose interruption for each dosing instance will also be provided.

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

9.3.2 Concomitant Medications

Concomitant medications include all medications and therapies during the study except for planned IP administration. Concomitant medications will be coded by WHO-DD and will be summarized by preferred name and actual treatment group from study day 1 through the end of study. Medications with a stop date before study day 1 will not be summarized.

9.3.3 Medical History

Medical conditions at screening will be summarized by PT and primary SOC separately by status (unresolved versus resolved).

9.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject demographics, baseline characteristics, and randomization stratification factors will be summarized descriptively by treatment group in each of the analysis sets defined in Section 6.

The following demographics and baseline characteristics and stratification factors will be summarized:

- age (in years, at time of signing informed consent), and age group (≤ 60 vs. >60)
- race (American Indian or Alaska native vs. Asian – Non-Japanese vs. Asian – Japanese vs. Black or African American vs. Native Hawaiian or other Pacific Islander vs. White vs. Other)
- gender (male vs. female)
- ethnicity (Hispanic vs. non-Hispanic vs. Not allowed to collect)
- geographic region (Eastern Europe vs. Western Europe/Other vs. North America vs. Japan)
- height
- weight
- Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1 vs. 2 vs. 3 vs. 4)
- time since original diagnosis in months

- staging of original diagnosis (Stage I vs. II vs. III vs. IV vs. IE vs. IIE vs. IIIE vs. IIIES vs. IIIS vs. Unknown)
- staging at screening (Stage II vs. III vs. IV vs. IIE vs. IIIE vs. IIIES vs. IIIS)
- staging subclassification (A vs. B)
- histologic grade at screening (I vs. II)
- previous radiation treatment (yes vs. no)
- time since last dose of prior radiation in months
- presence of B symptoms (yes vs. no)
- bone marrow involvement (yes/indeterminate vs. no)
- LDH (<lower limit of normal vs. >upper limit of normal vs. within normal range)
- # of nodal sites
- # of extranodal sites
- FLIPI score (0 vs.1 vs. 2 vs. 3 vs. 4 vs. 5)
- FLIPI (low vs. intermediate vs. high)

9.5 EFFICACY ANALYSES

9.5.1 Primary Variable

9.5.1.1 PRIMARY ANALYSIS

The primary analysis of ORR by week 28 will be based on the FAS according to randomized treatment, using data from the central, independent, blinded radiologists' and oncologist's assessments.

Clinical equivalence of the primary endpoint will first be demonstrated by comparing the 1-sided 95% lower confidence limit of the RD of ORR by week 28 between ABP 798 and rituximab with a noninferiority margin of -15%. If this is successful, the 1-sided upper 95% confidence limit of the RD of ORR by week 28 will be compared with a nonsuperiority margin of +35.5%.

To estimate the 1-sided 95% confidence limits of the RD of ORR by week 28, the generalized linear model adjusted for the stratification factors (geographic region and age group) will be fitted using the SAS® procedure "GENMOD". A sample SAS code fragment is provided below for reference:

```
proc genmod data=<data> descending;
        class trt <categorical_var>;
        model <binary var> = trt <categorical_var> stratification factors
```

```
                    <categorical_var>/ dist=binomial link=identity;
            estimate 'label of the estimate' trt -1 1 / alpha=0.1 ;
run;
```

In addition, a 2-sided 95% confidence interval (CI) will be calculated and evaluated against a symmetrical margin of 15% for noninferiority and nonsuperiority.

9.5.1.2 SECONDARY ANALYSIS

To assess the robustness of the primary ORR analysis results, the primary analysis will be repeated using the central, independent, blinded radiologists' and oncologist's assessments on the PP analysis set according to actual treatment received and using the FAS and the investigator's assessment of disease.

The RD for ORR by week 28 will also be examined in the subgroups as defined by the baseline covariates in Section 4.4. A forest plot will be created to summarize the variability in the RDs across the subgroups. In each case, the RDs and both 90% and 95% CIs will be calculated using the methods described in Section 9.5.1.1.

9.5.2 Methods for Handling Dropouts and Missing Data

Subjects without measurable disease at baseline or without post-baseline disease assessments will be counted as nonresponders in calculating the ORR.

9.5.3 Multiplicity

Inferential analyses will only be performed for the primary endpoint; therefore no adjustment for multiplicity is needed.

9.5.4 Pooling of Sites

All sites will be pooled together for all analyses.

9.5.5 Secondary Variables

9.5.5.1 RISK DIFFERENCE FOR OVERALL RESPONSE RATE AT WEEK 12

The RD for ORR at week 12 will be summarized the same way as the analyses described in Section 9.5.1. Subjects without a disease assessment at week 12 will be counted as nonresponders in calculating the RD for ORR at week 12.

9.6 PHARMACOKINETICS

Serum ABP 798 and rituximab concentrations will be summarized descriptively by treatment for each sampling visit using the safety analysis set.

The 90% CI for the geometric mean ratio (GMR) of test (ABP 798)-to-reference (rituximab) for serum concentrations at predose (trough) and immediately after the end of infusion at week 12 will be calculated.

The point estimates and 90% CI for the GMR for each visit will be estimated using an analysis of covariance model adjusted for the stratification factors as covariates as defined in Section 4.4. Sample SAS code for PROC MIXED is displayed below:

```
PROC MIXED;
  CLASS treatment  <stratification variables>;
  MODEL Natural Log PK concentration = treatment <stratification variables>;
  ESTIMATE 'ABP 798 vs rituximab' Treatment 1 -1  / e cl alpha=0.1;
RUN;
```

The geometric least squares mean 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. Ninety percent CIs will be obtained by exponentiating the CI for the difference between the means on the log scale.

9.7 PHARMACODYNAMICS

CD19+ cell count and total IgG and IgM levels (as well as change from baseline) will be summarized descriptively by treatment and visit. The percent of subjects with complete depletion of CD19+ cell count from baseline to day 8, week 3, week 4 and week 28 will also be summarized descriptively by treatment.

9.8 SAFETY ANALYSES

All safety analyses will be performed on the safety analysis set based on a subject's actual treatment received.

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.

Subject incidence of treatment-emergent AEs will be tabulated by treatment groups and by SOC, PT, and maximum severity grade per CTCAE v 4.03. Subject incidence of treatment-emergent AEs will also be summarized by SOC and PT.

Subject incidence of the following AEs will be tabulated by preferred term in descending order of frequency in the ABP 798 arm:

- treatment-emergent AEs
- ≥Grade 3 treatment-emergent AEs
- treatment-emergent AEs leading to discontinuation of IP
- treatment-emergent AEs leading to dose delay of IP
- each treatment-emergent event of interest category

Infusion reaction and tumor lysis syndrome EOIs will also be summarized by PT and maximum CTCAE grade.

Subject incidence of treatment-emergent AEs by PT in decending order of frequency in the ABP 798 arm and by SOC and PT will be also tabulated by gender, age (<65 vs. ≥ 65), race (White vs. non-White), and region (Eastern Europe vs. Western Europe/Other vs. North America vs. Japan).

AEs leading to discontinuation of IP are those with an action taken with Investigational Medicinal Product of "dose discontinued". AEs leading to delay of IP are those with an action taken with Investigational Medicinal Product of "dose delayed".

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 within that SOC or preferred term.

Exposure-adjusted AE incidence rates per 100 patient-years (p-y) will also be calculated for all treatment-emergent AEs. The exposure-adjusted incidence rate per 100 p-y is the number of subjects who experience an event divided by the total subject exposure time multiplied by 100.

Subjects with AEs leading to discontinuation of study therapy will be listed.

9.8.2 Fatal and Serious Adverse Events

Subject incidence of serious treatment-emergent AEs will be tabulated by treatment groups and by SOC, PT, and maximum severity grade per CTCAE v 4.03.

Subject incidence of the following AEs will be tabulated by preferred term in descending order of frequency in the ABP 798 arm:

- serious treatment-emergent AEs
- fatal AEs (AEs with a severity grade of 5 and/or outcome of fatal)

Subjects with serious AEs will also be listed.

9.8.3 Laboratory Data

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

Laboratory values and change from baseline will be summarized using descriptive statistics for each IP dose by treatment. For each IP dose, the lab assessment summarized will be the assessment closest to the date of IP dose and contained in the window of (IP dose date – 3 days) to IP dose date, inclusive. Shift tables of the minimum and maximum post-baseline values based on CTCAE v4.03 grading relative to baseline will be presented by treatment group for parameters that have CTCAE criteria. Shift tables will include all laboratory assessments. In addition, subject incidence tables and listings of Grade ≥ 3 laboratory toxicities will be provided. Standard ranges will be used for the laboratory analysis.

Lab assessments will be grouped for summary as follows:

- Hematology – white blood cell parameters: white blood cell count and absolute neutrophil count
- Hematology – red blood cell parameters: hemoglobin and packed cell volume or hematocrit
- Hematology – other parameters: platelets
- Serum chemistry – hepatobiliary parameters: alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, lactate dehydrogenase
- Serum chemistry – general chemistry: sodium, potassium, albumin, total protein, non-fasting glucose
- Serum chemistry – renal function tests: urea, creatinine, blood urea nitrogen, uric acid

9.8.4 Vital Signs

Vital sign assessments include blood pressures (diastolic and systolic), pulse, respiration rate, and temperature. Change from baseline in vital signs will be summarized by treatment group. Descriptive statistics will be shown for baseline, the result at each IP dose, and the change from baseline to each IP dose result. For each IP dose, the vitals assessment summarized will be the assessment closest to the date of IP dose and contained in the window of (IP dose date – 3 days) to IP dose date, inclusive.

9.8.5 Immunogenicity

The number and percentage of subjects developing binding and neutralizing ADA will be tabulated for each treatment. Pre-existing antibody incidence (on or before the first dose of study IP) and developing antibody incidence will be summarized. Pre-existing antibody incidence is defined as the number of subjects with a positive antibody result at baseline divided by the number of subjects with an immunoassay result at baseline. Developing antibody incidence is defined as the number of subjects with a negative or no antibody result at baseline and a positive antibody result at a post-baseline time point divided by the number of subjects with at least one

post-baseline immunoassay result. A transient antibody result is defined as a positive post-baseline result with a negative result at the subject's last timepoint tested within the study period.

9.8.6 Progression-free Survival

The primary analysis of PFS will be based on disease assessments determined by the central, independent, blinded radiologists' and oncologist's review.

The LIFETEST procedure in SAS® will be used to produce estimates of quartiles and 95% CIs via the method of Brookmeyer and Crowley (1982) and to produce KM survival plots. The standard error of the KM quartile estimates will be estimated using Greenwood's formula (Kalbfleisch and Prentice, 1980).

Estimates of the hazard ratio (HR) for treatment and the corresponding 1-sided 95% and 97.5% CIs will also be presented. They will be estimated using the stratified Cox proportional hazards regression model using the PHREG procedure in SAS®. The model will be stratified by the randomization stratification factors. HRs will be calculated using the rituximab arm as the reference group.

Progression-free survival will also be summarized based on the investigator assessment of progression.

9.8.7 Overall Survival

The analyses of OS will be performed per the analyses for PFS (see Section 9.8.6).

9.8.8 Electrocardiogram

The standard 12-lead electrocardiogram results at baseline and week 28/EOS visit will be summarized as normal, abnormal - clinically significant, or abnormal - not clinically significant.

9.9 ANALYSES FOR JAPAN

For Japan, the evaluation of equivalence of efficacy will based on a 2-sided 95% CI for the RD of ORR.

Subject disposition, demographic and study baseline characteristics, IP exposure, and key efficacy and safety endpoints will be summarized for the subgroup of Japanese subjects.

10. VALIDATION

PRA seeks to ensure the quality of the results provided for the study in the form of TFLs, and the derived datasets used in their creation, through the following processes:

- Derived datasets are independently reprogrammed by a second programmer. The separate datasets produced by the two programmers must match 100%. Detailed

specifications for the derived datasets are documented and the documentation is provided to the client at study conclusion.

- Tables are independently reprogrammed by a second programmer for numeric results.
- Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.
- Listings are checked for consistency against corresponding tables, figures, and derived datasets.

The entire set of TFLs is checked for completeness and consistency prior to its delivery to the client by the lead clinical programmer, 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 TFLs are redelivered using different data. Execution of this validation process is documented and the documentations is provided to the client at study conclusion.

11. REFERENCES

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APPENDIX 1 GLOSSARY OF ABBREVIATIONS

Glossary of Abbreviations:	
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CR	Complete Response
CRu	Complete Response Unconfirmed
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOI	Event of Interest
EOS	End of Study
FAS	Full Analysis Set
FLIPI	Follicular Lymphoma International Prognostic Index
GMR	Geometric Mean Ratio
HR	Hazard Ratio
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	Investigational Product
IV	Intravenous
IXRS	Interactive Voice/Web Response System

KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PDV	Protocol Deviations and Violations
PFS	Progression-free Survival
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
P-Y	Patient-Year
Q1	25^{th} Percentile
Q3	75^{th} Percentile
RD	Risk Difference
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDTM	Standard Data Tabulation Model
SI	International System of Units
SMQ	Standard MedDRA Query
SOC	System Organ Class
SPD	Sum of the Products of the Greatest Diameters
TFL	Tables, Figures, and Listings
WHO-DD	World Health Organization Drug Dictionary

APPENDIX 2 RESPONSE DETERMINATION BY IWG (1999) CRITERIA

Responses will be categorized as complete response (CR), CR/unconfirmed, partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

11.1 COMPLETE RESPONSE

To satisfy criteria for CR, all of the following criteria must be met:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (eg, lactate dehydrogenase) definitely assignable to NHL.
2. All lymph nodes and nodal masses must have regressed to normal size ($\leq$ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to $\leq$ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate ($\geq$ 20 mm biopsy core).

11.2 CR/UNCONFIRMED

CR/unconfirmed (CRu) includes patients who fulfill criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass greather than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

11.3 PARTIAL RESPONSE

PR requires the following:

1. ≥ 50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features:
   • (a) they should be clearly measurable in at least two perpendicular dimensions,
   • (b) they should be from as disparate regions of the body as possible, and
   • (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, eg, large-cell lymphoma or low-grade lymphoma (ie, small, lymphocytic small cleaved, or mixed small and large cells).
6. No new sites of disease.

11.4 STABLE DISEASE

Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

11.5 RELAPSED DISEASE

Relapsed disease (CR, CRu) requires the following:

1. Appearance of any new lesion or increase by ≥50% in the size of previously involved sites.
2. ≥50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

11.6 PROGRESSIVE DISEASE

Progressive disease (PR, nonresponders) requires the following:

1. ≥ 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.
2. Appearance of any new lesion during or at the end of therapy.

Cheson BD, Horning SJ, Coiffier B, Shipp MA, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17(4):1244. Erratum in: J Clin Oncol 2000;18(11):2351

APPENDIX 3 LIST OF POST-TEXT TABLES, FIGURES, LISTINGS, AND SUPPORTIVE SAS OUTPUT APPENDICES

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APPENDIX 4 SHELLS FOR POST-TEXT TABLES, FIGURES, AND LISTINGS

See version 1.1 of separate TFL shells document for protocol 20130109.