1 TITLE PAGE

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

Protocol Number: 20130109 **EudraCT number:** 2013-005542-11

Study Phase: 3

Date and Version: **5.0, 17 July** 2017

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

CONFIDENTIAL

NCT Number: NCT02747043
This NCT number has been applied to the document for purposes of posting on clinicaltrials.gov

SIGNATURES

Representatives of Sponsor and Clinical Research Organization

I have read and agree to the protocol 20130109, titled "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)." I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities.

Accepted for the Sponsor – Amgen Inc.:

[redacted] Medical Director

Print Name Title

[redacted] 27 JUL 2017

Signature Date

Accepted for the Clinical Research Organization – PRA:

[redacted] Medical Director

Print Name Title

[redacted] 27-Jul-2017

Sign Date

Investigator

I have read and agree to the protocol 20130109, entitled "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)." I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

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Signature Date

Coordinating Investigator Signature (if applicable):

_____ _____
Print Name Title

_____
Institution/ Country

_____ _____
Signature Date

2 SYNOPSIS

NAME OF SPONSOR: Amgen	**PROTOCOL No.:** 20130109
NAME OF STUDY TREATMENT: ABP 798	
TITLE OF STUDY: 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)	
STUDY CENTERS: Approximately **150** sites in Europe, North America, **Latin America,** and Asia Pacific	
STUDY PERIOD: Approximately 250 subjects will be randomized in a 1:1 ratio to receive ABP 798 or rituximab (Rituxan®). The clinical study will be completed when the last subject completes the week 28 visit or withdraws early from the study.	**PHASE OF DEVELOPMENT:** Phase 3
PLANNED STUDY DATES: The study consists of a screening period of up to 4 weeks and a treatment period of 28 weeks, for a total of up to 32 weeks. The expected enrollment duration is approximately **24** months.	
OBJECTIVES: **Primary Objective:** The primary objective for this study is to evaluate the efficacy of ABP 798 compared with rituximab. **Secondary Objective(s):** The secondary objective is to assess the pharmacokinetics (PK), pharmacodynamics, safety, tolerability, and immunogenicity of ABP 798 compared with rituximab.	
STUDY DESIGN AND METHODOLOGY: This is a randomized, double-blind study in adult subjects with Grade 1, 2, or 3a 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 area and age (> 60 vs ≤ 60 years). 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.	
STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION: **Inclusion Criteria:** Subjects cannot be randomized before all inclusion criteria (including test results) are confirmed. 1. Males and females 18 years of age **and older** 2. Histological confirmed (by lymph node or extranodal region biopsy), Grade 1, 2, or 3a follicular B-cell NHL expressing CD20 within 12 months before randomization 3. Stage 2, 3, or 4 (per Cotswold's Modification of Ann Arbor Staging System; Appendix 3) with measurable disease (per International Working Group) • subjects must have a baseline scan (computed tomography [CT]) of the neck (if palpable lymph node > 1.0 cm), chest, abdomen, and pelvis to assess disease burden within **6 weeks** before randomization • subjects must have had a baseline bone marrow biopsy within 12 months before randomization. Previously confirmed positive bone marrow involvement does not need to be repeated for purposes of screening. 4. Low tumor burden based on the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria (Appendix 4) • largest nodal or extranodal mass **≤** 7 cm • no more than 3 nodal sites with diameter > 3 cm • no **splenomegaly > 16 cm by CT scan and no symptomatic splenomegaly** • no significant pleural or peritoneal serous effusions by CT • **lactate dehydrogenase ≤ upper limit of normal (ULN)**	

- no B symptoms (night sweats, fever [temperature > 38°C], weight loss > 10% in the previous 6 months)

5. Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1
6. Blood counts:
   - absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L (1,500/μL)
   - lymphocytes < 1.5 x the ULN
   - platelets $\geq$ 100 x 10^9/L (100,000/μL)
   - hemoglobin $\geq$ 10.0 g/dL
7. Adequate hepatic function as defined by:
   - total bilirubin < 1.5 x the ULN
   - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2 x ULN
   - Subjects with an elevated unconjugated bilirubin (Gilbert's syndrome) will be eligible if hepatic enzymes and function are otherwise within normal limits (ie, AST, ALT, and alkaline phosphatase are within normal limits) and there is no evidence of hemolysis.
8. Adequate renal function as defined by creatinine < 1.5 x ULN or estimated creatinine clearance $\geq$ 50 mL/min calculated by the Cockcroft-Gault method
9. Subjects must sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form before any study specific procedures.

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

1. Diffuse large cell component and/or Grade 3b follicular NHL
2. History or known presence of central nervous system metastases
3. Palliative radiotherapy within 3 months before randomization
4. Malignancy other than NHL within 5 years (except treated in-situ cervical cancer, or squamous or basal cell carcinoma of the skin)
5. Major surgical procedure within 4 weeks before randomization or planned major surgical procedure during the treatment phase
6. Any of the following in the 6 months before randomization:
   - clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure [New York Heart Association $\geq$ Class III], serious uncontrolled cardiac arrhythmia); peripheral vascular disease, cerebrovascular accident, or transient ischemic attack
7. Medically uncontrolled hypertension or systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg
8. Known active or history of active tuberculosis (TB)
9. Positive for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus antibody at screening
10. Known to be human immunodeficiency virus positive
11. Recent infection requiring a course of systemic anti-infective agents that was completed $\leq$ 7 days before randomization (with the exception of uncomplicated urinary tract infection)
12. Other investigational procedures **that can impact the study data, results, or patient safety** while participating in this study are excluded; **participation in observational studies is allowed**.
13. Subject is currently enrolled in or has not yet completed at least 30 days or 5 half-lives (whichever is longer) since ending other investigational device or drug study(s), including vaccines, or subject is receiving other investigational agent(s)
14. Previous use of either commercially available or investigational chemotherapy, biological, or immunological therapy for NHL (including rituximab or biosimilar rituximab, or other anti-CD20 treatments)
15. Systemic corticosteroid use **within** 3 months before randomization (inhaled are allowable)
16. Live vaccines within 28 days prior to the first dose of IP
17. History of neurologic symptoms suggestive of central nervous system demyelinating disease

18. Woman of childbearing potential who is pregnant or is breastfeeding
19. Woman of childbearing potential who does not consent to use highly effective methods of birth control (eg, true abstinence, sterilization, birth control pills, Depo Provera injections, or contraceptive implants) during treatment and for an additional 12 months after the last administration of the protocol specified-treatment
20. Man with a partner of childbearing potential who does not consent to use highly effective methods of birth control (eg, true abstinence, vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman) during treatment and for an additional 12 months after the last administration of the protocol specified treatment
21. Subject has known sensitivity to any of the products to be administered during the study, including mammalian cell derived drug products
22. Subject previously has been randomized in this study
23. Subject likely to not be available to complete all protocol-required study visits or procedures
24. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the Investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

NUMBER OF SUBJECTS: Approximately 250 subjects will be randomized in a 1:1 ratio to receive ABP 798 or rituximab. [redacted]

STUDY TREATMENT(S):
Test Product, Dose and Mode of Administration:
ABP 798 at a dose of 375 mg/m^2 administered as an IV infusion weekly for 4 weeks followed by dosing at weeks 12 and 20.
Reference Therapy, Dose and Mode of Administration:
Rituximab at a dose of 375 mg/m^2 administered as an IV infusion weekly for 4 weeks followed by dosing at weeks 12 and 20.

DURATION OF TREATMENT: The study includes a screening period of up to 4 weeks. Subjects will receive IP at day 1 (visit 1) and weeks 2 (visit 2), 3 (visit 3), 4 (visit 4), 12 (visit 5), and 20 (visit 6) and will have an end-of-study visit at week 28. Individual total study duration will be 32 weeks.

STUDY EVALUATIONS:
Primary Efficacy Criterion:
- Risk difference of ORR by week 28

Secondary Efficacy Criteria:
- Risk difference of ORR at week 12

Pharmacokinetic and Pharmacodynamic Criteria:
- Percentage of subjects with complete depletion of CD19+ cell count from baseline to study day 8 and total IgG and IgM antibody levels
- Serum concentrations at predose and immediately after the end of infusion at week 12

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

STATISTICAL METHODS:

Clinical equivalence of the primary endpoint will be demonstrated by first assessing non-inferiority by comparing the 1-sided 95% lower confidence interval (CI) limit of the RD of ORR by week 28 between ABP 798 and rituximab with a -15% margin. If the test of non-inferiority is successful, then the study will sequentially assess non-superiority by comparing the 1-sided 95% upper CI limit of the RD of ORR by week 28 with a 35.5% margin. Additionally, a 2-sided 95% CI will be calculated and evaluated against a symmetrical margin of 15% for noninferiority and nonsuperiority. The CIs for RD will be estimated using a generalized linear model adjusted for stratification factors. Analyses of efficacy endpoints will be conducted on the full analysis set (consisting of all randomized subjects) according to randomized treatment.

In addition, categorical variables will be summarized using the number and percentage of subjects falling into each category. Continuous variables will be summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects with observations.

Pharmacokinetics endpoints will be summarized as point estimates of the geometric mean ratio and 90% CIs of test (ABP 798)-to-reference (rituximab). The pharmacodynamic endpoint of percentage of subjects with complete depletion of CD19+ cell count from baseline to study day 8 will be summarized descriptively. Pharmacokinetics and pharmacodynamic endpoints will be conducted on safety analysis set (consisting of subjects receiving at least 1 dose of IP) according to actual treatment received.

Safety endpoints will be summarized descriptively as well. Subgroup analyses (by gender, race, and stratification factors as appropriate) may be presented. Safety will be assessed in the safety analysis set with treatment assignment based on actual treatment received. All verbatim terms for any reported AEs will be coded to the appropriate system organ class and preferred term according to the current version of the Medical Dictionary for Regulatory Activities dictionary, and graded by the Investigator for severity as per Common Toxicity Criteria for Adverse Events version 4.03. The number and percentage of subjects reporting AEs (all, serious, related, and deaths), and developing antidrug antibodies will be tabulated by treatment. Vital signs and laboratory data will also be summarized descriptively by visit and treatment. The safety endpoints of PFS and OS will be analyzed including all events up to the time of the last subject's end-of-study visit. Median PFS and OS time and survival curves may also be estimated using Kaplan-Meier methods. Descriptive 1-sided 95% and 97.5% CIs on the hazard ratios of PFS and OS will be estimated based on Cox models, stratified by stratification factors.

Independent safety reviews will be performed by the DMC periodically throughout the study, including an initial safety review after the first 12 subjects have received at least 2 doses of IP. Blinded study data will also be monitored on an ongoing basis by the blinded clinical study team to ensure subjects' safety.

DATE AND VERSION: 5.0, 17 July 2017

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	**Definition**
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
CRO	Clinical research organization
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EOI	Event of interest
EU	**European Union**
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GELF	The Groupe d'Etudes des Lymphomes Folliculaires criteria
GMR	Geometric mean ratio
HBcAb	**Hepatitis B core antibody**
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HBV	**Hepatitis B virus**
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IP	Investigational Product

IRB	Institutional Review Board
IV	Intravenous
IWG	International Working Group
IXRS	Interactive voice and web response system
LDH	Lactate dehydrogenase
LPL	Lymphoplasmacytoid lymphoma
LPD	Longest perpendicular diameter
LVD	Longest vertical dimension
MedDRA	Medical Dictionary for Regulatory Activities
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PIN	Personal Identification Number
PK	Pharmacokinetic(s)
PR	Partial response
QTc	Corrected QT interval
RD	Risk difference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SLL	Small lymphocytic lymphoma
SOC	System organ class
SOP	Standard operating procedures
SPD	Sum of the products
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
ULN	Upper limit of normal
US	**United States**
WHO	World Health Organization
WM	Waldenstrom macroglobulinemia

5 ETHICS

5.1 Ethics Committee

This study will be conducted in compliance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the United States (US) Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B[R3]), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the study protocol/amendment(s), written informed consent form (ICF), any consent form updates, subject recruitment procedures (eg, advertisements), any written information to be provided to subjects and a statement from the IRB/IEC that they comply with GCP requirements. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 (R1); FDA CFR (21 CFR § 50, 56, 312), the general principles indicated in the Declaration of Helsinki and all applicable regulatory requirements.

5.3 Subject Information and Consent

The Investigator will explain the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative and obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study and before initiation of any study-related procedure (including administration of study drug).

The Sponsor will provide a sample ICF, based on the elements of informed consent in Section 17.1. The final, version dated form must be agreed to by the Sponsor and the IRB/IEC and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the

subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed ICF.

The ICF may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance approval should always be given by the IRB/IEC and existing subjects informed of the changes and reconsented. This is documented in the same way as previously described.

The Investigator should, with the consent of the subject, inform the subject's primary physician about participation in the clinical study as needed.

6 INTRODUCTION

6.1 Disease Review

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy, with 69,740 new cases and 19,020 deaths expected in the United States (US) in 2013 (American Cancer Society, 2013) and approximately 74,000 new cases and 31,000 deaths annually in Europe (Ferlay et al, 2010). Non-Hodgkin lymphoma comprises a diverse group of malignancies, most of B-cell origin (80% to 85%; Friedberg et al, 2008). Of the B-cell NHLs, 4 subtypes, follicular lymphoma, small lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma (LPL)/Waldenstrom macroglobulinemia (WM), and marginal zone lymphoma (MZL), have differing pathological features (Swerdlow et al, 2008), but are generally included among those characterized as indolent in nature because they have a slowly progressive natural history (Pileri et al, 2004). Together these indolent lymphomas comprise approximately 30% to 40% of B-cell NHLs in North America and Europe (Morton et al, 2006).

Follicular lymphoma is the second most common lymphoma diagnosed in the US and Western Europe. The median age at diagnosis is 60 years, and there is a slight female predominance (approximately 54%; American Cancer Society, 2013). Follicular lymphomas are malignant counterparts of normal germinal center B-cells (IARC, 2008). Approximately 85% of patients with follicular lymphoma have t(14;18), which results in the overexpression of the BCL-2 protein, a member of a family of proteins that blocks apoptosis. However, it is likely that multiple genetic events are required for the development of follicular lymphoma. Follicular lymphoma has the immunophenotype CD19-, CD20-, and CD22-positive and CD5-negative (Chen et al, 2012). Patients with follicular lymphoma generally present with asymptomatic lymphadenopathy, with waxing and waning present for years. Involvement of bone marrow is present in 70% of patients, whereas involvement of other normal organs is uncommon. Less than 20% of patients present with B symptoms, and < 20% of patients present with an increased serum lactate dehydrogenase (LDH). Involvement of the intestine is a unique site of presentation of this disease, usually early stage, and with a favorable prognosis (Schmatz et al, 2011).

Less than 10% of patients with follicular lymphoma present with early stage (I/II) disease (Friedberg et al, 2006). Radiation therapy is often recommended for limited stage follicular lymphoma. If significant morbidity is possible from radiotherapy based on the

location of the disease area or if the patient chooses not to receive radiation, observation may be a reasonable alternative, especially for Stage II patients (Advani et al, 2004).

The overwhelming majority of patients have advanced stage disease at diagnosis. Patients with asymptomatic follicular lymphoma do not require immediate treatment unless they have symptomatic nodal disease, compromised end organ function B symptoms, symptomatic extranodal disease, or cytopenias (Ardeshna et al, 2003). The addition of anti-B-cell antibodies has meant a change in how asymptomatic or modestly symptomatic disease is treated.

6.2 Rituximab

Rituximab (Rituxan®, MabThera®) is a genetically engineered chimeric murine/human monoclonal immunoglobulin (Ig)G1 kappa antibody directed against the B-cell specific CD20 antigen. Rituximab monotherapy presents an opportunity to significantly delay disease progression and death with limited side effects (as compared to standard chemotherapy (Ardeshna et al, 2010; 2014). Rituximab has changed the paradigm of treating follicular lymphoma, both as monotherapy and in combination with chemotherapy (usually in the symptomatic setting; Herold et al, 2007), resulting in an overall increase in survival of follicular lymphoma patients (Chen et al, 2012; Fischer et al, 2005). Rituximab monotherapy is replacing watchful waiting as the first-line response to asymptomatic follicular lymphoma.

6.3 Compound Review

ABP 798 is being developed as a biosimilar to Rituxan® (rituximab), for the treatment of NHL and other indications. The active ingredient of ABP 798 is an anti-CD20 monoclonal antibody that has the same amino acid sequence as rituximab and equivalent pharmacologic function based on comprehensive bioanalytical assays. ABP 798 has the same pharmaceutical form and dosage strength as US-licensed rituximab [rituximab (US), Rituxan®] and European Union (EU)-licensed rituximab [rituximab (EU), Mabthera®].

Refer to the Investigator's Brochure for additional information.

6.4 Study Rationale

Similarity of ABP 798 to rituximab has been shown using bioanalytical methods and pre-clinical studies (refer to the Investigator's Brochure for additional information). As outlined in the guideline on similar biological medicinal products containing monoclonal

antibodies (EMA/CHMP/BMWP/403543/2010), applicants are expected to provide data on similarity of pharmacokinetics (PK)/pharmacodynamics, safety, and efficacy.

In the US, EU, and much of the world, laws, regulations, and guidances have been or are being put in place to increase availability of biological treatments by developing and licensing biosimilar products (CHMP/437/04 Rev 1; EMEA/CHMP/BWP/247713/2012; EMEA/CHMP/BMWP/42832/2005 Rev 1; US FDA 2012a; US FDA 2012b).

A biosimilar product, generally, is one that is highly similar to a licensed biologic reference product, and there are no clinically meaningful differences between the biosimilar and reference product in terms of safety, purity, and potency. Biosimilarity is demonstrated by the totality of the evidence, including quality, nonclinical, and clinical evidence. The quality and nonclinical data for ABP 798 and rituximab are summarized in the Investigator's Brochure. The current study is designed to evaluate efficacy, PK, and safety, specifically, to demonstrate that there is no clinically meaningful difference between ABP 798 and rituximab in terms of overall response rate (ORR), peak and trough drug concentration, complete depletion of CD19+ cell count, safety, and immunogenicity.

7 STUDY OBJECTIVES

7.1 Primary Study Objective

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

7.2 Secondary Study Objectives

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

8 INVESTIGATIONAL PLAN

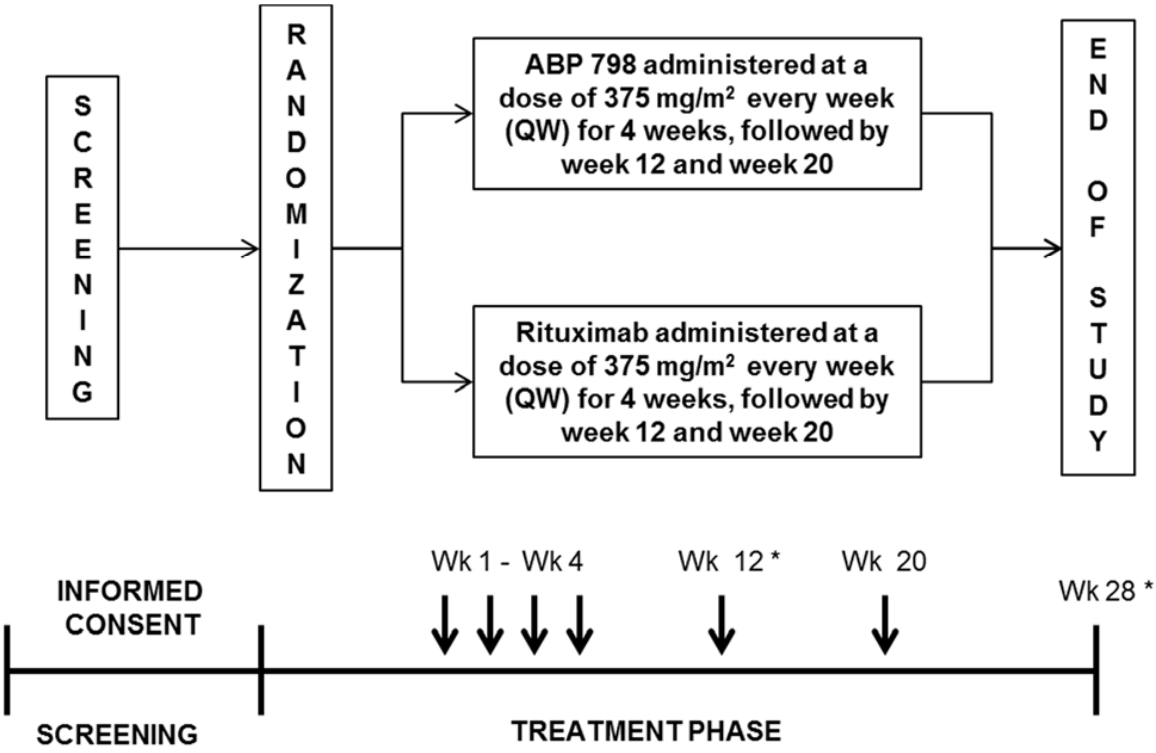
8.1 Overall Study Design and Plan

This is a randomized, double-blind study in adult subjects with Grade 1, 2 or 3a follicular B-cell 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 area and age (> 60 vs $\leq$ 60 years).

A subject will remain in the treatment phase 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 (EOS) 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.

Figure 1. Study Diagram



* Response assessments at study weeks 12 and 28
Wk = week

8.2 Discussion of Study Design

This study is randomized and double-blinded to prevent bias in treatment allocation and in the subjective assessment of effect. The assessment of the primary endpoint will be at week 28.

8.3 Study Duration

The study includes a screening period of up to 4 weeks. Subjects will receive IP at day 1 (visit 1) and weeks 2 (visit 2), 3 (visit 3), 4 (visit 4), 12 (visit 5), and 20 (visit 6) and will have an EOS visit at week 28. **There is an additional visit at week 5 (visit 4a) for subjects who have agreed to the optional additional PK sampling (see Section 9.4).** Individual total study duration will be 32 weeks.

Enrollment will continue until approximately 250 subjects have been randomized to treatment. The study will be completed when the last subject completes the week 28 visit or withdraws early from the study.

8.4 Study Population

8.4.1 Inclusion Criteria

Subjects **MUST** satisfy all of the following entry criteria before they will be allowed to participate in the study:

1. Males and females 18 years of age **and older**
2. Histological confirmed (by lymph node or extranodal region biopsy), Grade 1, 2, or 3a follicular B-cell NHL expressing CD20 within 12 months before randomization
3. Stage 2, 3, or 4 (per Cotswold's Modification of Ann Arbor Staging System; Appendix 3) with measurable disease (per International Working Group)
   - subjects must have a baseline scan (computed tomography [CT]) of the neck (if palpable lymph node > 1.0 cm), chest, abdomen, and pelvis to assess disease burden within **6 weeks** before randomization
   - subjects must have had a baseline bone marrow biopsy within 12 months before randomization. Previously confirmed positive bone marrow involvement does not need to be repeated for purposes of screening
4. Low tumor burden based on the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria (Appendix 4)
   - largest nodal or extranodal mass ≤ 7 cm
   - no more than 3 nodal sites with diameter > 3 cm
   - no **splenomegaly > 16 cm by CT scan and no symptomatic splenomegaly**
   - no significant pleural or peritoneal serous effusions by CT
   - **lactate dehydrogenase ⩽ upper limit of normal (ULN)**
   - no B symptoms (night sweats, fever [temperature > 38°C], weight loss > 10% in the previous 6 months)
5. Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1
6. Blood Counts:
   - absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L (1,500/μL)
   - lymphocytes < 1.5 x the ULN
   - platelets $\geq$ 100 x 10^9/L (100,000/μL)
   - hemoglobin $\geq$ 10.0 g/dL
7. Adequate hepatic function as defined by:
   - total bilirubin < 1.5 x the ULN
   - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2 x ULN
   - Subjects with an elevated unconjugated bilirubin (Gilbert's syndrome) will be eligible if hepatic enzymes and function are otherwise within normal limits (ie, AST, ALT, and alkaline phosphatase are within normal limits) and there is no evidence of hemolysis.
8. Adequate renal function as defined by creatinine < 1.5 x ULN or estimated creatinine clearance $\geq$ 50 mL/min calculated by the Cockcroft-Gault method
9. Subjects must sign an IRB/IEC-approved ICF before any study specific procedures.

8.4.2 Exclusion Criteria

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

1. Diffuse large cell component and/or Grade 3b follicular NHL
2. History or known presence of central nervous system metastases
3. Palliative radiotherapy within 3 months before randomization

4. Malignancy other than NHL within 5 years (except treated in-situ cervical cancer, or squamous or basal cell carcinoma of the skin)
5. Major surgical procedure within 4 weeks before randomization or planned major surgical procedure during the treatment phase
6. Any of the following in the 6 months before randomization:
   - clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure [New York Heart Association $\geq$ Class III], serious uncontrolled cardiac arrhythmia); peripheral vascular disease, cerebrovascular accident, or transient ischemic attack
7. Medically uncontrolled hypertension or systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg
8. Known active or history of active tuberculosis (TB)
9. Positive for hepatitis B surface antigen (HbsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at screening
10. Known to be human immunodeficiency virus positive
11. Recent infection requiring a course of systemic anti-infective agents that was completed $\leq$ 7 days before randomization (with the exception of uncomplicated urinary tract infection)
12. Other investigational procedures **that can impact the study data, results, or patient safety** while participating in this study are excluded; **participation in observational studies is allowed**.
13. Subject is currently enrolled in or has not yet completed at least 30 days or 5 half-lives (whichever is longer) since ending other investigational device or drug study(s), including vaccines, or subject is receiving other investigational agent(s)
14. Previous use of either commercially available or investigational chemotherapy, biological, or immunological therapy for NHL (including rituximab or biosimilar rituximab, or other anti-CD20 treatments)
15. Systemic corticosteroid use **within** 3 months before randomization (inhaled are allowable)
16. Live vaccines within 28 days prior to the first dose of IP
17. History of neurologic symptoms suggestive of central nervous system demyelinating disease
18. Woman of childbearing potential who is pregnant or is breastfeeding
19. Woman of childbearing potential who does not consent to use highly effective methods of birth control (eg, true abstinence, sterilization, birth control pills, Depo Provera injections, or contraceptive implants) during treatment and for an additional 12 months after the last administration of the protocol-specified treatment
20. Man with a partner of childbearing potential who does not consent to use highly effective methods of birth control (eg, true abstinence, vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman) during treatment and for an additional 12 months after the last administration of the protocol specified treatment
21. Subject has known sensitivity to any of the products to be administered during the study, including mammalian cell derived drug products
22. Subject previously has been randomized in this study
23. Subject likely to not be available to complete all protocol-required study visits or procedures
24. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the Investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

8.4.3 Withdrawal and Replacement of Subjects

8.4.3.1 Criteria for Subject Withdrawal

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

Subjects (or a legally acceptable representative) can decline to continue receiving IP and/or other protocol-required procedures at any time during the study. If this occurs, the Investigator is to discuss with the subject the appropriate processes for discontinuation from IP. Additionally, the subject should be followed and complete the EOS visit 8 weeks (±7 days) after the last dose of IP.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and, where permitted, publicly available data can be included after withdrawal of consent. The Investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

Reasons for removal of a subject from the study might include:

- disease progression
- subject request to end IP(s) administration
- safety concern (eg, due to an adverse event [AE], failure to follow contraception, and/or protocol requirements)
- pregnancy
- withdrawal of consent from study
- received proscribed therapy (eg, commercial rituximab, other anticancer therapy)
- decision by Sponsor

8.4.3.2 Evaluations at Withdrawal

For any subject who is withdrawn before completing all treatment visits, the Investigator should:

- perform all the procedures scheduled for the EOS visit (ie, week 28 visit [Section 9.6]). The week 28/EOS assessments will be performed 8 weeks (±7 days) after the last dose of IP (unless the subject withdraws consent to do so). Computed tomography is only required at early withdrawal if it has not been performed within the previous 28 days. **Computed tomography is to be performed before the start of new anti-cancer treatment.**
- complete all appropriate electronic case report form (eCRF) screens, providing the date of and explanation for the subject's withdrawal/discontinuation.
- when indicated, arrange for appropriate follow up and/or alternative medical care of the discontinued subject.

8.4.3.3 Replacement of Subjects

Subjects who are withdrawn will not be replaced.

8.5 Treatment

8.5.1 Treatments Administered

The Investigator must ensure that the IP will be used only in accordance with the protocol. ABP 798 and rituximab will be considered the IP.

Subjects will be randomly assigned to 1 of 2 treatment groups, as follows:

- ABP 798 at a dose of 375 mg/m^2 administered as an IV infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.
- rituximab at a dose of 375 mg/m^2 administered as an IV infusion once weekly for 4 weeks followed by dosing at weeks 12 and 20.

ABP 798/rituximab will be administered after all other procedures are completed for each visit. The dose for ABP 798/rituximab will be calculated based on the height and weight obtained **within 8 days of visit 1** and the dose will remain the same throughout the study.

Subjects should receive premedications before each infusion. Premedications should be given according to local practice for administration of rituximab therapy.

Investigational product will be administered only as an IV infusion by a healthcare professional with appropriate medical support to manage severe infusion reactions. Do not administer as an IV push or bolus.

Intravenous infusions should be performed according to local practice for administration of rituximab therapy. The first dose should not be initiated at a rate greater than 50 mg/hour. In the absence of infusion toxicity, the infusion rate can be increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. If the first dose is tolerated, subsequent infusions may be initiated at a rate of 100 mg/hour. In the absence of infusion toxicity, the infusion rate can be increased by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

All subjects will be monitored for hypersensitivity reactions to IP by assessment of vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature) at the following time points:

- before IP infusion on IP administration visit 1 and visit 2
- approximately every 60 minutes during IP infusion on IP administration visit 1 and visit 2
- at the end of IP infusion on IP administration visit 1 and visit 2

- at approximately 60 minutes after the end of IP infusion on IP administration visit 1 and visit 2

Subjects with signs and symptoms of a hypersensitivity reaction to IP will have vital signs assessed and oxygen saturation monitored by pulse oximetry.

Refer to Section 8.5.6 for IP infusion rate adjustments and stopping rules.

Refer to the Investigator's Brochure for ABP 798 or the Package Insert and Summary of Product Characteristics for rituximab to obtain additional information regarding the IP.

A manual containing detailed information regarding the labeling, packaging, storage, preparation, and administration of each IP (ABP 798 and rituximab) is to be provided separately in the Pharmacy Guide.

8.5.2 Study Treatment Formulation

8.5.2.1 Study Drug

ABP 798 is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen with an identical amino acid sequence to that of rituximab. ABP 798 has an approximate molecular weight of 145 kD. ABP 798 is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium. ABP 798 is a sterile, clear, preservative-free liquid concentrate for IV administration. ABP 798 is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium citrate dihydrate (7.35 mg/mL), sodium chloride (9 mg/mL) and Water for Injection. The pH is 6.5.

8.5.2.2 Comparator

Rituximab (Rituxan®) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD and a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium citrate dihydrate (7.35 mg/mL), sodium chloride (9 mg/mL) and Water for Injection. The pH is 6.5.

8.5.3 Study Treatment Labeling and Packaging

A manual containing detailed information regarding the labeling, packaging, storage, preparation, and administration of each IP (IP[s], comparator product[s], etc) are to be provided separately in the Pharmacy Guide.

8.5.4 Blinding of Study Medication

Since the IP containers are different for ABP 798 and rituximab, IP (ABP 798 or rituximab) will be prepared by an unblinded Pharmacist, or designee, into a common IV preparation for administration to the subject. Subjects, Amgen, designated PRA, and other clinical site staff will be blinded to the IP allocation for each subject. Randomization data will be kept strictly confidential, filed securely by the Sponsor (or designee), and accessible only to authorized persons per Sponsor (or designee)'s standard operating procedures (SOPs) until the time of unblinding. Select PRA staff (eg, clinical research associates), not involved in the monitoring or the daily operations of the study, will be unblinded to subject IP allocation in order to perform IP accountability.

For details of the emergency procedure for unblinding of individual subjects see Section 8.5.10, below.

At randomization, randomization numbers will be assigned to each subject by the interactive voice and web response system (IXRS).

8.5.5 Study Treatment Storage and Accountability

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

8.5.5.1 Study Treatment Storage

IP should be stored in a secure limited access location. ABP 798 and rituximab vials should be stored protected from direct sunlight at 2°C to 8°C and according to the storage and expiration information (where required) provided on the label that is affixed to the package containing the IP. Do not freeze or shake.

8.5.5.2 Study Treatment Accountability

All supplies of IP will be accounted for in accordance with GCP. There will be an individual study drug accountability record for each subject and the Pharmacist, or designee, should maintain accurate records of the disposition of all study medication supplies received during the study. These records should include the amounts and dates clinical drug supplies were received and destroyed/returned to Amgen or its designee. If errors or damages in the clinical drug supply shipments occur, the

Investigator should contact Amgen or its designee immediately. Copies of the study medication accountability records will be provided by each Investigator for inclusion in the Trial Master File after database lock. The study monitor will periodically check the supplies of study medication held by the Investigator or pharmacist to verify accountability of all medication used.

The Investigator will administer the medication only to the identified subjects of this study, according to the procedures described in this study protocol. After the EOS, all unused medication and all medication containers should be destroyed on-site or returned to Amgen or its designee, as appropriate for destruction. In either instance, complete documentation will be returned to the Sponsor.

8.5.6 Dose Adjustments, Dose Escalation and Stopping Rules

8.5.6.1 Dose Adjustments and Dose Escalations

There are no recommended dose adjustments or escalations for IP (ABP 798 or rituximab).

If any scheduled dose of IP in the first 4 visits (ie, visit 1, visit 2, visit 3, and visit 4) is delayed from the scheduled visit date (by more than 3 days), then the dose will be administered as soon as possible and subsequent doses will be adjusted accordingly to remain once per week from the adjusted dose date.

Regardless of previous dose delays, doses at visits 5 and 6 should be given according to the original schedule on weeks 12 and 20. If the scheduled dose for visits 5 and 6 is delayed by more than 15 calendar days from the scheduled visit date, then this will be considered a missed dose. The next dose should be given on the next scheduled visit date.

8.5.6.2 Stopping Rules

In the event of National Cancer Institute (US) Common Toxicity Criteria for Adverse Events (CTCAE) Grade 2, Grade 3, and Grade 4 infusion-related reactions, including events of allergic reaction, anaphylaxis, or cytokine release syndrome, the infusion should immediately stop, and medical therapy and supportive care deployed as appropriate for the presenting symptoms (eg, antihistamine, bronchodilators, oxygen, and vasopressors). Symptoms may include shivering, tachycardia, nausea, rash, significant decrease in blood pressure, and dyspnea. For Grade 2 and Grade 3 events that have resolved, infusion **can be initially resumed at not more than 50% of the previous rate** at the discretion of the investigator. If a subject experiences a Grade 4

infusion-related reaction, IP will be discontinued and the subject will have an EOS visit 8 weeks after the last dose of IP.

Immediately stop the infusion for any subject developing tumor lysis syndrome. Administer supportive care as per local standard, including aggressive hydration with correction of electrolyte abnormalities, while monitoring renal function and fluid balance. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumor lysis syndrome and pulmonary infiltration have been resolved or ruled out. In all subjects, the infusion should not be restarted until complete resolution of all symptoms. The infusion can be initially resumed at not more than 50% of the previous rate.

8.5.7 Prior and Concomitant Therapy

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

- any non-study anti-cancer treatment (other than palliative radiotherapy to nonindex lesions)
- commercial rituximab
- any experimental (biological or non-biological) therapy (within or outside a clinical study)
- live and attenuated vaccinations

Any other treatment (not explicitly excluded) which is considered necessary for the subject's welfare may be given at the discretion of the Investigator.

All subjects who discontinue the study medication should be offered alternative treatment if applicable. Treatment should be given according to normal clinical practice, after the end-of-treatment (week 28) visit.

8.5.8 Treatment Compliance

Investigational product will be administered by site staff and recorded in the eCRF and subject records. Records of study medication used and intervals between visits will be kept during the study. Drug accountability will be noted by the study monitor during site visits and at the completion of the study. To maintain treatment blinding of the Investigator, IP dispensation should be delegated from the Investigator to a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained.

8.5.9 Assignment to Treatment

When subjects enter the screening period for the study, the Investigator (or designee) will contact the IXRS and receive a unique 11-digit subject identification number before

any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. [redacted] Signing of the ICF establishes entry into the screening period.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, enrollment, or randomization. This number will not necessarily be the same as the randomization number assigned for the study.

Upon completion of screening, the Investigator (or designee) will contact the IXRS to randomize the subject centrally to receive either ABP 798 or rituximab in a 1:1 manner. The randomization will be stratified by geographic region and age (> 60 vs ≤ 60 years).

8.5.10 Unblinding Procedures

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The Investigator is strongly encouraged to contact the Amgen Medical Monitor (or designee) before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

The identity of IP assigned to subject numbers or to individual boxes of IP will be available for emergency situations through the IXRS. Authorized site staff will be provided with a unique Personal Identification Number (PIN) to access the IXRS to obtain unblinding information. This PIN is unique to the individual and must not be shared.

8.6 Efficacy and Safety Variables

8.6.1 Efficacy and Safety Measurements Assessed

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

Table 1. Schedule of Assessments and Procedures

	Screen ≤ 28 days	Treatment Phase							End of Study /Week 28 (± 7 days)
		Visit 1 Baseline Day 1, Week 1	Visit 2 Week 2 (± 3 days)	Visit 3 Week 3 (± 3 days)	Visit 4 Week 4 (± 3 days)	OPTIONAL Visit 4a Week 5 (± 3 days)	Visit 5 Week 12 (± 7 days)	Visit 6 Week 20 (± 7 days)	
General Assessments									
Informed consent form	X								
Post-infusion observation (4 hour)		X [a]							
Medical and medication history	X								
Physical examination	X	X [b]	**X**	**X**	**X**		**X**	**X**	X
Vital signs [c]	X	X [d]	X [d]	X	X		X	X	X
Electrocardiogram [e]	X								X
ECOG performance status	X								X
Clinical disease assessment		X	X	X	X		X	X	X
Concomitant medication	X	X	X	X	X		X	X	X [f]
Adverse event recording	X [g]	X	X	X	X		X	X	X
Treatments									
Dosing of ABP 798 / rituximab [h]		X	X	X	X		X	X	
Disease Assessments									
CT Scan	X [i]						X		X [j]
Bone marrow biopsy [k]	X								X [k]
Laboratory Assessments									
Serology (HBsAg, HBcAb, HCV)	X								
Serum chemistry [l,m]	X	X [m]	X	X	X		X	X	X
Hematology [m]	X	X [m]	X	X	X		X	X	X
Pregnancy [n]	X								
PK sampling [o,p,q]		X [p]	X	X	X [p]	**X** [p]	X	X	X
Pharmacodynamic (CD19+ cell count) [q,r]		X	X	X	X				X
Antidrug antibodies [q,s]		X					X	X	X
IgG and IgM [q]		X	X	X	X				X

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus antibody; Ig = Immunoglobulin.
(See footnotes below)

[a] The first 12 randomized subjects will be observed for safety for 4 hours after the first administration of IP.
[b] Includes weight and height **within 8 days of visit 1**.
[c] Systolic blood pressure and diastolic blood pressure will be measured on the same arm (preferentially on the left arm) after the subject has been in a supine/sitting position for 5 minutes.
[d] All subjects will be monitored for hypersensitivity reactions to IP by assessment of vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature) on visit 1 and visit 2 at the following time points: before IP infusion; approximately every 60 minutes during IP infusion; at the end of IP infusion; at approximately 60 minutes after the end of IP infusion. Subjects with signs and symptoms of a hypersensitivity reaction to IP will have vital signs assessed and oxygen saturation monitored by pulse oximetry.
[e] 12-lead electrocardiogram recordings will be obtained after the subject has been supine for 5 minutes.
[f] Includes any additional treatment for NHL.
[g] Only serious adverse events will be reported from signing of the informed consent until day 1.
[h] The ABP 798/rituximab dose will be calculated based on the height and weight obtained within 8 days of visit 1. ABP 798/rituximab dose to be administered after all assessments are completed for each visit. If any scheduled dose of IP in the first 4 visits (ie, visit 1, visit 2, visit 3, and visit 4) is delayed from the scheduled visit date (by more than 3 days), then the dose will be administered as soon as possible and subsequent doses will be adjusted accordingly to remain once per week from the adjusted dose date. See Section 8.5.6 for more details regarding dose adjustments, dose escalation, and stopping rules.
[i] Subjects must have a baseline scan (CT of the neck [if palpable lymph node >1.0 cm]), chest, abdomen, and pelvis to assess disease burden within **6 weeks** before randomization. For subjects with contraindications to the contrast agent, the decision as to whether a non-contrast CT is used should be based on anatomic location of the disease and comparability with images previously taken in the course of the study.
[j] **End-of-study CT scan can be taken within 28 days prior to EOS visit. Subjects who discontinue from the study due to disease progression should have a CT scan (as described in Section 9.6) prior to initiation of new anti-cancer treatment, if deemed clinically acceptable.**
[k] Subjects must have a bone marrow biopsy within 12 months before randomization. Previously confirmed positive bone marrow involvement does not need to be repeated for purposes of screening. An end-of-study biopsy is required if bone marrow involvement is identified at baseline **for complete response (CR) confirmation. If a confirmatory bone marrow assessment is not obtained, these subjects should be considered as only having a partial response (PR).**
[l] Clinical laboratory tests will be performed at local laboratories. Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator.
[m] Serum chemistry and hematology for baseline (day 1) can be performed up to 3 days before baseline (day 1).
[n] Serum or urine pregnancy tests for females of childbearing potential only at a local laboratory.
[o] Pharmacokinetics samples will be collected at baseline on day 1/visit 1/week 1, predose at weeks 2, 3, 4, 12, and 20, and immediately after the end of infusion at week 12, and a single PK sample at week 28/EOS.
[p] **Subjects who agree to optional additional PK sampling will also be required to have PK samples collected at 2 hours (± 1 hour) postdose at week 1 and week 4 and at visit 4a (week 5)**
[q] Pharmacokinetics, pharmacodynamic, antidrug antibody and IgG and IgM samples will be sent to a central laboratory. Details will be provided in a laboratory manual.
[r] Pharmacodynamic CD19+ cell count will be analyzed at baseline on day 1/week 1 and at weeks 2 (day 8), 3, 4 and 28.
[s] Antidrug antibodies will be analyzed by Amgen or a designee. Sampling will be at baseline on day 1/week 1, prior to fifth dose at week 12, prior to the sixth dose at week 20 and at week 28/EOS. Subjects with positive antidrug antibody results will be assessed for neutralizing antibodies. Additional blood samples may be obtained to rule out antidrug antibodies.

8.6.1.1 Efficacy Measurements

The primary efficacy endpoint is the risk difference (RD) of ORR by week 28. Response will be determined according to Cheson et al (1999).

Secondary efficacy criteria include RD of ORR at week 12.

8.6.1.2 Pharmacokinetic/Pharmacodynamic Endpoints

The PK endpoints will be the serum concentrations at predose and immediately after the end of the infusion at week 12. Pharmacodynamic assessment includes percentage of subjects with complete depletion of CD19+ cell count from baseline to week 2 (day 8) and total IgG and IgM antibody levels.

8.6.1.3 Safety Measurements

Safety endpoints include the following:

- treatment-emergent AEs and serious adverse events (SAEs)
- clinically significant changes in laboratory values and vital signs
- incidence of antidrug antibodies
- on study progression-free survival (PFS)
- on study overall survival (OS)

9 STUDY EVALUATIONS BY VISIT

After signing the informed consent, there are 8 **planned** visits, including a screening visit, a treatment visit on day 1 (day of first treatment; visit 1; week 1), treatment visits at visit 2 (week 2), visit 3 (week 3), visit 4 (week 4), visit 5 (week 12), visit 6 (week 20), and an EOS visit at week 28. **Subjects who agree to optional additional PK sampling will be required to attend an additional visit (4a at week 5) as well as remain in the clinic for sampling 2 hours (± 1 hour) after infusion on visits 1 (day 1) and 4 (week 4).** The first 12 subjects treated will remain at the clinic for 4 hours following the first (day 1) infusion for additional safety observation.

9.1 Screening

Unless otherwise stated, the following assessments/procedures will be performed within 28 days before randomization. Assessments/procedures performed as routine standard of care, prior to the subject signing informed consent, and according to the criteria outlined in Section 10, can be used for screening purposes as long as the assessments/procedures were performed within 28 days before randomization (except for bone marrow biopsy **and CT scan**).

- informed consent form
- medical history, including history of NHL
- physical examination, including evaluation of body systems
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- standard 12-lead electrocardiogram (ECG)
- ECOG performance status
- baseline CT of the neck (if palpable lymph node >1.0 cm), chest, abdomen, and pelvis **within 6 weeks before randomization**
- bone marrow biopsy within 12 months before randomization**.** Previously confirmed positive bone marrow involvement does not need to be repeated for purposes of screening
- clinical laboratory testing, including serology, serum chemistry, and hematology
- serum or urine pregnancy test for women of childbearing potential

At the screening assessment, all concomitant medications from 3 months before the planned start of study treatment will be recorded. Any AEs occurring during the screening period will be recorded as medical history; any SAEs will be recorded using the eCRF. SAEs will be reported as outlined in Section 11.2.2. After screening but within 8 days before starting treatment, for eligible subjects the Investigator will contact the IXRS for randomization. **(Height and weight are required for IXRS randomization and must be collected within 8 days of visit 1).**

9.1.1 Screen Failures

Subjects determined to be screen failures will not be eligible for immediate participation and must be registered as a screen failure in the IXRS. Laboratory assessments used to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure. Screen failed subjects may be re-screened up to 2 times at the Investigator's discretion (ie, total of 3 screens including initial screening). The subject will maintain the same subject identification number provided at the initial screening. Subjects must be re-consented if more than 30 days have elapsed between date of initial informed consent and date of re-screen/randomization.

9.2 Baseline (Day 1, first day of administration of investigational product)

Day 1 will be defined as the first day of administration of IP. After subjects are confirmed to meet the entry criteria (Section 8.4), the Investigator (or designee) will contact the IXRS to randomize the subject centrally to receive blinded IP (ABP 798 or rituximab) within 8 days before the baseline visit. The following assessments/procedures will be performed before treatment:

- physical examination, including evaluation of body systems and **baseline** height and weight; **baseline height and weight will be measured within 8 days of visit 1 to allow use in randomization of subjects within 8 days of visit 1**
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- clinical disease assessment
- clinical laboratory testing, including serum chemistry and hematology (can be performed up to 3 days before baseline [day 1])
- collection of samples for pretreatment PK samples, pretreatment antidrug antibodies, pretreatment samples for CD19+ cell count, and IgG and IgM levels

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

After completion of pretreatment procedures and premedications, ABP 798 or rituximab will be administered as an IV infusion in a double-blinded fashion. The dose calculation for ABP 798 or rituximab will be based on the height and weight obtained **within 8 days of visit 1**. Starting at the time of first treatment, all AEs, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF.

All subjects will be monitored for hypersensitivity reactions to IP by assessment of vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature) at the time points outlined in Section 8.5.1 (every 60 minutes during IP infusion, at the end

of the IV infusion, and approximately 60 minutes after the end of the IV infusion). **Subjects who have agreed to additional optional PK sampling will have a 2 hour (± 1 hour) post dose PK sample collected.** Subjects with signs and symptoms of a hypersensitivity reaction to IP will have vital signs assessed and oxygen saturation monitored by pulse oximetry. The first 12 subjects will be followed for 4 hours after the first (day 1) infusion for additional safety observation. Subsequent subjects may leave the site after completion of the infusion and the 60 minute vital signs follow-up, according to local standard of care.

Refer to Section 8.5.6 for IP infusion rate adjustments and stopping rules.

9.3 Visit 2 (Week 2), Visit 3 (Week 3), and Visit 4 (Week 4)

At visit 2 (week 2 ± 3 days), visit 3 (week 3 ± 3 days), and visit 4 (week 4 ± 3 days), the subject will return to the study center for treatment. The following assessments/procedures will be performed before treatment at each of these time points:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- **physical examination and** clinical disease assessment
- clinical laboratory testing, including serum chemistry and hematology
- collection of samples for pretreatment PK samples, pretreatment samples for CD19+ cell count, and IgG and IgM levels

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

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

At visit 2, all subjects will be monitored for hypersensitivity reactions to IP by assessment of vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature) at the time points outlined in Section 8.5.1.

For visit 3 and visit 4, subjects will be monitored during and after the infusion according to local standard of care and the approved product labeling.

At visit 4, subjects who have agreed to additional optional PK sampling will have a 2 hour (± 1 hour) post dose sample collected.

Subjects with signs and symptoms of a hypersensitivity reaction to IP will have vital signs assessed and oxygen saturation monitored by pulse oximetry.

Refer to Section 8.5.6 for IP infusion rate adjustments and stopping rules.

9.4 Visit 4a (Week 5): Optional PK Sampling

At visit 4a (week 5 ± 3 days) subjects who have agreed to additional optional PK sampling should return for PK sample collection. No study treatment will be given at this visit.

9.5 Visit 5 (Week 12) and Visit 6 (Week 20)

At visit 5 (week 12 ± 7 days) and visit 6 (week 20 ± 7 days), the subject will return to the study center for treatment. The following assessments/procedures will be performed before treatment at each of these time points:

- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- **physical examination and** clinical disease assessment
- computed tomography (week 12 only) of the neck (if palpable lymph node > 1.0 cm or if performed at baseline), chest, abdomen, and pelvis
- clinical laboratory testing, including serum chemistry and hematology
- collection of pretreatment PK samples and pretreatment samples for antidrug antibodies

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

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

Subjects will be monitored during and after the infusion according to local standard of care and the approved product labeling.

Subjects with signs and symptoms of a hypersensitivity reaction to IP will have vital signs assessed and oxygen saturation monitored by pulse oximetry.

Refer to Section 8.5.6 for IP infusion rate adjustments and stopping rules.

The following procedure / assessment will be performed for all subjects after treatment on week 12 only:

- Immediately after completion of the infusion, postdose PK samples will be collected.

9.6 Week 28/End of Study

For subjects completing the treatment phase, the EOS visit will be at week 28, 8 weeks (± 7 days) after the last dose of IP. For subjects who do not complete the treatment phase, the EOS visit will be 8 weeks (± 7 days) after the last dose of IP**. Subjects who discontinue from the study due to disease progression should have a CT scan (as described below) prior to initiation of new anti-cancer treatment, if deemed clinically acceptable.**

At the EOS visit **(week 28 or 8 weeks after the last dose of IP),** the following assessments will be performed:

- physical examination, including evaluation of body systems
- vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature)
- standard 12-lead ECG
- ECOG performance status
- clinical disease assessment
- CT (not required if performed within the previous 4 weeks) of the neck (if palpable lymph node >1.0 cm or if performed at baseline), chest, abdomen, and pelvis.
- bone marrow biopsy (only required if bone marrow involvement is identified at baseline **for CR confirmation; if a confirmatory bone marrow assessment is not obtained, these subjects should be considered as only having a PR). The bone marrow biopsy can be performed at ± 14 days in relation to the study visit date.**
- clinical laboratory testing, including serum chemistry and hematology
- collection of samples for PK, antidrug antibodies, CD19+ cell count, and IgG and IgM levels

Any changes in concomitant medications since the last assessment will be recorded. Any additional treatment for lymphoma will be recorded. All AEs, including increases in severity or frequency of pre-existing conditions, will be recorded in the eCRF through the week 28 visit. SAEs will be reported as outlined in Section 11.2.2. Any SAEs ongoing at week 28 will be followed until they resolve or are considered chronic or stable.

10 METHODS OF ASSESSMENT

10.1 Response Assessments

Response to treatment will be assessed according to standardized criteria (Cheson et al, 1999). At the times indicated in Table 1, Investigators will assess the status of each subject's follicular B-cell NHL. Assessment will include physical examination and radiographic examination. Computed tomography scan is the preferred method for radiographic tumor assessment. For subjects with contraindications to the contrast agent, the decision as to whether a non-contrast CT is used should be based on anatomic location of the disease and comparability with images previously taken in the course of the study.

For radiographic assessments, the same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline. However, if a subject is imaged without contrast at baseline, subsequent assessments should be performed with contrast, unless the subject cannot tolerate the contrast.

Copies of all scheduled and unscheduled screening and on-study CT scans performed to monitor or diagnose NHL must be submitted to the central imaging vendor. This includes any such images deemed to be negative by the local radiologist and any standard-of-care or routine disease monitoring images performed, even if not specified by the protocol. Detailed procedures for image management will be provided in the study manual.

Clinical disease assessments, **which will be performed in conjunction with physical examinations,** will be performed by the investigator or sub-investigator and will be submitted to the central imaging vendor, if applicable.

Determination of response is outlined in Section 17.2.

10.2 Pregnancy Test

Pregnancy will be determined by evaluation of β-human chorionic gonadotropin in serum or urine. Subjects who are pregnant are excluded from the study.

The Investigator will inform the Sponsor immediately of any case of pregnancy and collect information on any female subject who becomes pregnant while participating in this study and in case of pregnancy among female partners of male subjects. The subject will also be followed to determine the outcome of the pregnancy.

10.3 Physical Examination

Physical examinations will be performed by a physician and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and nervous system. An assessment of normal or abnormal will be recorded. Clinically relevant changes from baseline will be reported as AEs.

Body weight (kg) will be measured without shoes or jacket. Height and weight will be determined **within 8 days of visit 1**.

10.4 Vital Signs

Systolic blood pressure and diastolic blood pressure will be measured on the same arm (preferentially on the left arm) after the subject has been in a supine/sitting position for 5 minutes. Pulse will be recorded simultaneously with blood pressure measurements. Respiration rate and temperature will also be recorded.

During the study, the measurement of vital signs may be repeated at the discretion of the Investigator for safety reasons. Clinically relevant abnormal findings will be reported as AEs.

All subjects will be monitored for hypersensitivity reactions to IP by assessment of vital signs (systolic and diastolic blood pressure, pulse, respiration rate, and temperature) at the following time points:

- before IP infusion on IP administration visit 1 and visit 2
- approximately every 60 minutes during IP infusion on IP administration visit 1 and visit 2
- at the end of IP infusion on IP administration visit 1 and visit 2
- at approximately 60 minutes after the end of IP infusion on IP administration visit 1 and visit 2

Subjects with signs and symptoms of a hypersensitivity reaction to IP will have vital signs assessed and oxygen saturation monitored by pulse oximetry.

10.5 Electrocardiogram

Computerized 12-lead ECG recordings will be obtained after the subject has been supine for 5 minutes. Each lead will be recorded for at least 3 to 5 beats at a speed of 25 mm/sec paper speed and 10 mm/mV amplitude. At a minimum, heart rate, P, PR, QRS, QT, and corrected QT (QTc) intervals (msec) will be recorded from the 12-lead ECG. A copy of the ECGs will be retained on site. For the purposes of screening, the

Investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically acceptable for inclusion, if abnormal.

10.6 Clinical Laboratory Testing

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

Serology (local laboratory): HBsAg, hepatitis B core antibody, and HCV antibody.

Hematology (local laboratory): Hemoglobin, packed cell volume, white blood cell count and ANC, platelet count.

Clinical chemistry (local laboratory): Sodium, potassium, urea, creatinine, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase, LDH, non-fasting glucose, uric acid, beta-2-microglobulin (beta-2-microglobulin at screening only).

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

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

Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity, and presence of immune complexes. Additional blood samples may be obtained to rule out antidrug antibodies. Subjects who test positive for neutralizing antibodies to ABP 798 or rituximab at the final scheduled study visit may be asked to return for additional follow-up testing.

The subjects with a neutralizing antibody at the end of the study may be followed if there are any clinical sequelae. This testing may occur approximately every 3 months starting from when the site has been notified of the positive result, until:

1. Neutralizing antibodies are no longer detectable OR
2. The subject has been followed for a period of at least 1 year (± 4 weeks) post-administration of ABP 798 or rituximab.

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

10.7 Blood Samples for Pharmacokinetic Analysis

During treatment, a series of serum samples will be taken according to Table 1, and PK analyses will be performed by a central PK laboratory. The exact times of blood sampling will be recorded.

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

10.8 Blood Samples for Pharmacodynamic Analysis

Pharmacodynamic analyses will include CD19+ cell count and IgG and IgM levels and will be performed by a central laboratory. Samples will be collected at the time points indicated in Table 1.

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

11 SAFETY DATA COLLECTION, RECORDING, AND REPORTING

11.1 Adverse Events

11.1.1 Definition of Adverse Events

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

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. In the case of worsening of a pre-existing condition, the start date of the event is the date when the first signs of worsening were observed. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an AE.

11.1.2 Reporting Procedures for Adverse Events

The Investigator is responsible for ensuring that all AEs observed by the Investigator or reported by the subject that occur from the day of randomization through the EOS visit are reported using the applicable eCRF Adverse Event Summary page. AEs observed by the Investigator or reported by the subject that occur after signing of informed consent but before randomization will be recorded as medical history.

The Investigator must assign the following AE attributes:

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

AEs must be graded for severity according to the CTCAE version 4.03 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

The Investigator must assess whether the AE is possibly related to the IP. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?"

Progression or recurrence of NHL should not be reported as an adverse event. However, any specific symptoms or sequelae of the disease progression or recurrence (eg, organ failure, respiratory distress, etc) will be considered adverse events and will be captured on the eCRF.

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as AEs. However, laboratory value changes that require treatment or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

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

11.2 Serious Adverse Events

11.2.1 Definition of Serious Adverse Events

A SAE is defined as an AE that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a health care facility (eg, overnight stay).

If an Investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a SAE under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

11.2.2 Reporting Procedures for Serious Adverse Events

The Investigator is responsible for ensuring that all SAEs observed by the Investigator or reported by the subject that occur after signing of the ICF through the EOS visit are recorded in the subject's medical record and are submitted to Amgen.

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

If the electronic data capture (EDC) system is not functional, the SAE can be reported by faxing a completed paper SAE Fax Cover Sheet and SAE report form or by direct telephone communication with PRA Safety Risk Management at the numbers provided below. The event must be updated electronically in the EDC by the clinical site once the EDC function resumes.

Fax information to Safety Risk Management/PRA, to the attention of:

PRA Drug Safety Center

For Europe, Asia, and Pacific Region Clinical Sites:
FAX: +44 1792 525 720
Phone: +49.621.8782.154
MHGSafety@prahs.com

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

New information relating to a previously reported SAE must be submitted to Amgen, or its designee. All new information for SAEs must be sent to Amgen, or its designee, within 24 hours following knowledge of the new information. The Investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the SAE must be consistent with that recorded on the applicable eCRF (eg, AE Summary eCRF).

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

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

receive notification of related SAE reports sent to regulatory authorities in accordance with local requirements.

Determination of expectedness for Amgen products will be based on the contents of the Investigator's Brochure/Development Core Safety Information for IPs and the regional prescribing information for products being studied for an approved use. Expectedness assessments are to be made for all IPs (Amgen and non-Amgen) using the appropriate reference safety information per local regulatory reporting requirements. Suspected unexpected serious adverse reactions (SUSARs) reported for subjects receiving a non-Amgen IP are to be expedited according to local requirements.

Amgen, or its designee, reports SAEs and/or SUSARs as required to regulatory authorities, Investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and GCPs.

The Investigator is to notify the appropriate IRB/IEC of SAEs occurring at the site and of other AE reports received from Amgen, in accordance with local procedures and statutes.

After the protocol-required reporting period defined above, the Investigator does not need to actively monitor subjects for SAEs. However, if the Investigator becomes aware of a SAE after this protocol-required reporting period, the Investigator will report the event to Amgen within 24 hours following the Investigator's knowledge of the event. SAEs reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

11.3 Events of Interest

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

11.4 Pregnancy Reporting

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. All pregnancies with or without an adverse event will be collected and reported in the safety database. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be reported to Amgen, or its designee, and must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

Pregnancies among female partners of male subjects will also be reported and followed for outcome.

12 DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by PRA, an external clinical research organization (CRO).

12.1 Data Management

Previous and concomitant medications will be coded using the latest available World Health Organization (WHO) Drug Reference Dictionary. Coexistent diseases and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

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

12.2 Sample Size Estimation

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

12.3 Statistical Analysis Plan

A SAP will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Table, listing, and figure shells will also be included.

12.4 Randomization

Randomization will be performed by an IXRS. The randomization schedule will be prepared by a statistician not involved in the conduct of the study. Randomization will be stratified by geographic region and age (> 60 vs ≤ 60 years).

12.5 Analysis Sets

The primary analysis of the 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, pharmacokinetic and pharmacodynamic endpoints will be conducted on the safety analysis set.

12.5.1 Full Analysis Set

The FAS includes all subjects randomized in the study.

12.5.2 Per-protocol Set

The per-protocol analysis set is a subset of the FAS that 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.

12.5.3 Safety Analysis Set

The safety analysis set includes all randomized subjects who received at least 1 dose of IP.

12.6 Statistical Methods

Categorical variables will be summarized using the number and percentage of subjects falling into each category. Continuous variables will be summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects with observations. Kaplan-Meier estimates will be provided for time-to-event endpoints.

12.6.1 Missing Data

Subjects without measurable disease at baseline and those without post-baseline disease assessments will be counted as nonresponders in the primary analysis. Additional imputation rules will be presented in the SAP before unblinding of the study for the primary analysis.

12.6.2 Demographic and Baseline Data

The following demographics and baseline characteristics will be summarized: age (in years, at time of signing informed consent), race, gender, ethnicity, height, and weight. Disease history and baseline disease characteristics will also be summarized.

12.6.3 Subject Disposition

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

- number of subjects randomized will be tabulated by country and site
- subject disposition (including number of subjects who were screened, randomized, treated with ABP 798/rituximab, completed study, and discontinued study early with reason for discontinuation)
- summaries of analysis populations with reason for exclusion
- important protocol deviations
- number and percentage of subjects on study at each visit
- randomization list of subjects and their actual versus randomized treatment group

12.6.4 Efficacy

The primary efficacy hypothesis for this study is that there are no clinically meaningful differences between ABP 798 and rituximab in ORR by week 28. Clinical equivalence will be demonstrated by first comparing the 1-sided 95% lower confidence interval (CI) 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 95% upper CI limit of the RD of ORR by week 28 between ABP 798 and rituximab will be compared with a nonsuperiority margin of +35.5%. In addition, a 2-sided 95% CI will be calculated and evaluated against a symmetrical margin of 15% for noninferiority and nonsuperiority. The CIs for RD will be estimated using a generalized linear model adjusted for the stratification factors.

The primary analyses of ORR will be conducted based on central, independent, blinded radiologists' assessments on the FAS according to randomized treatment. The sensitivity analysis will be conducted based on central, independent, blinded radiologists' assessments on the per-protocol analysis set according to actual treatment received and based on the Investigator's assessment of disease on the FAS according to randomized treatment.

Determination of response is outlined in Section 17.2.

Inferential analyses will only be performed for the primary endpoint. The secondary endpoints RD of ORR at week 12 will be summarized descriptively.

12.6.5 Pharmacokinetics

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. Point estimates and CIs for the GMR will be estimated from an analysis of covariance model. The analysis will be conducted on the safety analysis set according to actual treatment received. Additional details on the PK analysis will be provided in the SAP.

12.6.6 Pharmacodynamics

Pharmacodynamic endpoints (complete depletion of CD19+ cell count from baseline to week 2 (day 8), total IgG and IgM antibody levels) will be summarized descriptively for the safety analysis set by actual treatment received.

12.6.7 Safety

Safety will be assessed in the safety analysis set with treatment assignment based on actual treatment received. Independent safety reviews will be performed by the DMC periodically throughout the study, including an initial safety review after the first 12 subjects have received at least 2 doses of IP. Blinded study data will also be monitored on an ongoing basis by the blinded clinical study team to ensure subjects' safety. Safety analysis will include analyses of drug exposure, AEs, PFS and OS, clinical laboratory tests, vital signs, ECGs, and antidrug antibodies.

12.6.7.1 Investigational Product Administration

For the IP (ABP 798 or rituximab), summary statistics will be provided for the total number of doses and total duration of IP exposure throughout the study.

12.6.7.2 Adverse Events

All verbatim terms for any reported AEs will be coded to the appropriate system organ class and preferred term according to the current version of the MedDRA dictionary, and graded by the Investigator for severity as per CTCAE version 4.03. The number and percentage of subjects reporting AEs (all, serious, treatment related, and deaths) will be reported.

Only treatment-emergent AEs will be summarized. Treatment-emergent events are those that begin or increase in severity or frequency at or after the time of first treatment up to the EOS visit. All treatment-emergent AEs will be summarized by treatment arm and according to the MedDRA system organ class (SOC) and preferred term. Summaries will be provided for the incidence of all treatment-emergent AEs by severity. Additional summaries will be presented for SAEs. All AE data will be listed by subject, and a separate listing will include all SAEs, including any deaths on study.

Adverse events of interest (Section 11.3) will be summarized by treatment arm and preferred term.

12.6.7.3 Immunogenicity

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

12.6.7.4 Progression-free Survival and Overall Survival

Progression-free survival is defined as the time from randomization until the first occurrence of disease progression or death from any cause according to the standard criteria in Cheson et al, 1999. For subjects alive and progression-free at the week 28/EOS visit, PFS will be censored at the date of the last tumor evaluation demonstrating lack of progression.

Overall survival is defined as the time from randomization to death from any cause. 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.

For these time-to-event outcomes, the hazard ratio and 1-sided 95% and 97.5% CIs for ABP 798 relative to rituximab will be estimated from a Cox model stratified by stratification factors. In addition, Kaplan-Meier curves and median survival time will be provided descriptively.

12.6.7.5 Concomitant Medications and Therapies

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

12.6.7.6 Clinical Laboratory Test

Clinical laboratory test results and change from baseline will be summarized by time point. In addition, shift tables, from baseline to the worst on-study laboratory toxicity based on CTCAE v4.03 grading, will be presented.

12.6.7.7 Vital Signs and Physical Examinations

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be listed by subject and assessed for clinical significance and included in the AE listings and summaries.

12.6.7.8 Electrocardiograms

Electrocardiogram results will be summarized using descriptive statistics.

12.6.8 Interim Analysis

A safety analysis will be performed by a DMC (Section 12.6.9) after the first 12 subjects have received at least 2 doses of IP.

No interim analyses of efficacy or pharmacodynamics are planned.

12.6.9 Data Monitoring Committee

A DMC external to Amgen and PRA will be formed with members consisting of individuals chosen for their expertise in follicular NHL. 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 first assessment will be when 12 subjects have received at least 2 doses of IP).

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

Records of all meetings will be archived. Selected Amgen, or its designee, staff may serve as liaisons to the external DMC, but will not be voting members and will not be unblinded to the results. Details regarding the DMC will be provided in the DMC charter.

13 MONITORING PROCEDURES (QUALITY ASSURANCE)

Amgen has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to maintain current of study progress, Amgen monitors, or Amgen's designees, will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

13.1 Routine Monitoring

Amgen, or its designee, assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Amgen, or its designee, authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and must assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Whenever a subject name is revealed on a document that is to be collected for the Sponsor the name must be blacked out permanently by the site personnel, leaving the initials visible, and must be annotated with the subject number as identification.

13.2 Inspections and Auditing Procedures

Amgen, or its designee, may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact Amgen, or its designee, immediately

if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

14 STUDY MANAGEMENT AND MATERIALS

14.1 Electronic Case Report Forms

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed, and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Complete data should be entered into the eCRF by examining personnel or the appropriate site staff. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

14.2 Data Collection

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes will contain:

- the date of the visit and the corresponding day or visit in the study schedule (eg, screening, day 1, and week 2)
- general condition and status remarks by the subject, including any *significant* medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is study drug-related
- changes in concomitant medications or dosages.
- a general reference to the procedures completed
- the signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change is made by the Investigator

or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

14.3 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent for each subject shall be filed with records kept by the Investigator and a copy shall be given to the subject.

14.4 Record Maintenance

All data derived from the study will remain the property of Amgen Inc.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs and study drug inventory must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IPs. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor, and will give the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

14.5 Confidentiality

All information obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each subject's anonymity is maintained. On eCRFs and other documents submitted to the Sponsor or the CRO, subjects must not be identified by name. Instead, subjects will only be known by the unique subject number allocated to them in order to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review subjects' medical records as they relate to this study. Only the subject's unique number on the eCRFs will identify him/her, but his/her full name may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor or the CRO (eg, consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site and subject identity will remain confidential in all publications related to the study.

15 ADMINISTRATION PROCEDURES

15.1 Regulatory Approval

Amgen Inc., or their appointed agents, will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No subject may enter the study until this approval has been obtained. A copy of the approval (where one is provided as requested, according to local country requirements) will be provided to the Investigator and to the IRB(s)/IEC(s).

15.2 Protocol Amendments

In accordance with ICH Topic E 6 (R1) Guideline for GCP the Investigator should not implement any deviation from or changes to the protocol without agreement by the Sponsor and documented approval from the IRB/IECs of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor[s], change of telephone number[s]).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB/IECs assuming this responsibility. The Investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects. In these cases, the IRB/IEC must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB/IEC, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the subject, the currently approved written ICF will require modification. The modified ICF must also be reviewed and approved by the Sponsor, appropriate regulatory authorities, and the IRB/IEC. In such cases, repeat informed consent must be obtained from subjects enrolled in the study before participation continues.

15.3 Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

15.4 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit is to be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors are to meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals are to fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors are to qualify for authorship, and all those who qualify are to be listed.
- Each author is to have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement between the institution, Investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

15.5 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated.

15.6 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and Amgen, or its designee, will sign a clinical study agreement prior to the start of the study, outlining overall Amgen, or its designee, and Investigator responsibilities in relation to the study. Financial Disclosure Statements will be completed only as required by local regulations.

15.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

15.8 Discontinuation of the Study

This study may be terminated by Amgen at any time. In terminating the study, Amgen, the CRO (PRA) and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Amgen will not provide ABP 798 or rituximab after termination of the trial or upon discontinuation of the study for the subject.

15.9 Study Center File Management

The Investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

1. Investigator's Brochure
2. Current, signed version of the protocol and any previous versions of the protocol
3. Protocol amendments (if applicable)
4. Operations Manual (if applicable)
5. Current ICF (blank) and any previous versions of the ICF
6. Curricula Vitae of Investigator(s) and sub-investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug regulations), signed by all Principal Investigators. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations
7. Documentation of IRB/IEC approval of the protocol, the ICF, any protocol amendments, and any ICF revisions
8. All correspondence between the Investigator, IRB/IEC, and the Sponsor/CRO relating to study conduct

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

16 REFERENCE LIST

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17 APPENDICES

17.1 Appendix 1: Elements of Informed Consent

ELEMENTS OF INFORMED CONSENT

Both the informed consent discussion and the written informed consent form (ICF) and any other written information to be provided to subjects should include explanations of the following:

- That the study involves research.
- The purpose of the study.
- The study treatment(s) and the probability for random assignment to each treatment.
- The study procedures to be followed including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the study that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of study-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
- The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The expected duration of the subject's participation in the study.
- The approximate number of subjects involved in the study.

17.2 Appendix 2: Response Determination by IWG (1999) Criteria

Responses will be categorized as CR, 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.

17.2.1.1 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).

17.2.1.2 CR/unconfirmed

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

1. A residual lymph node mass greater 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).

17.2.1.3 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.

17.2.1.4 Stable Disease

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

17.2.1.5 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.

17.2.1.6 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.

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17.3 Appendix 3: Cotswold Modification of Ann Arbor Staging System

Stage	Description
Stage I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic (E) site (Stage IE)
Stage II	Involvement of two or more lymph node regions on the same site of the diaphragm (II) or localized contiguous involvement of only one extranodal organ or side and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (Stage IIE) Note: the number of anatomic regions involved may be indicated by a subscript (eg,Stage II_3)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (Stage III), which also may be accompanied by involvement of the spleen (Stage IIIS) or by localized contiguous involvement of only one extranodal organ side (Stage IIIE) or both (Stage IIISE)
Stage IV	Disseminated (multifocal) involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

Designations applicable to any disease stage

- A: No symptoms
- B: Fever (temperature > 38°C, night sweats, unexplained loss of more than 10% body weight during the previous 6 months)
- X: Bulky disease
- E: Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

Armitage, JO. Staging non-Hodgkin lymphoma. CA Cancer J Clin. 2005;55:368-376.

17.4 Appendix 4: Groupe d'Etudes des Lymphomes Folliculaires (GELF) Criteria

- Involvement of **>** 3 nodal sites, each with a diameter of **>** 3 cm
- Any nodal or extranodal tumor mass with a diameter of **>** 7 cm
- B symptoms (night sweats, fever [temperature > 38°C], weight loss > 10% in the previous 6 months)
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L)
- Leukemia (> 5.0 x 10^9/L malignant cells)

Solal-Celigny P. Lepage E, Brousse N, et al. Doxorubicin containing regimen with or without interferon alfa 2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Group d'Etude des Lymphomes Folliculaire 86 trial. J Clin Oncol. 1998;16:2332-2338.

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)

SUMMARY OF CHANGES

Test Drug: ABP 798

Protocol Number: 20130109 **EudraCT number:** 2013-005542-11

Study Phase: 3

Date and Version: 5.0, 17 July 2017

Key Contact:

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Fax: 1-888-772-6919
E-mail: CHOSafety@prahs.com

Europe, Asia, and Pacific Region
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FAX: +44 1792 525 720
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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Council for Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

Rationale:

This amendment is issued to make the following changes:

- To make minor, non-substantive grammatical and typographic corrections (changes not detailed in this summary)
- To add an optional additional PK sampling visit, and to clarify that subjects who agree to the optional additional PK sampling will also be required to have PK samples collected at week 1 and week 4 and at visit 4a (week 5)
- To adjust the allowed subject age for inclusion in the study to ≥ 18 years
- To update the requirements for CT scans by increasing the allowed time from within 28 days to within 6 weeks for baseline CT scan, specifying that CT scans can be taken within 28 days prior to the EOS visit, and indicating that a CT scan is required before subjects take any new anti-cancer treatments.
- To redefine the criteria for defining low tumor burden as part of the study inclusion criteria
- To clarify the parameters for exclusion criteria pertaining to participation in other investigational procedures and systemic corticosteroid use
- To specify the allowable time to within 8 days of visit 1 for obtaining height and weight for calculating study treatment dose levels
- To clarify the infusion rate at which infusions may resume after Grade 2 and Grade 3 events have resolved
- To specify on which visits the physical examination and PK sampling procedures are required
- To clarify that the EOS biopsies for complete response confirmation are required if bone marrow involvement is identified at baseline, and if bone marrow assessments are not obtained, then complete response subjects are to be classified as partial responders

Summary of Changes

Any changes in the synopsis that also appear in the body of the protocol will appear only once in this summary of changes document, under the section number.

Abbreviations table:

Add:

EU European Union

HBcAb Hepatitis B core antibody

HBV Hepatitis B virus

US United States

Remove:

IND Investigational New Drug

LD Longest diameter

rituximab (US) Food and Drug Administration US licensed rituximab

Section 8.1:

Figure 1. Study Diagram

Add footnote:

* Response assessments at study weeks 12 and 28

Wk = week

Section 8.3 Study Duration

Add:

There is an additional visit at week 5 (visit 4a) for subjects who have agreed to the optional additional PK sampling (see Section 9.4). Individual total study duration will be 32 weeks.

Section 8.4.1 Inclusion Criteria

Replace:

1. Males and females ⩾ 18 and < 80 years of age
3. Stage 2, 3, or 4 (per Cotswold's Modification of Ann Arbor Staging System; Appendix 3) with measurable disease (per International Working Group)
   - subjects must have a baseline scan (computed tomography [CT]) of the neck (if palpable lymph node > 1.0 cm), chest, abdomen, and pelvis to assess disease burden within 28 days before randomization

4. Low tumor burden based on the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria (Appendix 4)
   - no spleen enlargement by CT assessment
   - normal LDH

With:

1. Males and females ⩾ 18 years of age **and older**

3. Stage 2, 3, or 4 (per Cotswold's Modification of Ann Arbor Staging System; Appendix 3) with measurable disease (per International Working Group)
   - subjects must have a baseline scan (computed tomography [CT]) of the neck (if palpable lymph node > 1.0 cm), chest, abdomen, and pelvis to assess disease burden within **6 weeks** before randomization

4 Low tumor burden based on the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria (Appendix 4)
   - **no splenomegaly > 16 cm by CT scan and no symptomatic splenomegaly**
   - **lactate dehydrogenase ≤ upper limit of normal (ULN)**

Section 8.4.2 Exclusion Criteria

Replace:

12. Other investigational procedures while participating in this study are excluded

15. Systemic corticosteroid use for 3 months before randomization (inhaled are allowable)

With:

12. Other investigational procedures **that can impact the study data, results, or patient safety** while participating in this study are excluded**; participation in observational studies is allowed**.

15. Systemic corticosteroid use **within** 3 months before randomization (inhaled are allowable)

Section 8.4.3.2 Evaluations at Withdrawal

Add:

- perform all the procedures scheduled for the EOS visit (ie, week 28 visit [Section 9.6]). The week 28/EOS assessments will be performed 8 weeks (±7 days) after the last dose of IP (unless the subject withdraws consent to do so). Computed tomography is only required at early withdrawal if it has not been

performed within the previous 28 days. **Computed tomography is to be performed before the start of new anti-cancer treatment.**

Section 8.5.1 Treatments Administered

Replace:

The dose for ABP 798/rituximab will be calculated based on the height and weight obtained at baseline (Day 1) and the dose will remain the same throughout the study.

With:

The dose for ABP 798/rituximab will be calculated based on the height and weight obtained **within 8 days of visit 1** and the dose will remain the same throughout the study.

Section 8.5.6.2 Stopping Rules

Replace:

For Grade 2 and Grade 3 events that have resolved, infusion may resume with a 50% reduction in infusion rate at the discretion of the investigator.

With:

For Grade 2 and Grade 3 events that have resolved, infusion **can be initially resumed at not more than 50% of the previous** rate at the discretion of the investigator.

Section 8.6.1 Efficacy and Safety Measurements Assessed

Table 1. Schedule of Assessments and Procedures

Add a new column, between Visits 4 and 5:

- OPTIONAL: Visit 4a/Week 5

Add an "X" for the following:

- Physical examination on Visit 2/Week 2, Visit 3/Week 3, Visit 4/Week 4, Visit 5/Week 12, Visit 6/Week 20
- PK sampling on OPTIONAL: Visit 4a/Week 5

Table 1: Footnotes:

Replace:

[b] Includes weight and height at baseline.

[h] The ABP 798/rituximab dose will be calculated based on the height and weight obtained at baseline (visit 1).

[i] Subjects must have a baseline scan (computed tomography [CT]) of the neck (if palpable lymph node >1.0 cm), chest, abdomen, and pelvis to assess disease burden within 28 days before randomization.

With:

[b] Includes weight and height **within 8 days of visit 1**.

[h] The ABP 798/rituximab dose will be calculated based on the height and weight obtained **within 8 days of visit 1**.

[i] Subjects must have a baseline scan (CT of the neck [if palpable lymph node >1.0 cm]), chest, abdomen, and pelvis to assess disease burden within **6 weeks** before randomization.

Add footnote "j" for CT scan at End of Study Visit:

[j] **End-of-study CT scan can be taken within 28 days prior to EOS visit. Subjects who discontinue from the study due to disease progression should have a CT scan (as described in Section 9.6) prior to initiation of new anti-cancer treatment, if deemed clinically acceptable**.

Replace:

[j] Subjects must have a bone marrow biopsy within 12 months before randomization. Previously confirmed positive bone marrow involvement does not need to be repeated for purposes of screening. An end-of-study biopsy is required if bone marrow involvement is identified at baseline or disease progression is identified during the treatment phase.

With:

[k] Subjects must have a bone marrow biopsy within 12 months before randomization. Previously confirmed positive bone marrow involvement does not need to be repeated for purposes of screening. An end-of-study biopsy is required if bone marrow involvement is identified at baseline **for complete response (CR) confirmation. If a confirmatory bone marrow assessment is not obtained, these subjects should be considered as only having a partial response (PR).**

Update:

All footnote reference letters after "i" to adjust for the adition of footnote "j."

Add:

Footnote “p” for PK sampling on Visit 4/Week 4 and OPTIONAL Visit 4a/Week 5:
p **Subjects who agree to optional additional PK sampling will also be required to have PK samples collected at 2 hours (± 1 hour) postdose at week 1 and week 4 and at visit 4a (week 5).**

Section 9 STUDY EVALUATIONS BY VISIT

Replace:

After signing the informed consent, there are 8 visits, including a screening visit, a treatment visit on day 1 (day of first treatment; visit 1; week 1), treatment visits at visit 2 (week 2), visit 3 (week 3), visit 4 (week 4), visit 5 (week 12), visit 6 (week 20), and an EOS visit at week 28. The first 12 subjects treated will remain at the clinic for 4 hours following the first (day 1) infusion for additional safety observation.

With:

After signing the informed consent, there are 8 **planned** visits, including a screening visit, a treatment visit on day 1 (day of first treatment; visit 1; week 1), treatment visits at visit 2 (week 2), visit 3 (week 3), visit 4 (week 4), visit 5 (week 12), visit 6 (week 20), and an EOS visit at week 28. **Subjects who agree to optional additional PK sampling will be required to attend an additional visit (4a at week 5) as well as remain in the clinic for sampling 2 hours (± 1 hour) after infusion on visits 1 (day 1) and 4 (week 4).** The first 12 subjects treated will remain at the clinic for 4 hours following the first (day 1) infusion for additional safety observation.

Section 9.1 Screening

Replace:

Assessments/procedures performed as routine standard of care, prior to the subject signing informed consent, and according to the criteria outlined in Section 10, can be used for screening purposes as long as the assessments/procedures were performed within 28 days before randomization (except for bone marrow biopsy).

- baseline computed tomography (CT) of the neck (if palpable lymph node >1.0 cm), chest, abdomen, and pelvis

With:

Assessments/procedures performed as routine standard of care, prior to the subject signing informed consent, and according to the criteria outlined in Section 10, can be used for screening purposes as long as the assessments/procedures were performed within 28 days before randomization (except for bone marrow biopsy **and CT scan**).

- baseline CT of the neck (if palpable lymph node >1.0 cm), chest, abdomen, and pelvis **within 6 weeks before randomization**

Add:

(Height and weight are required for IXRS randomization and must be collected within 8 days of visit 1).

Section 9.2 Baseline (Day 1, first day of administration of investigational product)

Replace:

- physical examination, including evaluation of body systems and height and weight

The dose calculation for ABP 798 or rituximab will be based on the height and weight obtained at baseline (day 1).

With:

- physical examination, including evaluation of body systems and **baseline height and weight; baseline height and weight will be measured within 8 days of visit 1 to allow use in randomization of subjects within 8 days of visit 1**

The dose calculation for ABP 798 or rituximab will be based on the height and weight obtained **within 8 days of visit 1**.

Add:

Subjects who have agreed to additional optional PK sampling will have a 2 hour (± 1 hour) post dose PK sample collected.

Section 9.3 Visit 2 (Week 2), Visit 3 (Week 3), and Visit 4 (Week 4)

Replace:

- clinical disease assessment

With:

- **physical examination and** clinical disease assessment

Add:

At visit 4, subjects who have agreed to additional optional PK sampling will have a 2 hour (± 1 hour) post dose sample collected.

Add: **Section 9.4 Visit 4a (Week 5): Optional PK Sampling**

At visit 4a (week 5 ± 3 days) subjects who have agreed to additional optional PK sampling should return for PK sample collection. No study treatment will be given at this visit.

Section 9.5 Visit 5 (Week 12) and Visit 6 (Week 20)

Replace:

- clinical disease assessment

With:

- **physical examination and** clinical disease assessment

Add:

The following procedure / assessment will be performed for all subjects after treatment on week 12 only:

- Immediately after completion of the infusion, postdose PK samples will be collected.

Section 9.6 Week 28/End of Study

Add:

Subjects who discontinue from the study due to disease progression should have a CT scan (as described below) prior to initiation of new anti-cancer treatment, if deemed clinically acceptable.

Replace:

At the week 28/EOS visit or at the time of early discontinuation, the following assessments will be performed:

- bone marrow biopsy (only required if bone marrow involvement is identified at baseline or disease progression is identified during the treatment phase)

With:

At the EOS visit (**week 28 or 8 weeks after the last dose of IP**), the following assessments will be performed:

- bone marrow biopsy (only required if bone marrow involvement is identified at baseline **for CR confirmation; if a confirmatory bone marrow assessment is not obtained, these subjects should be considered as only having a PR). The bone marrow biopsy can be performed at ± 14 days in relation to the study visit date.**

Section 10.1 Response Assessments

Replace:

Clinical disease assessments will be performed by the Investigator or sub investigator and will be submitted to the central imaging vendor, if applicable.

With:

Clinical disease assessments**, which will be performed in conjunction with physical examinations,** will be performed by the nvestigator or sub-investigator and will be submitted to the central imaging vendor, if applicable.

Section 10.3 Physical Examination

Replace:

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

With:

Body weight (kg) will be measured without shoes or jacket. Height and weight will be determined **within 8 days of visit 1**.

Section 10.6 Clinical Laboratory Testing

Add:

Serology (local laboratory): **HBsAg**, hepatitis B core antibody, and HCV antibody.

Section 16 REFERENCE LIST

Remove:

Fisher RI, LeBlanc M, Press OW, et al. New treatment options have changed the survival of patients with follicular lymphoma. J Clin Oncol. 2005; 23:8447–8452.

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)

SUMMARY OF CHANGES

Test Drug: ABP 798

Protocol Number: 20130109 **EudraCT number:** 2013-005542-11

Study Phase: 3

Date and Version: 4.0, 24 June 2016

Key Contact:

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

Rationale:

This amendment is issued to make the following changes:

- To make minor, non-substantive grammatical and typographic corrections (changes not detailed in this summary)
- To update Amgen key contact information
- To update International Council for Harmonisation (ICH) terminology
- To add a citation in support of rituximab monotherapy
- To modify the Inclusion Criteria:
    1. To specify the biopsy sites for histologic confirmation
    2. To extend the window for histologic confirmation to 12 months to conform to standard of care for non-Hodgkin lymphoma (NHL)
    3. To extend the window for bone marrow biopsy to 12 months to conform to standard of care
    4. To eliminate the need for subjects to undergo a bone marrow biopsy within 12 months if they previously had a bone marrow biopsy with a positive result
    5. To correct the nodal or extranodal mass size according to Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria
    6. To specify splenic enlargement according to GELF criteria should be assessed by computed tomography (CT)
    7. To specify the site of serous effusions according to GELF criteria
    8. To elaborate on the specific nature of GELF B symptoms
- To specify the dose of ABP 798/rituximab will be calculated based on height and weight obtained at baseline, and that the dose will remain the same throughout the study
- To add stopping criteria for infusion-related reactions
- To add additional monitoring requirements for infusion-related hypersensitivity reactions
- To specify investigational product dispensation delegation to maintain treatment blinding
- To detail the conditions for use of a non-contrast CT for disease burden assessment
- To allow for a 3 day window for collection of baseline hematology and serum chemistry parameters

- To specify the timeframe for randomization (within 8 days before the baseline visit)
- To specify that clinical disease assessments should be performed by the investigator or sub-investigator