Official Title: A Phase II Comparative, Open Label, Randomized, Multicenter, China-Only Study to Investigate the Pharmacokinetics, Efficacy and Safety of Subcutaneous Rituximab Versus Intravenous Rituximab, Both in Combination With CHOP in Previously Untreated Patients With CD20 Positive Diffuse Large B Cell Lymphoma

NCT Number: NCT04660799

Document Date: Protocol Version 1.0: 20-April-2020

PROTOCOL

TITLE:	**A PHASE II COMPARATIVE, OPEN LABEL, RANDOMIZED, MULTICENTER, CHINA-ONLY STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY AND SAFETY OF SUBCUTANEOUS RITUXIMAB VERSUS INTRAVENOUS RITUXIMAB, BOTH IN COMBINATION WITH CHOP IN PREVIOUSLY UNTREATED PATIENTS WITH CD20 POSITIVE DIFFUSE LARGE B CELL LYMPHOMA**
PROTOCOL NUMBER:	YO42207
VERSION NUMBER:	1.0
NCT NUMBER:	To be determined
TEST PRODUCT:	Rituximab (RO0452294) (MabThera®)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
20-Apr-2020 09:30:00	Company Signatory	[redacted]

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE II COMPARATIVE, OPEN LABEL, RANDOMIZED, MULTICENTER, CHINA-ONLY STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY AND SAFETY OF SUBCUTANEOUS RITUXIMAB VERSUS INTRAVENOUS RITUXIMAB, BOTH IN COMBINATION WITH CHOP IN PREVIOUSLY UNTREATED PATIENTS WITH CD20 POSITIVE DIFFUSE LARGE B CELL LYMPHOMA**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II COMPARATIVE, OPEN LABEL, RANDOMIZED, MULTICENTER, CHINA-ONLY STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY AND SAFETY OF SUBCUTANEOUS RITUXIMAB VERSUS INTRAVENOUS RITUXIMAB, BOTH IN COMBINATION WITH CHOP IN PREVIOUSLY UNTREATED PATIENTS WITH CD20 POSITIVE DIFFUSE LARGE B CELL LYMPHOMA**
PROTOCOL NUMBER:	YO42207
VERSION NUMBER:	1.0
IND NUMBER:	To be determined
TEST PRODUCT:	Rituximab (RO0452294) (MabThera®)
PHASE:	II
INDICATION:	Previously untreated CD20 positive Diffuse Large B Cell Lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of subcutaneous (SC) rituximab compared with intravenous (IV) rituximab, both in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), in previously untreated patients with CD20 positive diffuse large B cell lymphoma (DLBCL). Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objectives

The primary objective of this study is to demonstrate the non-inferiority of rituximab serum C_{trough} obtained at Cycle 7, 21 days after SC administration, with that obtained at Cycle 7, 21 days after IV administration on the basis of the following endpoint:

- Ratio of $C_{trough,SC}/C_{trough,IV}$ during Cycle 7

Secondary Objectives

The secondary objectives of this study are to compare and assess other PK parameters, efficacy and safety profiles (including immunogenicity) of rituximab SC and rituximab IV, both in combination with CHOP, on the basis of the following endpoints and outcome measures:

- Ratio of AUC_{SC}/AUC_{IV} during Cycle 7
- Other PK parameters, such as AUC and C_{trough} at other treatment cycles, maximum serum concentration (C_{max}), total clearance, volume of distribution at steady state, and terminal half-life ($t_{1/2}$) (if feasible or appropriate) as appropriate
- Complete response rate (CRR) at the end of the study treatment, as determined by the Independent Review Committee (IRC) using Lugano Response Criteria for Malignant Lymphoma as key efficacy endpoint
- Objective response rate (ORR), defined as complete response (CR) or partial response (PR) at the end of the study treatment, as determined by investigator and IRC using Lugano Response Criteria for Malignant Lymphoma
- CRR (CR, complete response unconfirmed [CRu]) at the end of study treatment, as determined by IRC using International Working Group (IWG) Response Criteria for Non-Hodgkin's lymphoma (NHL) 1999 Guidelines

- CRR at the end of the study treatment, as determined by the investigator using Lugano Response Criteria for Malignant Lymphoma
- Safety outcomes as assessed by adverse events, including rituximab administration-related reactions (ARRs), laboratory assessments, and vital signs; and immunogenicity as assessed by anti-rituximab antibodies and anti-rHuPH20 antibodies

Study Design

Description of Study

This is a Phase II, multicenter, randomized, controlled, open-label, China-only study to investigate the PK, efficacy, and safety of rituximab SC in combination with CHOP versus rituximab IV in combination with CHOP in previously untreated patients with CD20 positive DLBCL. This study will be conducted at approximately 8 sites in China. Approximately 50 patients will receive eight cycles of rituximab SC or rituximab IV combined with six or eight cycles of standard CHOP chemotherapy. Centers must choose whether they plan to administer six or eight cycles of CHOP chemotherapy prior to study start. Previous results have demonstrated that a fixed rituximab SC dose at 1400 mg is expected to achieve non-inferior C_{trough} values to the rituximab IV regimen (375 mg/m^2) prior to Cycle 8 (Study BO22334). In this study, a sample size of 50 patients (approximately 18 evaluable patients per arm) who have completed Cycle 7 will be adequate for testing non-inferiority for the estimated ratio $C_{trough,SC}/C_{trough,IV}$. Previously untreated patients with CD20 positive DLBCL will be randomized into the following two treatment groups at a 1:1 ratio (crossover to the experimental arm is not permitted):

- R^{SC}-CHOP: Cycle 1 rituximab IV plus seven cycles of rituximab SC in combination with six or eight cycles of CHOP chemotherapy administered every 3 weeks; rituximab IV will be used at the standard dose of 375 mg/m^2 and rituximab SC will be given at a dose of 1400 mg as confirmed in the Phase III Study BO22334.
- R^{IV}-CHOP: eight cycles of rituximab IV in combination with six or eight cycles of CHOP chemotherapy administered every 3 weeks; rituximab IV will be used at the standard dose of 375 mg/m^2.

Eligible patients will be stratified during randomization according to International Prognostic Index (IPI) scores (IPI 0-2 versus IPI 3–5).

Patients will be assessed for disease response by the investigator and IRC, on the basis of regular clinical and laboratory examinations, physical examinations, computed tomography (CT) scans, positron emission tomography (PET)-CT scans, and bone marrow examinations, according to the Lugano Response Criteria for Malignant Lymphoma. PET-CT and dedicated CT scans will be obtained at screening and 6-8 weeks after completion of study treatment, or sooner in the event that a patient discontinues early. An interim assessment will be obtained after Cycle 4 and should include PET-CT and dedicated CT. If local practice prohibits obtaining both assessments after Cycle 4, PET-CT alone (preferred) or CT alone may be obtained at this time point. During the follow-up period, imaging (may be CT only) will be performed every 3 months, i.e., Week 12 and 24 after last treatment, in accordance with study visits and will include the neck (if involved at baseline), chest, abdomen, and pelvis.

After the end of study treatment, patients will be followed-up every 3 months for 6 months (i.e., 12 and 24 weeks after the last dose of study treatment). Assessments will include clinical evaluation of tumor response/progression, PK and immunogenicity (blood sampling), physical examination, standard hematologic and biochemistry assessments, vital signs and weight measurements, liver and spleen size and B-symptoms assessments.

Safety will be evaluated by monitoring all adverse events, and abnormalities identified through physical examination, vital signs, and laboratory assessments. Such events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5.0). Laboratory safety assessments will include the routine monitoring of hematology and blood chemistries.

Number of Patients

Approximately 50 patients with previously untreated CD20 positive DLBCL will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent and to comply with the study protocol
- Age ≥18 and ≤80 years at time of signing Informed Consent Form
- Previously untreated CD20 positive DLBCL histologically documented
- Patients with an IPI score of 1 to 5 or IPI score of 0 with bulky disease, defined as one lesion ≥7.5 cm
- At least one bi-dimensionally measurable lesion defined as ≥1.5 cm in its largest dimension on CT scan
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- Left ventricular ejection fraction (LVEF) ≥50% on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram
- A negative serum pregnancy test or a negative urine pregnancy test within 7 days prior to study treatment must be available both for pre-menopausal women (including those who have had a tubal ligation) and for women who are less than 2 years after the onset of menopause; if negative serum pregnancy test is within 14 days of study treatment start, a confirmatory urine pregnancy test must be available within 7 days prior to study treatment start
- For men who are not surgically sterile, agreement to use a barrier method of contraception during the treatment period and until ≥12 months after the last dose of rituximab SC or rituximab IV or according to institutional guidelines for CHOP chemotherapy, whichever is longer, and agreement to request that their partners use an additional method of contraception, such as oral contraceptives, intrauterine device, barrier method, or spermicidal jelly
- For women of reproductive potential who are not surgically sterile, agreement to use adequate methods of contraception, such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly during the treatment period and until ≥12 months after the last dose of rituximab SC or rituximab IV or according to institutional guidelines for CHOP chemotherapy, whichever is longer
- Adequate hematologic function confirmed within 14 days prior to randomization which is independent to stimulating factors and transfusion (unless related to lymphoma infiltration of the bone marrow)
    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    - Platelet count $\geq 75 \times 10^9$/L

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Transformed NHL or types of NHL other than DLBCL and its subtypes according to World Health Organization classification
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to any of the individual components of CHOP, including prior receipt of anthracyclines
- Prior therapy for DLBCL, with the exception of nodal biopsy or local irradiation or surgery for diagnosis
- Prior treatment with cytotoxic drugs or rituximab for another condition (e.g., rheumatoid arthritis) or prior use of an anti-CD20 antibody
- Current or recent (within the 30 days prior to starting study treatment) treatment with another investigational drug or participation in another investigational therapeutic study

- Ongoing corticosteroid use, >30 mg/day of prednisone or equivalent
    - Patients receiving corticosteroid treatment with ≤30 mg/day of prednisone or equivalent must be documented to be on a stable dose for duration of at least 4 weeks prior to randomization.
- Primary central nervous system (CNS) lymphoma, blastic variant of mantle cell lymphoma, or histologic evidence of transformation to a Burkitt lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, and primary cutaneous DLBCL
- History of other malignancy that could affect compliance with the protocol or interpretation of results
    - Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible.
    - Patients with a malignancy that has been treated but not with curative intent will also be excluded unless the malignancy has been in remission without treatment for ≥5 years prior to enrollment.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including but not limited to significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Any of the following abnormal laboratory values:
    - Creatinine >1.5 × upper limit of normal (ULN) (unless creatinine clearance normal) or calculated creatinine clearance <40 mL/min (using the Cockcroft-Gault formula)
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × ULN
    - Total bilirubin ≥1.5 × ULN; patients with documented Gilbert disease may be enrolled if total bilirubin is ≤3.0 × ULN
    - International normalized ratio (INR) ≥1.5 × ULN in the absence of therapeutic anticoagulation
    - Partial thromboplastin time (PTT) or activated Partial thromboplastin time (aPTT) >1.5 × ULN in the absence of a lupus anticoagulant
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)
    - Patients with occult or prior HBV infection (defined as negative HBsAg and positive total hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing during the treatment period and the follow-up period.
- Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)
    - Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Known history of human immunodeficiency virus (HIV) seropositive status or infection
- Signs or symptoms of other active and/or severe infection
- Evidence of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or patient at high risk from treatment complications
- Any co-existing medical or psychological condition that would compromise ability to give informed consent

End of Study and Length of Study

The end of study is defined as the date when the last patient last visit (LPLV) occurs. LPLV is expected to occur approximately 6 months after the last patient enrolled has received the last study treatment, or sooner, if all patients have progressed, died, or withdrawn from the study. The Sponsor has the right to terminate the study at any time.

Investigational Medicinal Products

Test Product (Investigational Drug)

The experimental investigational medicinal product of the study is rituximab SC supplied as a ready-to-use liquid formulation with a nominal content of 120 mg/mL rituximab. The drug product contains 2000 U/mL rHuPH20 acting as a permeation enhancer, histidine/histidine-HCl (buffer), α,α-trehalose (bulking agent), methionine (stabilizer), and polysorbate 80 (surfactant) in Water for Injection (WFI) at a pH of 5.5. Rituximab SC will be administered by SC injection on Day 1 of Cycles 2 to 8 to patients randomized to the R^{SC}-CHOP treatment arm.

Comparator

The comparator investigational medicinal product of the study is rituximab IV provided as 500 mg/50 mL liquid-filled vials with a nominal content of 10 mg/mL rituximab. The drug product contains sodium acetate (buffer), sodium chloride (tonicity adjustment), and polysorbate 80 (surfactant) in WFI at a pH of 6.5. Rituximab IV will be administered by IV infusion on Day 1 of Cycles 1 to 8 to patients randomized to the R^{IV}-CHOP treatment arm and on Day 1 of Cycle 1 to patients randomized to R^{SC}-CHOP treatment arm.

Non-Investigational Medicinal Products

The CHOP chemotherapy will be prepared according to the standard practice at the institution.

Statistical Methods

Primary Analysis

All PK analyses will be based on all patients for whom PK assessments were made. PK analyses will be analyzed as treated. Patients will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete, where the PK analysis might be influenced. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

The primary PK endpoint is the ratio of $C_{trough,SC}/C_{trough,IV}$ during Cycle 7. The serum rituximab C_{trough} at Cycle 7 will be measured at pre-dose of Cycle 8. The lower limit of the two-sided 90% confidence interval (CI) should be above 0.80 in order to show non-inferiority of $C_{trough,SC}$ versus $C_{trough,IV}$.

Determination of Sample Size

Under the assumption of a coefficient of variation equal to 0.5 and assuming that the true C_{trough} of rituximab SC formulation is 20% above the rituximab IV formulation (i.e., mean $C_{trough,SC}$ to be 20% above $C_{trough,IV}$), 20 patients in each treatment arm are needed in order to achieve 80% power with one-sided alpha of 0.05 (i.e., 2-sided 90% confidence interval [CI]). Assuming that 20% of patients would not have valid PK data at Cycle 8 pre-dose, a total of approximately 50 patients will be enrolled into the study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated Partial thromboplastin time
ARR	administration-related reaction
AST	aspartate aminotransferase
AUC	area under the concentration–time curve
BSA	Body Surface Area
BUN	blood urea nitrogen
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
CL	clearance
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CRu	complete response unconfirmed
CRR	complete response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
Ctrough	trough serum concentration
CV	coefficient of variation
CVP	cyclophosphamide, vincristine, prednisone
DLBCL	diffuse large B cell lymphoma
EC	Ethics Committee
ECG	electrocardiogram
ECLIA	electrochemiluminescence immunoassay
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic csase report form
EDC	electronic data capture
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma

Abbreviation	Definition
G-CSF	granulocyte colony-stimulating factor
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICH	International Council for Harmonization
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous
IVRS	Interactive Voice Response System
IWG	International Working Group
IWRS	Interactive Web-based response system
IxRS	Interactive Voice or Web-based response system
LDH	lactate dehydrogenase
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NONMEM	non-linear mixed effects modeling
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics

Abbreviation	Definition
PO	oral
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
RIV	rituximab IV
RSC	rituximab SC
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SOC	standard-of-care
TLS	tumor-lysis syndrome
ULN	upper limit of normal
WBC	white blood cell
WFI	Water for Injection
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON NON-HODGKIN'S LYMPHOMA: DIFFUSE LARGE B-CELL LYMPHOMA AND CURRENT STANDARD OF CARE

Non-Hodgkin's lymphoma (NHL) ranked as the 5th to 9th most common cancer in most countries worldwide, with almost 510,000 new cases estimated in 2018. In China, 88,090 new cases of NHL are expected every year (Globocan 2018). The majority of NHLs are of B-cell origin and are characterized by the expression of a membrane antigen, CD20, which is important in cell cycle initiation and differentiation (Anderson et al. 1984).

Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of NHL in China, accounting for approximately 54% of B-NHL cases (Chen 2011). DLBCL arises from mature B cells, the majority of which express a CD20 positive cell surface protein. Patients with DLBCL present with rapidly enlarging masses, often with symptoms both local and systemic, fever, recurrent night sweats, or weight loss (B symptoms). Forty-five percent to 60% of patients present with advanced-stage disease (Ann Arbor Stage III or IV). The incidence of DLBCL increases with age, with a median age of 64 at presentation (Flowers et al. 2010).

The International Prognostic Index (IPI) for aggressive NHL (e.g., DLBCL) identifies five risk factors prognostic of overall survival (OS):

- Age ($\leq$60 vs. $>$60 years)
- Serum lactate dehydrogenase level (normal vs. elevated)
- Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2–4)
- Stage (I or II vs. III or IV)
- Extranodal site involvement (0 or 1 vs. 2–4)

Patients with two or more risk factors have a $>$50% chance of relapse after 5 years. Study LNH98-5 (GELA) identified patients at high risk of relapse on the basis of specific sites of involvement, including bone marrow, central nervous system (CNS), liver, lung, and spleen. Molecular profiles of gene expression created by using DNA microarrays may be used to help stratify patients for new therapies that are targeted to better predict survival after standard chemotherapy (Shipp et al. 1993; Rosenwald et al. 2002; Lossos et al. 2004; Abramson et al. 2005; Feugier et al. 2005; de Jong et al. 2007; Fu et al. 2008).

The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-based chemotherapy improves patient outcomes, as demonstrated in three randomized prospective studies consisting of approximately 2000 ($<$60 or $\geq$60 years of age, depending on the study) previously untreated patients with advanced DLBCL.

Study LNH98-5 (GELA) randomized 399 patients ≥60 years of age who had DLBCL in a 1:1 ratio to receive CHOP alone or rituximab in combination with CHOP (R-CHOP) (Coiffier et al. 2002). All patients received up to eight 3-week cycles of CHOP induction therapy. Patients in the R-CHOP arm received 375 mg/m^2 rituximab on Day 1 of each cycle. The median event-free survival was 1.1 years in the CHOP arm and 2.9 years in the R-CHOP arm, with OS rates of 58% and 69%, respectively, at 2 years. The 10-year follow-up of patients in Study LNH98-5 (GELA) showed OS rates of 44% in the R-CHOP arm and 28% in the CHOP arm (Coiffier et al. 2010).

Study E4494 randomized 632 patients ≥60 years of age who had DLBCL in a 1:1 ratio to receive treatment with CHOP alone or with R-CHOP. Patients received six or eight cycles of CHOP, with each cycle lasting 21 days. Patients in the R-CHOP arm received four doses of 375 mg/m^2 rituximab on Days −7 and −3 (prior to Cycle 1) and 48−72 hours prior to Cycle 3 and 5. Patients who received eight cycles of CHOP also received rituximab prior to Cycle 7. The median progression-free survival (PFS) was 3.1 years in the R-CHOP arm and 1.6 years in the CHOP arm, with OS rates of 74% and 63%, respectively, at 2 years (Habermann et al. 2006).

The MabThera International Trial (MInT) evaluated a total of 823 patients 18−60 years of age who had DLBCL (Pfreundschuh et al. 2006). Patients were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen given alone or in combination with rituximab. The survival rate at 2 years was 86% in the chemotherapy arm and 95% in the chemotherapy + rituximab arm (Pfreundschuh et al. 2006).

These three studies led to the approval of rituximab for the treatment of DLBCL in the United States, the European Union, China and other countries.

According to the 2009 European Society for Medical Oncology DLBCL clinical practice guidelines, for young, low- and low-intermediate–risk patients (age-adapted IPI <1), six or eight cycles of CHOP combined with six or eight doses of rituximab is the current standard treatment; for high- and high-intermediate–risk patients, six or eight cycles of CHOP combined with eight doses of rituximab is most frequently administered (Tilly et al. 2015). Among patients with advanced-stage disease, 50% are cured with doxorubicin-based combination chemotherapy and rituximab (Coiffier et al. 2002; Coiffier 2005; Habermann et al. 2006).

On the basis of the three studies, eight cycles of rituximab administered intravenously combined with six or eight cycles of CHOP is considered standard of care for patients with advanced DLBCL (National Comprehensive Cancer Network 2019; National Comprehensive Cancer Network 2017 [Chinese]) and will serve as the control arm for this study.

1.2 BACKGROUND ON RITUXIMAB SUBCUTANEOUS

In contrast to the intravenous (IV) infusion, rituximab subcutaneous (SC) injection takes only a few minutes. In previous studies, predominantly conducted in Caucasian patients leading to approval of rituximab SC in Europe, the USA and the rest of the world, the subcutaneous administration of rituximab was demonstrated to result in non-inferior rituximab levels compared with the IV rituximab admiration and comparable efficacy and safety while markedly reducing the treatment burden for patients and improving the resource utilization at the treatment facilities (de Cock E, et al. 2016; Rummel M, et al. 2017). The simplicity of the SC injection is therefore expected to significantly reduce the time a patient spends in the hospital and eliminate hospital burden associated with IV administration. In this context it is envisaged that a SC formulation of rituximab would bring significant and clinically meaningful benefits to patients as well as an improved resource utilization to treatment facilities also in China.

The active ingredient of the rituximab SC injection, the study drug, is rituximab. In order to reduce the volume needed for therapeutic doses, the rituximab SC formulation contains a 12-fold increased rituximab concentration (120 mg/mL) compared with the rituximab IV formulation (10 mg/mL).

In addition, rituximab SC contains human recombinant hyaluronidase, rHuPH20, developed by Halozyme Therapeutics, as an excipient at a concentration of 2000 U/mL for injection in order to allow the installation of the relatively large volume of 11.7 mL into the SC tissue. Halozyme Therapeutics received approval from the U.S. Food and Drug Administration (FDA) in 2005 for an injectable formulation of rHuPH20 (Hylenex®), which has been shown to increase the dispersion and absorption of co-administered drugs when given subcutaneously.

The rituximab SC formulation contains 2000 U/mL rHuPH20 excipient acting as a permeation enhancer. By reversible hydrolysis of hyaluron in the hypodermis, rHuPH20 temporarily opens the interstitial space in the SC tissue to allow the infusion of large volumes of rituximab with an improved delivery into systemic circulation.

The dose of rituximab SC that will be used in this trial was established in the Phase Ib Study BP22333 and further confirmed in the Phase III Study BO22334.

Study BP22333 was a two-stage, randomized, open-label, multicenter Phase Ib trial investigating the pharmacokinetics (PK), safety, and tolerability of rituximab SC in patients with follicular lymphoma (FL) as part of maintenance treatment. BP22333 was designed to determine and confirm the SC rituximab dose that yielded non-inferior steady-state concentration at the end of a dosing interval (C_{trough}) compared to the standard IV dose (375 mg/m^2) in the maintenance setting. Results from Stage 1 have been reported (Salar et al. 2010). Based on modeling and simulation of PK data from Stage 1, a fixed dose of 1400 mg (used in Stage 2) was established and considered to be non-inferior to the rituximab IV dose of 375 mg/m^2. The results of Stage 2 of the

BP22333 trial examining the rituximab levels after SC injection compared to IV infusion (SC/IV ratio) confirm that the selected SC dose of 1400 mg produces non-inferior rituximab levels. This has been assessed by non-inferiority testing with a lower boundary above 0.8 for the 90% confidence interval (CI). The estimated C_{trough} SC/IV ratio was 1.24 (90% CI: 1.02, 1.51) for the 2-monthly regimen and 1.12 (90% CI: 0.86, 1.45) for the 3-monthly treatment interval in patients with CD20 positive indolent NHL during maintenance. Additionally, the estimated area under the concentration–time curve (AUC) SC/IV ratio was 1.35 (90% CI: 1.23, 14.9) and 1.35 (90% CI: 1.23, 1.48) for the 2- and 3-monthly regimens, respectively. For Stage 1, the most informative safety data were derived following the single cycle of randomized rituximab IV/SC treatment. Aside from administration-related reactions (ARRs), the incidence and types of adverse events (AEs) were similar across treatment cohorts. There were no clear trends related to event incidence or intensity/seriousness and dose of study drug. Forty-three patients included in the SC extension had a longer exposure to rituximab SC than the other patients in Stage 1 (who received only a single dose of rituximab SC) and they received a cycle of rituximab SC, followed by cycles of rituximab IV, and then 1–5 further cycles of rituximab SC at the final selected dose of 1400 mg. Twenty-three of forty-three patients (53%) experienced at least one AE during the SC extension, the most commonly reported AE by preferred term being ARRs. Four patients (9%) each reported a Grade 3 AE, three of which were also considered serious. Four patients (9%) in total experienced serious adverse events (SAEs) during the SC extension. In Stage 2, the proportion of patients who experienced one or more AEs was similar following treatment with either rituximab SC 1400 mg or rituximab IV 375 mg/m^2. The incidence of severe (Grade $\geq$3) AEs, SAEs, and AEs leading to withdrawal was also balanced following SC and IV treatment. There was one fatal AE in each treatment group; both events were considered by the investigator to be unrelated to study drug. The incidence of ARRs was higher in the rituximab SC cohort than in the rituximab IV cohort; however, no ARRs across either cohort were reported to be serious or severe. The imbalance regarding ARRs reflects the expected change in ARR profile as a result of the SC route of administration and is assessed to be a change that is not medically relevant to the overall safety profile of rituximab.

Study BO22334 was a randomized, open-label, multicenter, two-stage, two-arm comparative Phase III study of rituximab SC with CHOP or cyclophosphamide, vincristine, prednisone (CVP) induction treatment followed by rituximab SC maintenance treatment versus rituximab IV with CHOP or CVP induction treatment followed by rituximab IV maintenance treatment. A total of 410 patients were randomized: 205 patients to rituximab IV and 205 patients to rituximab SC. The eligible patient population was adult patients with previously untreated, CD20 positive FL of Grade 1, 2, or 3a requiring therapy. The primary endpoint for Stage 1 of the study (non–inferiority of trough serum concentrations [C_{trough}] at Cycle 7) was met. Non-inferior C_{trough} with the fixed rituximab SC dose of 1400 mg was demonstrated compared with rituximab IV 375 mg/m^2 given every 3 weeks. The ratio $C_{trough,SC}/C_{trough,IV}$ at Cycle 7 was 1.62 (90% CI:

1.36,1.94). The coefficients of variation (CVs) for C_{trough} at Cycle 7 were 43.2% in the rituximab SC arm and 36.7% in the rituximab IV arm, demonstrating comparable variability in the two treatment arms. The geometric mean AUC was also higher in the rituximab SC arm, with observed rituximab serum $AUC_{(SC)}/AUC_{(IV)}$ ratio during Cycle 7 of 1.38 (90% CI: 1.24,1.53) and comparable variability between the two arms (coefficient of variation [CV] 33.7% in the rituximab SC arm and CV 28.0% in the rituximab IV arm). Data on B-cell levels (CD19+ counts) showed similar trends in both treatment arms, with significant depletion of peripheral B-cells following Cycle 1 (rituximab IV) and continued depletion with additional cycles in the induction and maintenance phases. Based on the investigator assessments, objective response rate (ORR) results at the end of induction were comparable between the arms: 84.9% (95% CI: 79.2%, 89.5%) in the rituximab IV arm versus 84.4% (95% CI: (78.7%, 89.1%) in the rituximab SC arm. Point estimates and 95% CIs for complete response (complete response [CR] or complete response unconfirmed [CRu]) at the end of induction were identical between the treatment arms: 32.2% (95% CI: 25.9%, 39.1%). Based on the unstratified analyses, the time-to-event endpoints of PFS (hazard ratio [HR] = 0.84; 95% CI: 0.57, 1.23), event-free survival (EFS) (HR = 0.91; 95% CI: 0.64, 1.31), OS (HR = 0.81; 95% CI: 0.42, 1.57), showed no evidence of difference in efficacy of SC formulation compared with the IV formulation and provided further evidence that the SC route of administration of rituximab had no impact on long-term efficacy, based on the median duration of observation of approximately of 37 months. The safety profile of rituximab SC was comparable to that of rituximab IV, with the exception of mainly mild to moderate ARRs and local cutaneous reactions reflecting the safety profile when switching to the SC route of administration.

See the rituximab SC Investigator's Brochure (IB) for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Rituximab IV is administered as an infusion over several hours (4 to 6 hours). Frequently observed infusion-related reactions (IRRs) may require prolonging the infusion time further. These long infusion times and the side effects related to the infusion were cited by some patients as uncomfortable consequences of the current therapeutic treatment (Coates et al. 1983). Furthermore, the required procedure to establish IV access is considered invasive and can be painful, particularly in patients with malignant diseases who are treated repeatedly. Rituximab for SC administration has been developed to address these limitations (e.g., IRRs, long administration times, hospital facilities requirements, difficulty in treating patients with poor venous vascular conditions). SC administration of rituximab takes significantly less time (several minutes) compared with IV infusion and this is expected to improve treatment convenience, patient satisfaction and compliance. Hence, the development of a rituximab SC formulation addresses an unmet medical need. The previously performed global clinical trial program consisted of several studies conducted with rituximab SC in different

settings of indolent NHL: maintenance (BP22333), induction and maintenance (BO22334), and chronic lymphocytic leukemia (CLL) (BO25341).

Previously, SC administration of rituximab has been hindered by the relatively large volume required. These hurdles have now been overcome by concentrating the IV rituximab formulation 12-fold and by adding rHuPH20 as a novel excipient and a permeation enhancer. As a recombinant human hyaluronidase, rHuPH20 hydrolyses hyaluronic acid fibers and reversibly opens the interstitial space in the subcutaneous tissue, allowing injection volumes larger than 2 to 3 mL. The approved indication for rHuPH20 includes “hypodermoclysis” (i.e., SC injection/infusion of fluid in large volume).

This study will explore the efficacy of rituximab SC and rituximab IV, respectively, in previously untreated DLBCL patients, based on the complete response rate (CRR) observed with each formulation.

Rituximab IV and SC have a well-established benefit-risk profile and are approved in more than 90 countries or regions. The SC formulation is expected to bring significant and clinically meaningful benefits to Chinese patients in terms of improved tolerability with potentially fewer and less severe ARRs. This expectation is based on rituximab peak serum concentrations after SC administration, which are attained more slowly than after IV, as well as an improved treatment convenience due to the faster and more convenient SC administration. Safety data collected for patients exposed to rituximab SC during study BP22334 and BO22334 revealed no safety signals other than those expected with exposure to rituximab IV. Therefore, the overall benefit-risk assessment of the current study is considered to be positive.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, efficacy, and safety of rituximab SC compared with rituximab IV, both in combination with CHOP, in previously untreated patients with CD20 positive DLBCL. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the treatment of rituximab SC + CHOP chemotherapy (R^{SC}-CHOP) and the treatment of rituximab IV + CHOP chemotherapy (R^{IV}-CHOP).

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate the non-inferiority of rituximab serum C_{trough} obtained at Cycle 7, 21 days after SC administration, with that obtained at Cycle 7, 21 days after IV administration on the basis of the following endpoint:

- Ratio of $C_{trough,SC}/C_{trough,IV}$ during Cycle 7

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to compare and assess other PK parameters, efficacy and safety profiles (including immunogenicity) of rituximab SC and rituximab IV, both in combination with CHOP, on the basis of the following endpoints and outcome measures:

- Ratio of AUC_{SC}/AUC_{IV} during Cycle 7
- Other PK parameters, such as AUC and C_{trough} at other treatment cycles, maximum serum concentration (C_{max}), total clearance, volume of distribution at steady state, and terminal half-life ($t_{1/2}$) (if feasible or appropriate) as appropriate
- Complete response rate (CRR) at the end of the study treatment, as determined by the Independent Review Committee (IRC) using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) as key efficacy endpoint
- Objective response rate (ORR), defined as CR or partial response (PR) at the end of the study treatment, as determined by investigator and IRC using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)
- CRR (CR, CRu) at the end of study treatment, as determined by IRC using International Working Group (IWG) Response Criteria for NHL 1999 Guidelines
- CRR at the end of the study treatment, as determined by the investigator using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)
- Safety outcomes as assessed by adverse events, including rituximab administration-related reactions (ARRs), laboratory assessments, and vital signs; and immunogenicity as assessed by anti-rituximab antibodies and anti-rHuPH20 antibodies

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

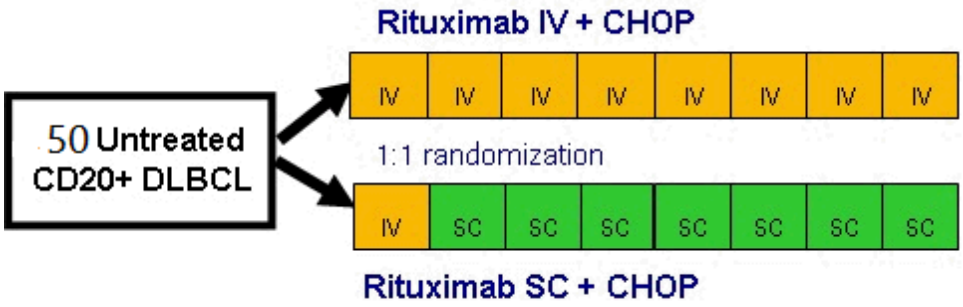
3.1.1 Overview of Study Design and Dosing Regimen

This is a Phase II, multicenter, randomized, controlled, open-label, China-only study to investigate the PK, efficacy, and safety of rituximab SC in combination with CHOP versus rituximab IV in combination with CHOP in previously untreated patients with CD20 positive DLBCL. This study will be conducted at approximately 8 sites in China. Approximately 50 patients will receive eight cycles of rituximab SC or rituximab IV combined with six or eight cycles of standard CHOP chemotherapy. Centers must choose whether they plan to administer six or eight cycles of CHOP chemotherapy prior to study start. Previous results have demonstrated that a fixed rituximab SC dose at 1400 mg is expected to achieve non-inferior C_{trough} values to the rituximab IV regimen (375 mg/m^2) prior to Cycle 8 (Study BO22334). In this study, a sample size of 50 patients (approximately 18 evaluable patients per arm) who have completed Cycle 7 will be adequate for testing non-inferiority for the estimated ratio $C_{trough,SC}/C_{trough,IV}$. The overall study design is illustrated in Figure 1. Previously untreated patients with CD20

positive DLBCL will be randomized into the following two treatment groups at a 1:1 ratio (crossover to the experimental arm is not permitted):

- R^{SC}-CHOP: Cycle 1 rituximab IV plus seven cycles of rituximab SC in combination with six or eight cycles of CHOP chemotherapy administered every 3 weeks; rituximab IV will be used at the standard dose of 375 mg/m^2 and rituximab SC will be given at a dose of 1400 mg as confirmed in the Phase III Study BO22334.
- R^{IV}-CHOP: eight cycles of rituximab IV in combination with six or eight cycles of CHOP chemotherapy administered every 3 weeks; rituximab IV will be used at the standard dose of 375 mg/m^2.

Figure 1 Dosing Schema



CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL = diffuse large B-cell lymphoma; IV = intravenous; SC = subcutaneous.

Fifty patients will be randomized into the study with intensive PK sampling to confirm the non-inferiority of the 1400 mg SC dose to IV 375 mg/m^2 dose.

Eligible patients will be stratified during randomization according to IPI scores (IPI 0-2 versus IPI 3–5).

IPI score is widely accepted as the prognostic index, which predicts the risk of disease recurrence and overall treatment outcome in this patient population through five adverse prognostic risk factors: disease stage, age, ECOG performance status, serum lactate dehydrogenase (LDH) levels, and the presence or absence of multiple extranodal sites of lymphoma (Appendix 5). Stratification during randomization will group patients with highest-risk disease (IPI 4-5) and high-intermediate risk disease (IPI 3), as these patients have been found across studies to have the poorest outcomes from R-CHOP treatment (Sehn et al. 2007; Zhou et al. 2014). The IPI 3-5 group will be stratified against IPI 0-2, a population with low and low-intermediate risks, who typically have better prognosis but continue to have unmet medical need.

Please refer to Section 4.3 for additional information on R^{IV}-CHOP and R^{SC}-CHOP administrations.

Patients will be assessed for disease response by the investigator and IRC, on the basis of regular clinical and laboratory examinations, physical examinations, computed tomography (CT) scans, positron emission tomography (PET)-CT scans, and bone marrow examinations, according to the Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix 3). PET-CT and dedicated CT scans will be obtained at screening and 6-8 weeks after completion of study treatment, or sooner in the event that a patient discontinues early. An interim assessment will be obtained after Cycle 4 and should include PET-CT and dedicated CT. If local practice prohibits obtaining both assessments after Cycle 4, PET-CT alone (preferred) or CT alone may be obtained at this time point. During the follow-up period, imaging (may be CT only) will be performed every 3 months, i.e., Week 12 and 24 after last treatment, in accordance with study visits and will include the neck (if involved at baseline), chest, abdomen, and pelvis. Diagnostic contrast enhanced CT scans obtained as part of a PET-CT scan may be used in lieu of dedicated CT scans. Contrast-enhanced CT scan should include the chest, abdomen, pelvis (including inguinal/femoral regions), and, if clinically indicated, the neck or other anatomic locations. In case of any suspected disease progression by the investigator, a full tumor assessment including anatomic scans must be performed. At all times during the course of the study, disease progression diagnosed based on clinical examination must be confirmed by imaging (e.g., CT, PET-CT) as soon as feasible (maximum, within 30 days) and prior to initiation of non-protocol specified anti-lymphoma therapy. See Section 4.5.5 and Appendix 1 for details on the tumor evaluation and response.

After the end of study treatment, patients will be followed-up every 3 months for 6 months (i.e., 12 and 24 weeks after the last dose of study treatment). Assessments will include clinical evaluation of tumor response/progression, PK and immunogenicity (blood sampling), physical examination, standard hematologic and biochemistry assessments, vital signs and weight measurements, liver and spleen size and B-symptoms assessments.

Safety will be evaluated by monitoring all adverse events, and abnormalities identified through physical examination, vital signs, and laboratory assessments. Such events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5.0). Laboratory safety assessments will include the routine monitoring of hematology and blood chemistries.

In addition, PK samples (see Section 4.5.7) and samples for assessing immunogenicity (see Sections 4.5.6 and 4.5.8) will be taken.

The schedules of assessments are provided in Appendix 1 and Appendix 2.

3.1.2 Independent Review Committee

An IRC composed of certified radiologists and a hematologist or oncologist with experience in malignant lymphoma will assess all patients for response according to

Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (see Appendix 3) and IWG Response Criteria for NHL 1999 Guidelines, respectively, on the basis of imaging results and biopsy results that are performed related to efficacy evaluation. Decisions will be guided by a Charter specific to the independent review.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study is defined as the date when the last patient last visit (LPLV) occurs. LPLV is expected to occur approximately 6 months after the last patient enrolled has received the last study treatment, or sooner, if all patients have progressed, died, or withdrawn from the study. The Sponsor has the right to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Rituximab Subcutaneous Dose and Schedule

The dose of 1400 mg rituximab SC that will be used in this trial was established in the Phase Ib study BP22333 and further confirmed in the pivotal Phase III study BO22334. The results of these 2 studies are summarized in Section 1.2 and details on study design, dose rationale, and results can be found in the respective clinical study reports (the reports will be available on request).

The efficacy, safety and PK results of the pivotal Phase III study BO22334 (a two-stage, randomized, controlled, open-label study to investigate the PK, efficacy and safety of rituximab SC in combination with CHOP or CVP versus rituximab IV in combination with CHOP or CVP in 410 patients with previously untreated FL) confirmed that the fixed SC dose of 1400 mg was efficacious and safe:

The primary endpoint of the study was met: non-inferior C_{trough} with the fixed rituximab SC dose of 1400 mg was demonstrated compared with rituximab IV 375 mg/m^2 given every 3 weeks in combination with CHOP or CVP chemotherapy as induction treatment. The ratio of $C_{trough,SC}/C_{trough,IV}$ at Cycle 7 was 1.62 (90% CI: 1.36,1.94). The CVs for C_{trough} at Cycle 7 were 43.2% in the rituximab SC arm and 36.7% in the rituximab IV arm, respectively, demonstrating comparable variability in the two treatment arms.

The efficacy data for ORR and CRR as well as PFS and OS data for rituximab SC were comparable to those of rituximab IV and indicated that the anti-lymphoma activity of rituximab was not impaired when given subcutaneously.

The safety profile of rituximab SC was comparable to that of rituximab IV with the exception of ARRs and local cutaneous reactions, which were manageable and expected. With the exception of the anticipated administration reactions, SC formulation did not cause any additional safety burden compared with the IV formulation during the induction and maintenance phases, hence demonstrating a positive benefit-risk profile of the SC formulation without compromising the safety of rituximab.

The PK, efficacy and safety following rituximab IV or SC are expected to be comparable between Asian and non-Asian patients, and therefore the fixed SC dose of 1400 mg rituximab will be used also in this trial, which is conducted in Chinese patients.

For a dose of 1400 mg, a patient will receive a subcutaneous dosing volume of 11.7 mL (see Section 4.3.1.2).

3.3.2 Rationale for Study Design

This is a Phase II, prospective, multicenter, randomized, controlled, open-label, China-only study to estimate the PK parameters, meanwhile collecting data of efficacy and safety for rituximab SC and rituximab IV, both in combination with CHOP chemotherapy, in approximately 50 adult patients with previously untreated CD20 positive DLBCL.

Screening and pre-treatment (baseline) evaluations will also include Ann Arbor staging, ECOG performance status, and IPI score. The IPI has been the primary clinical tool used to predict outcome for patients with aggressive NHL. Based on the number of negative prognostic factors present at the time of diagnosis (age >60 years, stage III/IV disease, elevated LDH level, ECOG performance status ≥2, more than one extranodal site of disease), 4 discrete outcome groups were identified (high risk, high–intermediate risk, low–intermediate risk and low risk) with a 5-year overall survival ranging from 26% to 73%.

Randomization will be stratified according to IPI score (IPI 0-2 versus IPI 3–5).

The key efficacy endpoint is the CRR at the end of study treatment determined by IRC using the Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014), i.e., 6–8 weeks after the last dose of study treatment or 4–8 weeks after last dose of study treatment for early discontinuation. The response will be assessed on the basis of radiographic (PET-CT scans, diagnostic CT scans [or magnetic resonance imaging (MRI) scans]) and clinical evidence of disease including bone marrow examinations, through use of the Lugano Response Criteria for Malignant Lymphoma (Appendix 4). The widely used Lugano criteria are based predominantly on PET-CT scan and include CT scan as part of the response assessment. PET using [^{18}F]fluorodeoxyglucose (FDG) has since emerged as a powerful functional imaging tool for staging, restaging, and response assessment of lymphomas. PET-CT and dedicated CT scans will be obtained at screening and 6-8 weeks after completion of study treatment, or sooner in the event that a patient discontinues early. An interim assessment will be obtained after Cycle 4 and should include PET-CT and dedicated CT. If local practice prohibits obtaining both assessments after Cycle 4, PET-CT alone (preferred) or CT alone may be obtained at this time point. During the follow-up period, imaging (may be CT only) will be performed every 3 months, i.e., Week 12 and 24 after last treatment, in accordance with study visits and will include the neck (if involved at baseline), chest, abdomen, and pelvis. Magnetic resonance imaging (MRI) may be used instead of CT scans with contrast in patients for whom CT scans with contrast are contraindicated.

The study treatment regimen selected for both treatment groups is consistent with the approved dosing for rituximab IV and standard treatment practices. Due to the inherent differences between the two rituximab formulations, treatment assignment will not be blinded in this study.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with previously untreated, CD20 positive advanced DLBCL who meet below eligibility criteria as defined in Sections 4.1.1 and 4.1.2 will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent and to comply with the study protocol
- Age ≥18 and ≤80 years at time of signing Informed Consent Form
- Previously untreated CD20 positive DLBCL histologically documented
- Patients with an IPI score of 1 to 5 or IPI score of 0 with bulky disease, defined as one lesion ≥7.5 cm (see Appendix 5)
- At least one bi-dimensionally measurable lesion defined as ≥1.5 cm in its largest dimension on CT scan
- ECOG performance status of 0, 1, or 2 (see Appendix 6)
- Left ventricular ejection fraction (LVEF) ≥50% on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram
- A negative serum pregnancy test or a negative urine pregnancy test within 7 days prior to study treatment must be available both for pre-menopausal women (including those who have had a tubal ligation) and for women who are less than 2 years after the onset of menopause; if negative serum pregnancy test is within 14 days of study treatment start, a confirmatory urine pregnancy test must be available within 7 days prior to study treatment start
- For men who are not surgically sterile, agreement to use a barrier method of contraception during the treatment period and until ≥12 months after the last dose of rituximab SC or rituximab IV or according to institutional guidelines for CHOP chemotherapy, whichever is longer, and agreement to request that their partners use an additional method of contraception, such as oral contraceptives, intrauterine device, barrier method, or spermicidal jelly
- For women of reproductive potential who are not surgically sterile, agreement to use adequate methods of contraception, such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly during the treatment period and until ≥12 months after the last dose of rituximab SC or rituximab IV or according to institutional guidelines for CHOP chemotherapy, whichever is longer

- Adequate hematologic function confirmed within 14 days prior to randomization which is independent to stimulating factors and transfusion (unless related to lymphoma infiltration of the bone marrow)
    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    - Platelet count $\geq 75 \times 10^9$/L

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Transformed NHL or types of NHL other than DLBCL and its subtypes according to World Health Organization classification
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to any of the individual components of CHOP, including prior receipt of anthracyclines
- Prior therapy for DLBCL, with the exception of nodal biopsy or local irradiation or surgery for diagnosis
- Prior treatment with cytotoxic drugs or rituximab for another condition (e.g., rheumatoid arthritis) or prior use of an anti-CD20 antibody
- Current or recent (within the 30 days prior to starting study treatment) treatment with another investigational drug or participation in another investigational therapeutic study
- Ongoing corticosteroid use, >30 mg/day of prednisone or equivalent
    - Patients receiving corticosteroid treatment with ≤30 mg/day of prednisone or equivalent must be documented to be on a stable dose for duration of at least 4 weeks prior to randomization.
- Primary CNS lymphoma, blastic variant of mantle cell lymphoma, or histologic evidence of transformation to a Burkitt lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, and primary cutaneous DLBCL
- History of other malignancy that could affect compliance with the protocol or interpretation of results
    - Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible.
    - Patients with a malignancy that has been treated but not with curative intent will also be excluded unless the malignancy has been in remission without treatment for ≥5 years prior to enrollment.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including but not limited to significant cardiovascular disease (such as New York Heart Association Class III or

IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)

- Any of the following abnormal laboratory values:
    - Creatinine >1.5 × upper limit of normal (ULN) (unless creatinine clearance normal) or calculated creatinine clearance <40 mL/min (using the Cockcroft-Gault formula)
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × ULN
    - Total bilirubin ≥1.5 × ULN; patients with documented Gilbert disease may be enrolled if total bilirubin is ≤3.0 × ULN
    - International normalized ratio (INR) ≥1.5 × ULN in the absence of therapeutic anticoagulation
    - Partial thromboplastin time (PTT) or activated Partial thromboplastin time (aPTT) >1.5 × ULN in the absence of a lupus anticoagulant
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)
    - Patients with occult or prior HBV infection (defined as negative HBsAg and positive total hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing during the treatment period and the follow-up period.
- Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)
    - Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Known history of human immunodeficiency virus (HIV) seropositive status or infection
- Signs or symptoms of other active and/or severe infection
- Evidence of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or patient at high risk from treatment complications
- Any co-existing medical or psychological condition that would compromise ability to give informed consent

4.2 METHOD OF TREATMENT ASSIGNMENT

4.2.1 Treatment Assignment

This is a randomized open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms of R^{IV}-CHOP or R^{SC}-CHOP. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to IPI scores (IPI 0-2 versus IPI 3-5).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are rituximab IV (comparator), and rituximab SC (experimental). Both rituximab IV and rituximab SC will be used in combination with CHOP. Both IMPs will be supplied by the Sponsor. For further information on the formulation, packaging and handling of rituximab IV and rituximab SC, see the rituximab Oncology IV IB and rituximab SC IB, respectively; for that of CHOP chemotherapy, see the local prescribing information.

4.3.1 Investigational Medicinal Product

4.3.1.1 Rituximab IV (Comparator Investigational Medicinal Product)

Rituximab IV will be provided as 500 mg/50 mL (RO0452294/V02) liquid-filled vials with a nominal content of 10 mg/mL rituximab. The drug product contains sodium acetate (buffer), sodium chloride (tonicity adjustment), and polysorbate 80 (surfactant) in Water for Injection (WFI) at a pH of 6.5. The drug product is a sterile, colorless to pale yellow liquid.

Preparation and Administration of Rituximab IV Formulation

The qualified individual responsible for dispensing the study drug will prepare the correct dose. This individual will write the date dispensed and patient number on the study drug vial label and on the Drug Accountability Record. This individual will also record the study drug batch or lot number received by each patient during the study.

Patients receiving rituximab IV will be administered a dose of 375 mg/m^2. The appropriate amount of solution should be withdrawn from the vial using the following calculation:

Volume (mL) = Body Surface Area (BSA) (m^2) × dose (375 mg/m^2)/concentration of reconstituted solution mg/mL (500 mg/50 mL)

The recommended initial rate for infusion is 50 mg/hour. After the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent doses of rituximab IV can be infused at an initial rate of 100 mg/hour and increased by 100 mg/hour increments at 30-minute intervals, to a maximum of 400 mg/hour.

The prepared rituximab IV solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.

Patients should be closely monitored for the onset of cytokine release syndrome. In patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm, or hypoxia, the infusion should be interrupted immediately. Patients should then be evaluated for evidence of tumor lysis syndrome, including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all patients, the infusion should not be restarted until the complete resolution of all symptoms and the normalization of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be evaluated on a case-by-case basis. Mild or moderate ARRs usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms. See Table 1 for further details on the administration of rituximab IV in the first and subsequent infusions.

Table 1 Administration and Dose Modification of First and Subsequent Infusions of Rituximab IV

First Infusion (Day 1)	Subsequent Infusions
• Begin infusion at an initial rate of 50 mg/hour. • If no infusion-associated or hypersensitivity reaction occurs, increase the infusion rate in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. • If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	• If patients experienced an infusion-associated or a hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/hour and follow instructions for the first infusion. • If the patient tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hour), begin the infusion at a rate of 100 mg/hour. • If no infusion reaction occurs, increase the infusion rate in 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. • If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

IV = intravenous.
Note: A fast infusion is not allowed.

4.3.1.2 Rituximab SC (Experimental Investigational Medicinal Product)

Rituximab SC (MabThera SC; RO0452294/F02-01) will be supplied as a ready-to-use liquid formulation with a nominal content of 120 mg/mL rituximab and must not be diluted prior to administration. The drug product contains 2000 U/mL rHuPH20 acting as a permeation enhancer, histidine/histidine-HCl (buffer), α,α-trehalose (bulking agent), methionine (stabilizer), and polysorbate 80 (surfactant) in WFI at a pH of 5.5. The drug product is a sterile, colorless to yellowish, clear to opalescent liquid in colorless 15-mL

vials (extractable volume: 11.7 mL). Vials contain no preservative and are for single use only. The same formulation was used in a Good Laboratory Practice toxicity study described in the rituximab SC IB.

Preparation and Administration of Rituximab SC Formulation

Patients receiving rituximab SC will be administered the study drug at a dose of 1400 mg, and 11.7 mL of solution should be withdrawn from the vial.

The SC injection needle will be inserted using sterile technique in the SC tissue of the abdomen. The needle should be fully inserted, being careful that the tip of the needle is deeper than the dermis but not as deep as the underlying muscle. The goal of the placement angle and needle depth is to achieve uniform placement into subcutaneous tissue. The study drug should not be injected into moles, scars, or bruises. The skin should be pinched and the needle inserted before the skin is released and the pressure on the syringe applied.

The injection should be manually pushed at a flow rate of approximately 2 mL/min, therefore an administration volume of 11.7 mL should take approximately 5 to 6 minutes. If there is a request by the patient to interrupt the injection, the pressure on the syringe should initially be eased to alleviate pain. If pain is not alleviated, the injection should be stopped and the patient should indicate when he/she is comfortable to resume the injection.

4.3.1.3 Storage, Packaging, and Labeling of Rituximab IV and SC Formulations

The recommended storage condition for rituximab SC is at 2°C–8°C, protected from light. The product should be used immediately after the first opening. Batch-specific details and information on shelf-life are given on the packaging label. Please refer to the IB of rituximab SC for further formulation, storage, and handling instructions for rituximab SC.

The recommended storage condition for rituximab IV is 2°C–8°C, protected from light. Prepared infusion solutions of rituximab are biologically and chemically stable at 2°C–8°C for 24 hours and at room temperature for an additional 12 hours. The product should not be used beyond the expiration date stamped on the carton. Rituximab IV vials should be protected from direct sunlight. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed. Please refer to the rituximab Oncology IV IB for further formulation, storage, and handling instructions for rituximab IV.

Packaging of the study drug will be monitored by the Roche Clinical Trial Supplies department and will bear a label with the protocol number, drug identification, dosage and identification as required by local law. The packaging and labeling of the study drug will be in accordance with Roche standards and local regulations.

Rituximab SC is supplied as a ready-to-use liquid formulation with a nominal content of 120 mg/mL rituximab in 15-mL vials (12.25 mL fill). Rituximab IV drug product will be provided in 500 mg/50 mL vials.

Upon arrival of the investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of vials, and temperature conditions, and report any deviations or product complaints to the study monitor.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1. Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage delay and modifications for patients who experience adverse events are provided in Section 5.1.

4.3.2.1 R^{IV}-CHOP

Patients scheduled to be treated with R^{IV}-CHOP will receive six or eight cycles of standard CHOP chemotherapy given in 21-day treatment intervals (see Table 2). The sites will elect prior to study start whether they will be administering six or eight cycles of CHOP chemotherapy for all patients.

Institutions should follow their standard administration regimens for R^{IV}-CHOP, including anti-emetics and hydration. All patients are required to receive the following oral premedication 30 to 60 minutes prior to starting each infusion of rituximab:

- 1000 mg paracetamol (acetaminophen)
- 50 mg to 100 mg diphenhydramine hydrochloride or alternative antihistamine

Rituximab IV will be prepared per the manufacturer's instructions and CHOP will be prepared according to the standard practice at the institution.

Table 2 Schedule of R^{IV}-CHOP for Cycles 1 to 8

Medication	Dose	Mode	D1	D2	D3	D4	D5
Rituximab IV	375 mg/m^2	IV	x [a]				
Cyclophosphamide	750 mg/m^2	IV	x				
Doxorubicin	50 mg/m^2	IV	x				
Vincristine	1.4 mg/m^2 (2 mg max)	IV	x				
Prednisone	100 mg/d	PO	x [b]	x	x	x	x

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; D = day; IV = intravenous; PO = oral.

[a] The first cycle of rituximab IV can be given on Day 1 or Day 2, depending on institutional practice.

[b] Rituximab should be administered after administration of the glucocorticoid component of the chemotherapy if applicable.

4.3.2.2 R^{SC}-CHOP

4.3.2.2.1 Cycle 1

Patients randomized to the R^{SC}-CHOP arm will receive rituximab IV + CHOP in Cycle 1 as shown in Table 3.

Table 3 Schedule of R^{SC}-CHOP in Cycle 1

Medication	Dose	Mode	D1	D2	D3	D4	D5
Rituximab IV	375 mg/m^2	IV	x [a]				
Cyclophosphamide	750 mg/m^2	IV	x				
Doxorubicin	50 mg/m^2	IV	x				
Vincristine	1.4 mg/m^2 (2 mg max)	IV	x				
Prednisone	100 mg/d	PO	x [b]	x	x	x	X

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; D = day; IV = intravenous; PO = oral.

[a] The first cycle of rituximab IV can be given on Day 1 or Day 2, depending on institutional practice.

[b] Rituximab should be administered after administration of the glucocorticoid component of the chemotherapy if applicable.

4.3.2.2.2 Cycles 2 to 8

Patients randomized to the R^{SC}-CHOP arm will receive rituximab SC + CHOP from Cycles 2 to 8. The second cycle of R^{SC}-CHOP will be the first subcutaneous administration of rituximab. Please see Table 4 for details.

All patients are required to receive the following oral premedication 30 to 60 minutes prior to starting each injection of rituximab SC:

- 1000 mg paracetamol (acetaminophen)
- 50 mg to 100 mg diphenhydramine hydrochloride or alternative antihistamine

Rituximab SC will be prepared and administered according to Section 4.3.1.2 and CHOP will be prepared according to the standard practice at the institution.

Table 4 Schedule of R^{SC}-CHOP in Cycles 2 to 8

Medication	Dose	Mode	D1	D2	D3	D4	D5
Rituximab SC	1400 mg	SC	x				
Cyclophosphamide	750 mg/m^2	IV	x				
Doxorubicin	50 mg/m^2	IV	x				
Vincristine	1.4 mg/m^2 (2 mg max)	IV	x				
Prednisone	100 mg/d	PO	x [a]	x	x	x	x

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; D = day; IV = intravenous; PO = oral; SC = subcutaneous.

[a] Rituximab should be administered after administration of the glucocorticoid component of the chemotherapy if applicable.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the Interactive Voice Response System (IVRS)/Interactive Web-based response system (IWRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

The standard-of-care (SOC) therapy for DLBCL involves chemotherapy with complementary mechanisms of action combined with immunotherapy. Up to eight cycles of rituximab plus CHOP given in 21-day intervals (R-CHOP-21) is considered to be the SOC therapy for patients with previously untreated DLBCL. The Sponsor does not have any plans to provide the Roche study drug (rituximab SC or rituximab IV) or any other study treatment to the patients after they complete the study considering the patient will have received SOC in the study duration.

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 28 days prior to initiation of study drug to study termination. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients should receive full supportive care including granulocyte colony-stimulating factor (G-CSF) support, transfusions of blood and blood products, antibiotics, anti-emetics etc., where applicable.

4.4.1 Permitted Therapy

4.4.1.1 Prophylaxis of Administration-Related Reactions

Premedication with oral acetaminophen and diphenhydramine approximately 30 minutes prior to rituximab administration is required as per institutional practice. If given, they must be documented on the Concomitant Medications eCRF.

Rituximab SC or IV should be administered on Day 1 of each cycle, after administration of the glucocorticoid component of CHOP chemotherapy (the interval between prednisone and rituximab depending on institutional practice). For patients who do not experience ARRs with their previous infusion or injection, premedication at subsequent infusions/injections may be omitted at the investigator's discretion.

4.4.1.2 Prophylaxis of Nausea and Vomiting

Premedication to prevent nausea and vomiting is allowed, as per institutional practice. This does include glucocorticosteroids (e.g., dexamethasone). If glucocorticosteroids are as part of the anti-emetic regimen, they should be administered prior to the rituximab administration and should be documented on the Concomitant Medications eCRF accordingly.

Please note that additional administrations of high-dose glucocorticosteroids in lymphoma-therapeutic doses given outside of the CHOP regimen are not permitted.

4.4.1.3 Antimicrobial and Antiviral Prophylaxis

Antimicrobial and antiviral prophylaxis may be used as per institutional practice. If given, they must be documented on the Concomitant Medications eCRF.

4.4.1.4 Prophylaxis for Hemorrhagic Cystitis

Patients should be adequately hydrated prior to and after cyclophosphamide administration and should be instructed to void the bladders frequently. Mesna (2-mercapto ethane sulfonate sodium) may be used as prophylaxis according to institutional practice and should be documented on the Concomitant Medications eCRF.

4.4.1.5 Tumor-Lysis Syndrome Prophylaxis

Patients with high tumor burden and who are considered by the investigator to be at risk for tumor lysis should also receive tumor-lysis prophylaxis prior to the initiation of treatment. Patients should be well hydrated. Starting one or two days before the first dose of rituximab, it is desirable to maintain a fluid intake of approximately 3 L/day. In addition, all patients with high tumor burden and who are considered by the investigator to be at risk for tumor lysis should be treated with 300 mg/day allopurinol PO or a suitable alternative treatment starting 48–72 hours prior to Cycle 1, Day 1 of treatment and hydration. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion/injection, if deemed appropriate by the investigator. Prophylaxis against tumor-lysis syndrome (TLS), may be given as per institutional practice and should be documented on the Concomitant Medications eCRF.

4.4.1.6 Central Nervous System Prophylaxis

CNS prophylaxis with intrathecal chemotherapy may be given as per institutional practice and should be documented on the Concomitant Medications eCRF.

4.4.1.7 Hepatitis B Reactivation Prophylaxis

Hepatitis B virus reactivation is a potential risk for R-CHOP. Patients who are both HBsAg negative and anti-hepatitis B core positive may be included into this study. Prophylactic antiviral therapy should be considered, lamivudine or entecavir, or as per institutional practice and should be documented on the Concomitant Medication eCRF. These patients should have HBV DNA levels obtained monthly during treatment and follow-up periods, as follows:

- If the HBV DNA assay becomes positive and is above the World Health Organization (WHO) cutoff of 100 IU/mL, study treatment chemotherapy will be held and the patient should be treated (for at least 6 months after the last dose of rituximab) with an appropriate nucleoside analog and immediately referred to a gastroenterologist or hepatologist for management as needed. Patients may resume study treatment once HBV DNA levels have decreased to undetectable levels.
- If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving antiviral medication, study treatment will be discontinued.

4.4.1.8 Pre-planned Consolidation Radiotherapy

Radiotherapy may be applied to initial sites of bulky or extranodal disease at a dose of 30–40 Gy (according to institutional practice). If indicated, pre-planned radiotherapy should be initiated within 8 weeks after the last study drug treatment and should start after all End of Treatment assessments, including PET-CT scans for disease response assessment, are completed. Any radiotherapy should be pre-planned by the center and documented prior to randomization and then entered in the eCRF once the patient is

randomized. All unplanned radiotherapy administered to patients will be considered as a new anti-lymphoma treatment.

4.4.2 Prohibited Therapy

The following concomitant medications or treatments will result in withdrawal of patients from study treatment:

- Other concomitant anti-tumor agents not defined in this protocol as study treatment, including lymphoma-therapeutic doses of glucocorticosteroids
- Unplanned radiotherapy or other concurrent investigational agents of any type

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1, and Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained from the patient or the patient's legally authorized representative before performing any study-related procedures (including screening evaluations) or any prohibited medications being withheld for purposes of study participation. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Tests that are performed as standard of care prior to obtaining informed consent may be used for screening and baseline assessments provided that they have been performed within the allowable timeframe as described in the schedule of assessments (see Appendix 1). Not all study assessments need to be obtained at every study visit; please refer to Appendix 1 and Appendix 2 for details on frequency.

4.5.2 Medical History, Demographic Data, IPI, Ann Arbor Staging, and ECOG Performance Status

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, demographic data (including age, sex, and self-reported race/ethnicity), IPI score, and Ann Arbor staging will be collected and recorded at screening. ECOG performance

status and B symptoms will be assessed at screening, Day 1 of Cycles 1 to 8, at each visit during the follow-up period, and at the end of study.

Please see Appendix 5 for the description of the IPI and Ann Arbor staging and Appendix 6 for the ECOG performance status scale.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. New or worsened abnormalities should be recorded as adverse events on the Adverse Event eCRF. As part of the tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. These will be recorded as non-target lesions on the Tumor Assessment eCRF. Targeted physical examinations should be limited to systems of primary relevance, including cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen).

4.5.4 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a supine position, pulse rate, respiratory rate, body temperature, height, weight, and determination of BSA at baseline. During rituximab IV or SC administration visits, vital signs will include the measurement of weight, systolic and diastolic blood pressure, respiratory rate, and pulse rate.

4.5.5 Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation until disease progression or end of follow-up (6 months after the last dose of the study treatment). Response assessments will be assessed by the investigator and IRC, on the basis of physical examinations, diagnostic CT scans (or MRI scans), PET-CT scans, and bone marrow examinations, using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix 4).

Diagnostic contrast enhanced CT scans are currently the best available and most reproducible methods for measuring target lesions selected for response assessment; conventional CT scans (or MRI scans, if CT is contraindicated) should be performed with contiguous cuts of ≤8 mm in slice thickness and contrast enhanced if not medically contraindicated. CT scans should include the chest, abdomen, and pelvis; CT scans of the neck or other anatomic locations should be included if clinically indicated.

In patients for whom contrast is contraindicated (e.g., patients with contrast allergy or impaired renal clearance), CT or combined PET-CT scans without contrast or MRI scans are permitted as long as they permit consistent and precise measurement of target lesions during the study treatment period. The same radiographic assessment modality

should be used for all response evaluations, in order to ensure consistency across different time points.

PET-CT scans in conjunction with diagnostic contrast enhanced CT scans will be obtained in this study. CT and PET-CT scans are required at screening (within 35 days prior to the initiation of study treatment unless otherwise approved by the Medical Monitor), during Cycle 4 (i.e., Day 19 [± 3 days] of Cycle 4), and at the end of study treatment (i.e., 6–8 weeks after the last dose of Cycle 8 treatment or 4-8 weeks after the last dose of study treatment in the event that a patient discontinues early). Diagnostic contrast enhanced CT scans obtained as part of a PET-CT scan may be used in lieu of dedicated CT scans. An interim assessment will be obtained after Cycle 4 and should include PET-CT and dedicated CT. If local practice prohibits obtaining both assessments after Cycle 4, PET-CT alone (preferred) or CT alone may be obtained at this time point. During the follow-up period, imaging (may be CT only) will be performed every 3 months. Contrast-enhanced CT scan should include the chest, abdomen, pelvis (including inguinal/femoral regions), and, if clinically indicated, the neck and other anatomic locations should be imaged.

In case of any suspected disease progression by the investigator, a full tumor assessment including anatomic scans must be performed. At all times during the study, diagnosis of disease progression based on clinical examination must be confirmed by imaging (e.g., CT, PET-CT) as soon as feasible (maximum, within 30 days) and prior to initiation of non-protocol specified anti-lymphoma therapy.

Bone marrow examinations are required at screening and should include biopsy for morphology. Repeat bone marrow examinations are required if the bone marrow was involved with tumor at screening and the repeat bone marrow examination is required to confirm a radiological assessment of CR at the end of therapy.

4.5.6 Laboratory Assessments

Central laboratory assessments will include the following:

- Anti-rituximab antibodies will be assessed for both treatment groups (i.e., R^{IV}-CHOP and R^{SC}-CHOP) (see Section 4.5.8).
- Anti-rHuPH20 antibodies will be assessed only in patients randomized to the R^{SC}-CHOP treatment group (see Section 4.5.8).
- For the subset of patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA levels at screening, monitoring of HBV DNA levels is mandatory for the patients. For instructions on the management of these patients, see Section 4.4.1.7.
- Rituximab PK Samples (see Section 4.5.7).

Samples for hematology, serum chemistry, pregnancy test, coagulation, hepatitis B and C serologies, quantitative immunoglobulin assessments, and cerebrospinal fluid assessment will be analyzed at the study site's local laboratory:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, percent or absolute differential count.
- Serum chemistry: At screening, serum chemistry will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, total bilirubin, total protein, albumin, AST, ALT, LDH, alkaline phosphatase, uric acid, and calculated creatinine clearance. During Cycles 1–8 and the follow-up period, serum chemistry will include sodium, potassium, creatinine, calcium, total bilirubin, total protein, albumin, AST, ALT, LDH, alkaline phosphatase, and uric acid.
- Pregnancy test: A negative serum pregnancy test or a negative urine pregnancy test within 7 days prior to study treatment must be available both for pre-menopausal women (including those who have had a tubal ligation) and for women who are less than 2 years after the onset of menopause; if a negative serum pregnancy test within 14 days prior to study treatment, there must be a confirmatory urine pregnancy test within 7 days prior to study treatment start. Another test will be performed at the end of study.
- Coagulation: aPTT or PTT, prothrombin time (PT), and INR
- Viral serology and detection:
    - Hepatitis B (HbsAg and total HBcAb)
    - Hepatitis C virus antibody
- Quantitative immunoglobulins (Igs): IgG, IgA, and IgM
- Cerebrospinal fluid assessment: Lumbar puncture is indicated for patients with high-risk disease or with one or more of the following sites of involvement: paranasal sinuses, testicular, paramenigeal, peri-orbital, CNS, paravertebral, or bone marrow.

The procedures for the collection, handling, and shipping of laboratory samples are specified in the laboratory manual.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The biological samples (blood samples for PK and immunogenicity analysis) will be destroyed no later than 6 months after the completion of the final Clinical Study Report.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.7 Pharmacokinetic Assessments

The PK parameter, observed C_{trough} levels of rituximab, serves as the primary endpoint in the study; therefore, it is of utmost importance to adhere to the visiting schedule and to take the PK samples on the exact day scheduled (see Appendix 1 and Appendix 2).

PK samples on the day of IV administration of rituximab must not be taken from the same arm as IV drug administration. In the case of a patient being unable to provide venous access on the opposite arm from the infusion arm, the leg may be used for PK blood sampling.

Rituximab serum concentrations will be measured by a specific and validated method. Details on sampling procedures, sample storage, and shipment will be provided in the Sample Collection, Handling, and Logistics Manual.

The total volume of blood that will be obtained for PK assessments over a period of 48 weeks will be approximately 77 mL (22 samples) for patients randomized to the rituximab IV arm and 70 mL (20 samples) for patients randomized to the rituximab SC arm.

4.5.7.1 PK Sampling for Patients Randomized to the R^{IV}-CHOP Arm

For patients randomized to the rituximab IV arm, PK sampling of rituximab will be performed at the following time points:

- Cycle 1: within 2 hours pre-dose and at end of infusion (+ 15 minutes)
- Cycle 2: within 2 hours pre-dose, at end of infusion (+ 15 minutes), 24 hours post-dose (± 4 hours), Day 3 (± 4 hours), Day 7 (± 24 hours), Day 15 (± 48 hours)
- Cycles 3 and 4: within 2 hours pre-dose
- Cycle 5: within 2 hours pre-dose and at end of infusion (+ 15 minutes)
- Cycle 6: within 2 hours pre-dose
- Cycle 7: within 2 hours pre-dose, at end of infusion (+ 15 minutes), 24 hours post-dose (± 4 hours), Day 3 (± 4 hours), Day 7 (± 24 hours), and Day 15 (± 48 hours)
- Cycle 8: within 2 hours pre-dose and Day 29 (± 24 hours)
- Follow-up phase: 24 weeks (± 7 days) after the last rituximab dose

If patients discontinue the study treatment prematurely, blood samples for PK will be taken when the patients return to the clinic for an early termination visit.

Please note that all PK samples obtained at the end of infusion must be taken from the side of the body opposite to the rituximab IV administration.

For more detailed PK sampling information, see Appendix 1 and Appendix 2.

4.5.7.2 PK Sampling for Patients Randomized to R^{SC}-CHOP Arm

For patients randomized to the R^{SC}-CHOP arm, PK sampling will be performed at the following time points:

- Cycle 1 (rituximab IV): within 2 hours pre-dose and at end of infusion (+ 15 minutes)
- Cycle 2: within 2 hours pre-dose, 24 hours post-dose (± 4 hours), Day 3 (± 4 hours), Day 7 (± 24 hours), Day 15 (± 48 hours)
- Cycles 3 and 4: within 2 hours pre-dose
- Cycle 5: within 2 hours pre-dose and Day 7 (± 24 hours)
- Cycle 6: within 2 hours pre-dose
- Cycle 7: within 2 hours pre-dose, 24 hours post-dose (± 4 hours), Day 3 (± 4 hours), Day 7 (± 24 hours), and Day 15 (± 48 hours)
- Cycle 8: within 2 hours pre-dose and Day 29 (± 24 hours)
- Follow-up phase: 24 weeks (± 7 days) after last rituximab dose

If patients discontinue the study treatment prematurely, blood samples for PK will be taken when the patients return to the clinic for an early termination visit.

For Cycle 1 please note that the PK sample obtained at the end of infusion must be taken from the side of the body opposite to the rituximab IV administration.

For more detailed PK sampling information, see Appendix 1 and Appendix 2.

4.5.8 Immunogenicity Assessments

Blood samples will be taken for the assessment of immunogenicity (i.e., anti-rituximab antibody samples [in all patients] and anti-rHuPH20 antibody samples [only in patients randomized to the SC arm]). These samples will be drawn prior to rituximab administration at each cycle and then at 12 weeks and 24 weeks after the last dose of rituximab during the follow-up period (Appendix 1). If patients discontinue the study treatment prematurely, blood samples for immunogenicity will be taken when the patients return to the clinic for an early termination visit.

In any patient who experiences a severe AE or SAE that is considered immunogenic and possibly related to study medication, a blood sample should be collected within 7 days of the event becoming known to the Investigator. These samples will be analyzed for immunogenicity and rituximab PK as appropriate.

Patients with anti-rituximab antibody titers may develop allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

A validated enzyme-linked immunosorbent assay (ELISA) will be used to detect and confirm the presence of anti-rituximab antibodies in serum.

A validated bridging electrochemiluminescence immunoassay (ECLIA) will be used to detect and confirm the presence of anti-rHuPH20 antibodies in plasma samples.

A three-tiered approach for immunogenicity sample analysis will be used for the analysis of anti-rituximab antibodies and anti-rHuPH20 antibodies. A panel of assays to detect, confirm, and characterize the antibody responses are outlined below:

- Screening assays to detect anti-rituximab antibodies or anti-rHuPH20 antibodies in samples (screen-positives)
- Confirmatory assays to assess the specificity of the screen-positive results by competition with excess rituximab or rHuPH20 (confirmed positives)
- Titration assays to determine the anti-rituximab or anti-rHuPH20 antibody titers for confirmed positive samples
- A neutralizing antibody assay to characterize the confirmed antibodies to rHuPH20.

The total volume of blood that will be obtained for anti-rituximab antibody assessments over a period of 48 weeks will be approximately 30 mL (10 samples) per patient.

The total volume of blood that will be obtained for anti-rHuPH20 antibody assessments over a period of 48 weeks will be approximately 30 mL (10 samples) per patient.

4.5.9 Electrocardiograms

A 12-lead electrocardiogram (ECG) is required at screening, at the end of study treatment, at the end of the study, and as clinically indicated (See Appendix 1). ECGs for each patient should be obtained using the same machine wherever possible.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

If at a particular postdose timepoint the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two

successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that time point, an unscheduled PK sample should be obtained. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)
- Any event that meets stopping criteria defined in Section 5.1
- Patient/investigator decision

Patient who discontinue study treatment prematurely are required to return to the clinic for an early termination visit within 4–8 weeks after the last dose of study treatment. The primary reasons for early discontinuation of treatment must be documented on the appropriate eCRF.

If a patient discontinues study treatment early because of toxicity, every effort should be made to continue study assessments until progression and standard follow-up (Appendix 1). In cases of study treatment discontinuation for reasons other than disease progression and withdrawal of consent, patients will enter the follow-up period. Once progression occurs, only the applicable follow-up of adverse event reporting will be assessed.

Patients who discontinue study treatment prematurely will not be replaced.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. See Appendix 1 for the list of assessments to be performed for patients who prematurely withdraw from the study during the treatment period. Patients who are withdrawn or

discontinued from study participation (and not just study treatment) will not be followed for any reason after consent has been withdrawn.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Pregnancy
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor
- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study
- In the best interest of the patient as determined by the investigator

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonization (ICH) guideline for Good Clinical Practice

- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

4.7 FOLLOW-UP

After the last administration of study treatment, patients will be followed up for 6 months (every 3 months). During the follow-up period, patients who continue the study and who have not progressed will be followed according to the protocol-specified follow-up schedule. All patients will be followed as specified unless the patient requests to be withdrawn from study follow-up; this request must be documented in the patient's medical record and signed by the investigator.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Rituximab IV has been approved in both China and other countries. Rituximab SC is approved in more than 90 countries across the world, but not yet approved in China. The safety plan for patients in this study is based on clinical experience with rituximab in completed and ongoing studies and post-marketing experience. The anticipated important safety risks for rituximab are outlined below. Please refer to local prescribing information for the detailed safety information on CHOP chemotherapy. Please refer to the rituximab SC IB and rituximab Oncology IV IB for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dose, are provided below.

5.1.1 Management of Patients Who Experience Adverse Events

Patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and laboratory measurements.

All adverse events occurring after the initiation of study treatment will be reported until 28 days after administration of the last dose of study treatment. Patients who have an ongoing adverse events resulting in treatment discontinuation will be followed until the event resolution, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient initiates a new anti-lymphoma treatment (whichever occurs earlier).

The NCI CTCAE v 5.0 will be used to grade toxicity. Rituximab IV or SC in combination with CHOP will be given as specified in Section 4.3.2. Before starting a new treatment

cycle, toxicity must have resolved (Section 5.1.2). See Section 5.1.2 for the details on the dose modifications for rituximab IV, rituximab SC and CHOP chemotherapy for toxicity.

5.1.2 Dose modifications of Rituximab IV, Rituximab SC and CHOP Chemotherapy for Toxicity

Dose reductions (CHOP chemotherapy) are based on all laboratory values obtained within 72 hours prior to a study treatment infusion or injection (i.e., R^{IV}-CHOP or R^{SC}-CHOP).

- There should be no dose modification for rituximab IV or rituximab SC. If chemotherapy is delayed, rituximab administration must also be delayed (so that they are given on Day 1 of the same cycles).
- Patients who experience a delay exceeding 14 days in the initiation of the next planned treatment cycle will be removed from receiving study treatment.
- For large changes in body weight compared with baseline (≥10%), the dose of chemotherapy may be adjusted according to institutional practice.

Chemotherapy doses can be re-escalated (even to the full dose) at the discretion of the investigator and per the site standards in subsequent cycles according to patient tolerance. In addition, resumption of dosing without complete resolution of toxicity may only be considered after careful weighing of the risks and benefits with the patient and agreement between the investigator and the Sponsor.

Patients who discontinue all study treatment for adverse events should remain on the study and continue to have disease assessments until progression and standard follow-up.

See the details for dose delay and modification for selected events described in Table 5. Guideline for dose delays and modifications of R-CHOP are shown in Table 6.

Table 5 Guidelines for Dose Delay or Modification of Rituximab IV, Rituximab SC and CHOP Chemotherapy (Cycle 2 to Cycle 6 [or 8], Day 1)

Event(s)	Dose Delay or Modification
Hematologic toxicity	
Grade 1 or 2 neutropenia and/or thrombocytopenia	No dose reduction or delay
Grade 3 or 4 neutropenia, with or without infection or fever, first episode	• Delay doses of R^{IV}-CHOP or R^{SC}-CHOP for a maximum of 2 weeks. • Growth factors, e.g., G-CSF for neutropenia are permitted. • If ANC counts recover to $\geq 1.0 \times 10^9$/L $\leq$ Day 7 after the scheduled date of the next cycle administer current dose of cyclophosphamide and/or doxorubicin. • If ANC recovers to $\geq 1.0 \times 10^9$/L $\geq$ 8 days after the scheduled date for the next cycle, consider reducing the dose of cyclophosphamide and/or doxorubicin to a lower dose level (Table 6). • Rituximab and prednisone should not be modified for this reason.
Recurrent Grade 3 or 4 neutropenia with/without fever and infection	• Delay all study treatment for a maximum of 2 weeks. • Growth factors, e.g., G-CSF for neutropenia are permitted. • If ANC counts recover to $\geq 1.0 \times 10^9$/L $\leq$ Day 7 after the scheduled date of the next cycle, administer current dose of cyclophosphamide and/or doxorubicin. • If ANC recovers to $\geq 1.0 \times 10^9$/L $\geq$8 days after the scheduled date for the next cycle, consider reducing the dose of cyclophosphamide and/or doxorubicin to the next dose level (Table 6). • Rituximab and prednisone should not be modified for this reason. • If Grade 3 or 4 neutropenia persists despite growth factor support and following cyclophosphamide and doxorubicin dose reductions, in the absence of fever, patient may continue study treatment at the investigator's discretion with consultation of the Medical Monitor.

Table 5 Guidelines for Dose Delay or Modification of Rituximab IV, Rituximab SC and CHOP Chemotherapy (Cycle 2 to Cycle 6 [or 8], Day 1) (cont.)

Event(s)	Dose Delay or Modification
Grade 3 or 4 thrombocytopenia, first episode	• Delay all study treatment for a maximum of 2 weeks • If platelet count recovers to $\geq 75 \times 10^9$/L $\leq$ Day 7 after the scheduled date of the next cycle, administer full dose of all study drugs. • If platelet count recovers to $\geq 75 \times 10^9$/L $\geq$ Day 8 after the scheduled date of the next cycle, consider reducing the dose of cyclophosphamide and/or doxorubicin to a lower dose level (Table 6). Full dose/current dose of all other study drugs may be given. • If the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of cyclophosphamide and/or doxorubicin.
Recurrent Grade 3 or 4 thrombocytopenia	• If patient develops recurrent Grade 3-4 thrombocytopenia following cyclophosphamide and/or doxorubicin dose reductions, consider reducing the dose of cyclophosphamide and doxorubicin to the next dose level (Table 6).
Non-hematologic toxicity	
Grade 1	No dose reduction or delay
Grade 2	• Delay R^{IV}-CHOP or R^{SC}-CHOP for a maximum of 2 weeks. • If improvement to Grade $\leq$1 or baseline, then administer the previous dose of CHOP with the full dose of rituximab IV or SC for subsequent cycles.
Grade $\geq$2 (excluding alopecia, nausea, and vomiting)	Delay treatment with R^{IV}-CHOP or R^{SC}-CHOP until resolution to Grade $\leq$1 (or baseline status for all except hemorrhagic cystitis) for a maximum of 14 days.
Grade 3 or 4 non-hematologic toxicity not specifically described above	• Delay R^{IV}-CHOP or R^{SC}-CHOP for a maximum of 2 weeks. First episode: If improvement to Grade $\leq$1 or baseline, decrease cyclophosphamide dose to 500 mg/m^2 and doxorubicin to 35 mg/m^2 for subsequent cycles with full dose of rituximab or at the discretion of the investigator per site's standard. • Second episode: If improvement to Grade $\leq$1 or baseline, decrease cyclophosphamide dose to 375 mg/m^2 and doxorubicin dose to 25 mg/m^2 for subsequent cycles. • Third episode: Discontinue CHOP. If improvement to Grade $\leq$1 or baseline, continue full dose of rituximab. • Fourth episode: Discontinue all study treatment.

Table 5 Guidelines for Dose Delay or Modification of Rituximab IV, Rituximab SC and CHOP Chemotherapy (Cycle 2 to Cycle 6 [or 8], Day 1) (cont.)

Event(s)	Dose Delay or Modification
Hemorrhagic cystitis	• Patients should be adequately hydrated prior to and after cyclophosphamide administration and should be instructed to void frequently. • Mesna may be used as prophylaxis according to institutional practice. • If gross hematuria develops, cyclophosphamide should be withheld until resolution of cystitis. • A dose reduction of 50% for cyclophosphamide may be considered at the next cycle. • Re-escalation of cyclophosphamide to the initial full dose is recommended if symptoms do not recur.
Hepatotoxicity	
Bilirubin >3.0 mg/dL	• Dose reduction should be avoided if hyperbilirubinemia is not related to hepatic injury (i.e., hemolysis or Gilbert's disease). In these cases, dose reduction considerations should be guided by direct bilirubin levels. • Withhold doxorubicin and vincristine until resolution to Grade ≤1 within 14 days. Evaluate for causality. Dosing of rituximab, cyclophosphamide, and prednisone may continue.
Bilirubin between 1.5 and 3.0 mg/dL	• Dose reduction should be avoided if hyperbilirubinemia is not related to hepatic injury (i.e., hemolysis or Gilbert's disease). In these cases, dose reduction considerations should be guided by direct bilirubin levels. • Reduce doxorubicin dose by 25% of baseline and vinctistine should be reduced to the next level (Table 6). With subsequent courses of treatment if bilirubin has returned to Grade 1, full doses may be given. Give full dose of rituximab, and continue current dose of cyclophosphamide and prednisone.
Cardiotoxicity	
Grade 2–4 heart failure or Grade 3 or 4 LVSD	Discontinue R^{IV}-CHOP or R^{SC}-CHOP chemotherapy permanently.
Neurotoxicity	
Grade 1 (peripheral neuropathy)	Continue treatment at full dose; vincristine may be decreased at the discretion of the investigator.
Grade 2 or 3	Hold R^{IV}-CHOP or R^{SC}-CHOP. If recovered to Grade ≤ 1 value within 14 days, administer full dose rituximab and continue current dose of cyclophosphamide and prednisone. Reduce vincristine dose by 50% for current cycle and all subsequent cycles.
Grade 4	• Discontinue R^{IV}-CHOP or R^{SC}-CHOP chemotherapy permanently. • Patients should be evaluated regarding the continuation of R-CHOP on the basis of their risk/benefit.

Table 5 Guidelines for Dose Delay or Modification of Rituximab IV, Rituximab SC and CHOP Chemotherapy (Cycle 2 to Cycle 6 [or 8], Day 1) (cont.)

Event(s)	Dose Delay or Modification
Administration-related reactions	
Grade 3, second episode	Discontinue rituximab IV or SC permanently. CHOP alone may be continued when recovered if not attributable to CHOP.
Grade 4	Discontinue rituximab IV or SC permanently. CHOP alone may be continued when recovered if not attributable to CHOP.
Mucositis (Grade ≥2)	Delay the next cycle of R^{IV}-CHOP or R^{SC}-CHOP delayed in 1-week increments for up to a maximum of 14 days until the event resolves to Grade ≤ 1.
Tumor lysis syndrome (Grade 3 or 4)	Hold all study treatment (R^{IV}-CHOP or R^{SC}-CHOP). The patient's next dose may be delayed for up to 14 days. Following complete resolution tumor lysis syndrome, rituximab may be re-administered at the full dose during next scheduled infusion or injection, in conjunction with prophylactic therapy and CHOP chemotherapy.
Anaphylaxis	Discontinue rituximab IV or SC permanently. CHOP alone may be continued when recovered if not attributable to CHOP.

ANC = absolute neutrophil count; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; G–CSF = granulocyte colony–stimulating factor; HBV = hepatitis B virus; LVSD = left ventricular systolic dysfunction; R = rituximab.

Table 6 Recommended Steps of Dose reduction for R-CHOP

Dose Level	Rituximab IV/SC	Cyclophosphamide	Doxorubicin	Vincristine
Starting dose	100% of starting dose per cycle	100% of starting dose per cycle	100% of starting dose per cycle	100% of starting dose per cycle
First dose reduction [a]	No modification allowed	75% of starting dose per cycle	75% of starting dose per cycle	75% of starting dose per cycle
Maximum dose reduction [a]	No modification allowed	50% of starting dose per cycle or discontinue drug	50% of starting dose per cycle or discontinue drug	50% of starting dose per cycle or discontinue drug
Subsequent dose reduction	No modification allowed	Discontinue drug	Discontinue drug	Discontinue drug

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; IV = intravenous; R = rituximab; SC = subcutaneous.

[a] Steps of dose reduction listed are suggested dose changes. Investigators may opt for alternative levels of dose reduction as clinically indicated.

5.1.2.1 Administration-Related Reactions

Rituximab IV can be associated with ARRs that may be related to the release of cytokines and/or other chemical mediators and which might be clinically

indistinguishable from hypersensitivity reactions. Severe ARRs (such as bronchospasm and hypotension) may occur in about 10% of the cases. The incidence of ARRs decreases substantially with subsequent infusions and occurs in less than 1% of patients by the eighth cycle of rituximab-containing treatments. Patients with a high tumor burden may be at a higher risk of developing severe ARRs. Severe ARRs usually manifest within 1 to 2 hours after starting the first rituximab infusion. Reactions are characterized by pulmonary events, and in some cases, include features of tumor lysis syndrome, fever, chills, rigors, hypotension, urticaria, angioedema, and other symptoms. These symptoms are usually reversible with the interruption of the infusion and should be treated with diphenhydramine and paracetamol (acetaminophen). Additional treatment with bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in infusion rate (e.g., from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved. Most patients who have experienced ARRs that are not life-threatening have been able to complete the full course of rituximab therapy. In order to reduce the incidence and severity of ARRs, all patients should receive premedication consisting of antipyretics and antihistaminics (e.g., paracetamol and diphenhydramine) before every infusion of rituximab.

After administration, rituximab SC is absorbed slowly from the interstitial tissue (time to C_{max} [T_{max}] of approximately 2 to 7 days), and the mean C_{max} will be approximately 50% decreased as compared with the IV administration. Therefore, the risk of experiencing a Grade 3 or 4 ARR after rituximab SC administration is expected to be minimal.

Patients randomized to the rituximab SC arm who experience a Grade 3 or 4 ARRs after the first rituximab infusion but who are able to receive the full dose of rituximab at Cycle 1 can receive the second dose of rituximab subcutaneously (Cycle 2, Day 1).

Patients randomized to the rituximab SC arm who are unable to receive the full dose of rituximab at Cycle 1 as a result of an ARR should receive the second rituximab administration intravenously. If the patients subsequently do not experience Grade 3 or 4 ARRs, they will receive the third rituximab administration subcutaneously (Cycle 3, Day 1).

Patients with Grade 3 or 4 ARRs after the second rituximab infusion will be withdrawn from study treatment.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- ARRs: Grade 3 and 4 ARRs will need to be reported to the Sponsor expeditiously. Unless otherwise stated by investigators, adverse events occurring within 24 hours after administration of rituximab (rituximab IV or rituximab SC) and considered related to the study drug, will be considered as 'administration-related reactions', based upon NCI CTCAE v 5.0. ARRs can present with one or more of the following symptoms: allergic reaction, arthralgia, bronchospasm, chills, cough, dizziness, dyspnoea, headache, hypertension, hypotension, myalgia, nausea, pruritus, pyrexia, rash, tachycardia, urticaria, vomiting. ARRs must be recorded on the Adverse Event eCRF. In order to capture potential differences in terms of clinical relevance of these events, it is important to report and assess the intensity of all symptoms of the ARRs.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after administration of the final dose of study treatment.

Patients who have an ongoing adverse events resulting in treatment discontinuation will be followed until the event resolution, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient initiates a new anti-lymphoma treatment (whichever occurs earlier).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE 5.0

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event", it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 8:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 8 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Administration-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion/injection should be captured as a diagnosis (e.g., "infusion-related reaction", "injection-site reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion Related Reaction or Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion Related Reaction or Injection Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event

eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of DLBCL should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of DLBCL

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For rituximab IV or SC, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with rituximab IV or SC, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for China

Medical Monitor: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 6 months after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >6 months after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 12 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than

24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 12 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event and adverse event of special interest that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, Institutional Review Boards (IRBs), Ethics Committees (ECs), and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed in Table 9:

Table 9 Reference Safety Information

Drug	Document
Rituximab IV	Rituximab IV Summary of Product Characteristics
Rituximab SC	Rituximab SC Investigator's Brochure
CHOP	Prescribing information on cyclophosphamide, doxorubicin, vincristine, and prednisone, respectively

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

A detailed Statistical Analysis Plan (SAP) will specify in more detail all analyses that are outlined in this section of the protocol.

6.1 DETERMINATION OF SAMPLE SIZE

Under the assumption of a coefficient of variation equal to 0.5 and assuming that the true C_{trough} of rituximab SC formulation is 20% above the rituximab IV formulation (i.e., mean $C_{trough,SC}$ to be 20% above $C_{trough,IV}$), 20 patients in each treatment arm are needed in order to achieve 80% power with one-sided alpha of 0.05 (i.e., 2-sided 90% CI). Assuming that 20% of patients would not have valid PK data at Cycle 8 pre-dose, a total of approximately 50 patients will be enrolled into the study (see Table 10).

Table 10 Sample Size for Primary Endpoint (i.e., Non-inferiority in C_{trough})

Parameter	Value
Test significance levels, α (one-sided)	0.050
Lower equivalence limit for μ_T/μ_S, Δ_L	0.800
Expected ratio, μ_T/μ_S	1.200
Coefficient of variation, σ_S/μ_S	0.500
Power (%)	80
Number of patients per group	18 (rounded to 20)
Number of patients (total)	36 (rounded to 40)

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, and weight) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 PHARMACOKINETIC ANALYSES

6.4.1 Pharmacokinetic Analysis Population

All PK analyses will be based on all patients for whom PK assessments were made. PK analyses will be analyzed as treated. Patients will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete, where the PK analysis might be influenced. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

6.4.2 Pharmacokinetic Endpoints

6.4.2.1 Pharmacokinetic Primary Endpoint

The primary PK endpoint is the ratio of $C_{trough,SC}/C_{trough,IV}$ during Cycle 7. The serum rituximab C_{trough} at Cycle 7 will be measured at pre-dose of Cycle 8. The lower limit of the two-sided 90% CI should be above 0.80 in order to show non-inferiority of $C_{trough,SC}$ versus $C_{trough,IV}$.

6.4.2.2 Pharmacokinetic Secondary Endpoint

The secondary PK endpoint is the ratio of observed rituximab area under the serum concentration curve of Cycle 7 (AUC_{SC}/AUC_{IV}). A two-sided 90% CI will be constructed.

6.4.3 Other Pharmacokinetic Parameters

Following rituximab PK parameters for both of the treatment groups of R^{SC}-CHOP and R^{IV}-CHOP will be analyzed:

- Area under the serum concentration-time curve (AUC) over the rituximab dosing interval of Cycle 2
- Trough serum concentration (C_{trough}), i.e., serum concentration at the end of dosing interval before the next dose administration at other treatment cycles
- Maximum observed serum concentration (C_{max})
- Total clearance (serum) (CL_{ss})
- Volume of distribution at steady state (V_{ss})
- Terminal half-life ($t_{1/2}$) (if feasible or appropriate)

6.4.4 Analysis of Pharmacokinetic Parameters

PK parameters of rituximab will be estimated using standard non-compartmental analysis. The data may also be analyzed as appropriate by a population approach using a PK model previously developed in non-linear mixed effects modeling (NONMEM) (Gibiansky E 2016). The influence of covariates (e.g., body weight, age, gender, and concomitant medications) on PK parameters may be investigated.

Individual and mean serum rituximab concentration versus time data will be tabulated and plotted by treatment arms. The serum pharmacokinetics of rituximab will be summarized by estimating AUC, C_{trough}, C_{max}, total clearance, volume of distribution at steady state, and terminal half-life (as appropriate for data collected). Estimates for these PK parameters will be tabulated and summarized by treatment group (arithmetic mean, standard deviation (SD), percent arithmetic mean CV%, geometric mean, percent geometric mean coefficient of variation (CV% geo mean), median, minimum, and maximum). Inter-patient variability will be also evaluated.

Additional PK analyses may be conducted as appropriate.

6.5 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment.

6.5.1 Efficacy Endpoints

The efficacy endpoints include CRR at the end of the study treatment as determined by the IRC using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) and IWG for NHL 1999 Guidelines; ORR (CR+PR) at the end of the study treatment as

determined by the investigator and IRC using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014); and CRR at the end of the study treatment as determined by the investigator using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014).

CRR at the end of treatment assessment as determined by the IRC using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014), will be used as the key efficacy endpoint.

6.5.2 Analysis of Efficacy Endpoints

CRR at the end of treatment will be analyzed in frequency tables, including 95% two-sided CIs (Pearson-Clopper) by treatment group. For the difference in response rates, 95% two-sided CIs (Hauck-Andersen) will be calculated.

ORR (CR+PR) at the end of treatment will be analyzed in frequency tables including 95% two-sided CIs (Pearson-Clopper) by treatment group. For the difference in response rates, 95% two-sided CIs (Hauck-Andersen) will be calculated.

6.6 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one anti-drug antibody (ADA) assessment. The ADAs include anti-rituximab antibodies and anti-rHuPH20 antibodies. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, and PK endpoints may be analyzed and reported via descriptive statistics.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other externally generated electronic study data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC

submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 10 sites in China will participate to enroll approximately 50 patients.

Enrollment will occur through an Interactive Voice or Web-based response system (IxRS).

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, immunogenicity analyses and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Tumor response and progression will be evaluated by the investigator and the IRC.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional

monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Assessment/Procedure	Screening		Treatment Period				End of Treatment		Follow–Up (6 months)
			C1–3	C4		C5–8	TCV	ETTV [a]	
	Days –28 to –1	Days –14 to –1	D1	D1	Interim Assessment D19 (±3)	D1	6–8 weeks after last treatment	4–8 weeks after last treatment	12 weeks and 24 weeks after last treatment
Written informed consent [b]	x								
Inclusion/exclusion criteria	x								
Demographic information and medical history		x							
Height		x							
BSA		x							
Weight		x	x	x		x	x	x	x
Vital Signs		x	x	x		x	x	x	x
Complete physical exam [c]	x								
Targeted physical exam [d]			x	x	x	x	x	x	x
ECOG performance status [e]		x	x	x		x			x
DLBCL diagnosis, staging, and IPI score [f]	x								
B symptoms		x	x	x		x	x	x	x
Tumor assessment [g]	x				x		x	x	x
12-lead-ECG and LVEF	x						x	x	x

Appendix 1: Schedule of Activities (cont.)

Assessment/Procedure	Screening		Treatment Period				End of Treatment		Follow–Up (6 months)
			C1–3	C4		C5–8	TCV	ETTV [a]	
	Days –28 to –1	Days –14 to –1	D1	D1	Interim Assessment D19 (±3)	D1	6–8 weeks after last treatment	4–8 weeks after last treatment	12 weeks and 24 weeks after last treatment
Hematology and serum chemistry [h]		x	x	x	x	x	x	x	x
Coagulation (aPTT or PTT, PT, and INR)		x							
Pregnancy test (if applicable) [i]		x							x
Serology testing for HCV, HBV [j]		x							
Hepatitis B DNA on PCR (as indicated) [k]		x	x	x		x	x	x	x
Lumbar puncture for CSF (as indicated) [l]	x								
Bone marrow aspirate + biopsy (as indicated) [m]	x						x	x	
Study treatment [n]			x	x		x			
Rituximab PK sample [o]			x	x		x		x	x [p]
Anti-rHuPH20 antibody sample [q]			x[r]	x[r]		x[r]		x	x [s]
Anti-rituximab antibody sample			x[r]	x[r]		x[r]		x	x [s]

Appendix 1: Schedule of Activities (cont.)

Assessment/Procedure	Screening		Treatment Period				End of Treatment		Follow–Up (6 months)
			C1–3	C4		C5–8	TCV	ETTV [a]	
	Days –28 to –1	Days –14 to –1	D1	D1	Interim Assessment D19 (±3)	D1	6–8 weeks after last treatment	4–8 weeks after last treatment	12 weeks and 24 weeks after last treatment
Sample for quantitative immunoglobulins (IgA, IgG, and IgM)		x						x	x
Adverse events [t]	x	x	x	x	x	x	x	x	x
Concomitant medications [u]	x	x	x	x	x	x	x	x	x

BSA = body surface area; C = cycle; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CSF = cerebrospinal fluid; D = day; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; ETTV = early treatment termination visit, FACS = fluorescence-activated cell sorting; HBV = hepatitis B virus; HCV = hepatitis C virus; IPI = International Prognostic Index; IV = intravenous; LVEF = left ventricular ejection fraction; TCV = treatment completion visit, SC = subcutaneous.

Note: After the end of the study treatment period, all patients will be followed until the end of the study according to local practice for resolution of adverse events related to rituximab therapy, survival, disease status, and whether a new lymphoma treatment has been started. The visit window during each cycle of study treatment is ±3 days. The window for the treatment discontinuation/early treatment termination and post-treatment study visits is ± 1 week (unless otherwise specified).

[a] Patients who discontinue the study treatment prematurely are required to return to the clinic for an early termination visit within 4–8 weeks after the last dose of study treatment.

[b] Written informed consent must be obtained prior to any study-specific procedures (including screening evaluations) performed or any prohibited medications being withheld for purposes of study participation. Please see Section 4.5.1 for more details.

[c] Includes evaluation of the head, eyes, ears, nose, and throat, and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. See Section 4.5.3 for more details.

[d] A targeted physical examination should be limited to systems of primary relevance, including cardiovascular, respiratory, those associated with symptoms, and those with tumor assessment (lymph nodes, liver, and spleen).

[e] ECOG performance status must be ≤2 for inclusion of the patient into the study.

[f] Diagnosis of DLBCL before treatment must have included histological diagnosis and initial CD20 expression confirmation. See Section 4.1.1 for more details.

Appendix 1: Schedule of Activities (cont.)

	Screening		Treatment Period				End of Treatment		Follow–Up (6 months)
			C1–3	C4		C5–8	TCV	ETTV [a]	
Assessment/Procedure	Days –28 to –1	Days –14 to –1	D1	D1	Interim Assessment D19 (±3)	D1	6–8 weeks after last treatment	4–8 weeks after last treatment	12 weeks and 24 weeks after last treatment

[g] Tumor assessments will be based on PET-CT scans (or MRI scans, if CT scans are contraindicated) of the neck (if clinically indicated), chest, abdomen, and pelvis where applicable. PET-CT scans will be obtained at screening, interim response assessment (i.e., Day 19 [±3 days] of Cycle 4) and End of Treatment assessment (6–8 weeks after the last dose of study treatment or 4–8 weeks after last dose of study treatment for early discontinuation). All other imaging may be CT only (i.e., follow-up period [12 and 24 weeks after the last dose of study treatment]).

[h] Hematology will include hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent or absolute differential count. At screening, serum chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, phosphorus, total bilirubin, total protein, albumin, AST, ALT, LDH, alkaline phosphatase, uric acid, and calculated creatinine clearance. During Cycles 1–8 and the follow-up period, serum chemistry will include sodium, potassium, creatinine, calcium, total bilirubin, total protein, albumin, AST, ALT, LDH, alkaline phosphatase, and uric acid.

[i] A negative serum pregnancy test or a negative urine pregnancy test within 7 days prior to study treatment must be available both for pre-menopausal women (including those who have had a tubal ligation) and for women who are less than 2 years after the onset of menopause; if a negative serum test within 14 days prior to study treatment, a confirmatory urine pregnancy test must be within 1 week prior to study treatment start.

[j] Patients known to have HIV, hepatitis C, active hepatitis B, or signs or symptoms of other active and/or severe infection must not be included in the study. Serology should be performed according to clinical judgment before and during treatment with rituximab. Patients found to have HIV, hepatitis C, or active hepatitis B must either not start or must stop rituximab therapy and enter active follow-up. Local guidelines for patient consent to viral testing must be adhered to.

[k] Patients with occult or prior HBV infection may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing.

[l] Lumbar puncture is indicated for patients with high-risk disease or with one or more of the following sites of involvement: paranasal sinuses, testicular, paramenigeal, peri-orbital, CNS, paravertebral, or bone marrow.

[m] Bone marrow examinations are required at screening and should include biopsy for morphology. Repeat bone marrow examinations are required if the bone marrow was involved with tumor at screening and the repeat bone marrow examination is required to confirm a radiological assessment of complete response at the end of therapy.

[n] See details on administration schedule of the study treatment in Section 4.3.2.

Appendix 1: Schedule of Activities (cont.)

	Screening		Treatment Period				End of Treatment		Follow–Up (6 months)
			C1–3	C4		C5–8	TCV	ETTV [a]	
Assessment/Procedure	Days –28 to –1	Days –14 to –1	D1	D1	Interim Assessment D19 (±3)	D1	6–8 weeks after last treatment	4–8 weeks after last treatment	12 weeks and 24 weeks after last treatment

[o] See details on rituximab PK sample in Appendix 2.

[p] Samples for rituximab PK will be collected 24 weeks after last rituximab administration.

[q] Only patients who are randomized to rituximab SC will be assessed for anti-rHuPH20 antibodies.

[r] Samples are drawn within 2 hours pre-dose.

[s] Samples for anti-rituximab antibodies and anti-rHuPH20 antibodies will be collected 12 weeks and 24 weeks after last rituximab dose.

[t] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[u] Any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 28 days prior to initiation of study drug to study termination. Any new lymphoma treatment initiated after the baseline visit will be recorded as concomitant treatments.

Appendix 2
Schedule of Pharmacokinetic Samples (Treatment Period and Follow-Up Period)

For patients randomized to the rituximab IV arm:

Treatment Period									Follow-Up Period
	C1 [a]	C2 [b]	C3 [b]	C4 [b]	C5 [b]	C6 [b]	C7 [b]	C8 [b]	
Within 2 hr pre-dose	x	x	x	x	x	x	x	x	
Within 15 min of end of infusion	x	x			x		x		
24 hr post-dose (±4 hr) [c]		x					x		
Day 3 (±4 hr)		x					x		
Day 7 (±24 hr)		x					x		
Day 15 (±48 hr)		x					x		
Day 29 (±24 hr)								x	
24 wks (± 7 days) after the last rituximab dose									x

[a] Rituximab at Cycle 1 can be given on either Day 1 or Day 2, depending on institutional practice.

[b] Rituximab at Cycles 2 to 8 is to be given on Day 1.

[c] Defined as 24 hours (±4 hr) after start of the previous dosing.

For patients randomized to the rituximab SC arm:

	Treatment Period								Follow-Up Period
	C1 [a]	C2 [b]	C3 [b]	C4 [b]	C5 [b]	C6 [b]	C7 [b]	C8 [b]	
Within 2 hr pre-dose	x	x	x	x	x	x	x	x	
Within 15 min of end of infusion	x								
24 hr post-dose (±4 hrs) [c]		x					x		
Day 3 (±4 hr) [d]		x					x		
Day 7 (±24 hr)		x			x		x		
Day 15 (±48 hr)		x					x		
Day 29 (±24 hr)								x	
24 wks (± 7 days) after the last rituximab dose									x

[a] Rituximab at Cycle 1 can be given on either Day 1 or Day 2, depending on institutional practice.

[b] Rituximab at Cycles 2 to 8 is to be given on Day 1.

[c] Defined as 24 hours (±4 hr) after start of the previous dosing.

[d] Defined as 48 hours (±4 hr) after start of the previous dosing.

Appendix 3
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.
7. Collect blood samples for immunogenicity testing (i.e., anti-rituximab antibody samples [in all patients] and anti rHuPH20 antibody samples [only in patients randomized to the SC arm])
8. Ask the patient to return for immunogenicity sample collection at the time of washout, if appropriate.

Appendix 4
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

Response should be determined on the basis of radiographic and clinical evidence of disease. For the end of treatment assessment, an FDG-PET (18F fluorodeoxyglucose positron emission tomography)/CT (computed tomography) scan will be performed 6–8 weeks after Cycle 6, Day 1 or the final dose of study treatment, as assessed by an Independent Review Committee and the investigator. Assessment of the PET-CT scan should follow the criteria presented below (Cheson et al. 2014).

Target and Non-Target Lesions

Up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. At baseline, a measurable node must be greater than 15 mm in longest diameter (LDi). Measurable extranodal disease may be included in the six representative, measured lesions. At baseline, measurable extranodal lesions should be greater than 10 mm LDi.

All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-measured disease as non-target lesions (e.g., cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, bone marrow).

Split Lesions and Confluent Lesions

Lesions may split or may become confluent over time. In the case of split lesions, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression. In the case of confluent lesions, the PPD of the confluent mass should be compared with the sum of the PPDs of the individual nodes, with more than 50% increase in PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and smallest diameter (SDi) are no longer needed to determine progression.

Appendix 4 Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to $\leq$1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Appendix 4 Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

Response and Site	PET-CT–Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable

Appendix 4 Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

Response and Site	PET-CT–Based Response	CT-Based Response
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Appendix 4 Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly (>13 cm), the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Appendix 4 Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography (scan); PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1 = no uptake above background; 2 = uptake ≤mediastinum; 3 = uptake >mediastinum but ≤liver; 4 = uptake moderately >liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

Appendix 5
International Prognostic Index and Ann Arbor Staging Classification

International Prognostic Index

Risk factors	
Ann Arbor Stage III or IV	
Age >60 years	
Elevated lactate dehydrogenase	
ECOG performance status ≥2	
Extranodal involvement ≥2	
IPI risk group	**Number of IPI risk factors**
Low	0 or 1
Low-intermediate	2
High-intermediate	3
High	4 or 5

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index.

Ann Arbor Staging Classification for Hodgkin and Non-Hodgkin's Lymphoma [a]

Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) [b]
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE) or both (IIIES)
Stage IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

[a] All cases are subclassified to indicate the absence (A) or presence (B) of the systemic ("B") symptoms of significant unexplained fever (>38°C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis. Clinical stage refers to the extent of disease determined by diagnostic tests following a single diagnostic biopsy. If a second biopsy of any kind is obtained, even if negative, the term pathologic stage is used.

[b] The designation "E" generally refers to extranodal contiguous extension (i.e., proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the only site of disease should be classified as IE rather than Stage IV.

Adapted from:

1. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971;31:1860–1.
2. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630–6.

Appendix 6
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about $>$ 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead