

Official Title: Open Label, Single-Arm, Phase IIIb Clinical Trial to Evaluate the Safety of Switching From Intravenous Rituximab to Subcutaneous Rituximab During First Line Treatment for CD20+ Non-Hodgkin's Follicular Lymphoma and Diffuse Large B-Cell Lymphoma.

NCT Number: NCT01987505

Document Date: Protocol Version 1: 30-May-2013



TITLE: OPEN LABEL, SINGLE-ARM, PHASE IIIb CLINICAL TRIAL TO EVALUATE THE SAFETY OF SWITCHING FROM INTRAVENOUS RITUXIMAB TO SUBCUTANEOUS RITUXIMAB DURING FIRST LINE TREATMENT FOR CD20+ NON-HODGKIN'S FOLLICULAR LYMPHOMA AND DIFFUSE LARGE B-CELL LYMPHOMA.

PROTOCOL NUMBER: ML28943
VERSION NUMBER: 1
EUDRACT NUMBER: 2013-001118-14
IND NUMBER: N/A
TEST PRODUCT: Rituximab (RO 45-2294)

SPONSOR: Roche Farma, S.A
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DATE FINAL: 30 May 2013

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Date: 30 MAY 2013

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PROTOCOL ACCEPTANCE FORM

TITLE: Open label, single-arm, phase IIIb clinical trial to evaluate the safety of switching from intravenous rituximab to subcutaneous rituximab during first line treatment for CD20+ Non-Hodgkin's Follicular Lymphoma and Diffuse Large B-cell Lymphoma..

PROTOCOL NUMBER: ML28943

VERSION NUMBER: 1.0

EUDRACT NUMBER: 2013-001118-14

IND NUMBER: N/A

TEST PRODUCT: Rituximab (RO 45-2294)

MEDICAL MONITOR: [REDACTED]
[REDACTED]

SPONSOR: Roche Farma, S.A

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

TITLE:	Open label, single arm, phase IIIb clinical trial to evaluate the safety of switching from intravenous rituximab to subcutaneous rituximab during first line treatment for CD20+ Non-Hodgkin's Follicular Lymphoma and Diffuse Large B-cell Lymphoma
PROTOCOL NUMBER:	ML28943
VERSION NUMBER:	1.0
EUDRACT NUMBER:	2013-001118-14
IND NUMBER:	N/A
TEST PRODUCT:	Rituximab (RO 45-2294)
PHASE:	IIIb
INDICATION:	CD20+ diffuse large B-cell lymphoma or CD20+ follicular non-Hodgkin's lymphoma grade 1, 2 or 3a
SPONSOR:	Roche Farma, S.A

Objectives

Primary Objective

- To evaluate the incidence of administration-associated reactions (AARs) following multiple doses of subcutaneous (SC) rituximab during Induction and/or Maintenance therapy in patients with CD20+ follicular non-Hodgkin's lymphoma (NHL) or CD20+ diffuse large B-cell lymphoma (DLBCL) who have previously received at least one dose of intravenous (IV) rituximab.

AARs are defined as all adverse events (AEs) occurring within 24 hours of rituximab SC administration and which are considered related to study drug. AARs include infusion/injection-related reactions (IIRRs), injection-site reactions, administration site conditions and all symptoms thereof.

Secondary Objectives

- To further evaluate the safety of rituximab SC in terms of:
 - Grade \geq 3 AEs
 - Grade \geq 3 IIRRs
 - Serious adverse events (SAEs)
- To evaluate the efficacy of rituximab SC in terms of:
 - event-free survival (EFS)
 - progression-free survival (PFS)
 - overall survival (OS)

- disease-free survival (DFS)
- Treatment response rate 4-6 weeks after the last dose of Induction classified as follows (see [Appendix 3](#)): complete response (CR) (including complete response unconfirmed (CRu), partial response (PR), stable disease (SD) and progression disease (PD).

Exploratory Objectives

Patient reported outcomes

- To evaluate and compare the methods of rituximab administration (SC vs IV) in terms of patients' satisfaction using the "Rituximab Administration Satisfaction Questionnaire" (RASQ) provided in [Appendix 7](#).
- To assess patients' quality of life and utilities by EUROQoL 5D instrument.

Study Design

Description of Study

This is an open-label, single-arm -clinical trial to evaluate the safety of switching from IV rituximab to SC rituximab administered during first line treatment for FL (Induction and/or Maintenance therapy) or DLBCL (treatment plus 24 months of follow up).

This study will include adult patients with CD20+ DLBCL or CD20+ follicular NHL (grades 1, 2 or 3a; NHL), who have already received at least one full dose of IV rituximab during induction or maintenance. Patients receiving Induction therapy must be eligible to receive at least 4 cycles of rituximab SC in addition to standard chemotherapy. Patients receiving Maintenance therapy must be eligible to receive at least 6 cycles of rituximab SC.

During administration of rituximab SC, patients will be assessed for safety and efficacy as detailed in the **Schedule of Assessments** (see [Appendix 1](#) and [Appendix 2](#)).

Induction Therapy:

Patients receiving Induction therapy prior to entry into the study must be eligible to receive at least four further cycles of rituximab SC.

A single staging visit 4-6 weeks after the end of Induction treatment will be required for patients with follicular NHL before continuing to Maintenance treatment and as part of efficacy assessment in patients with DLBCL.

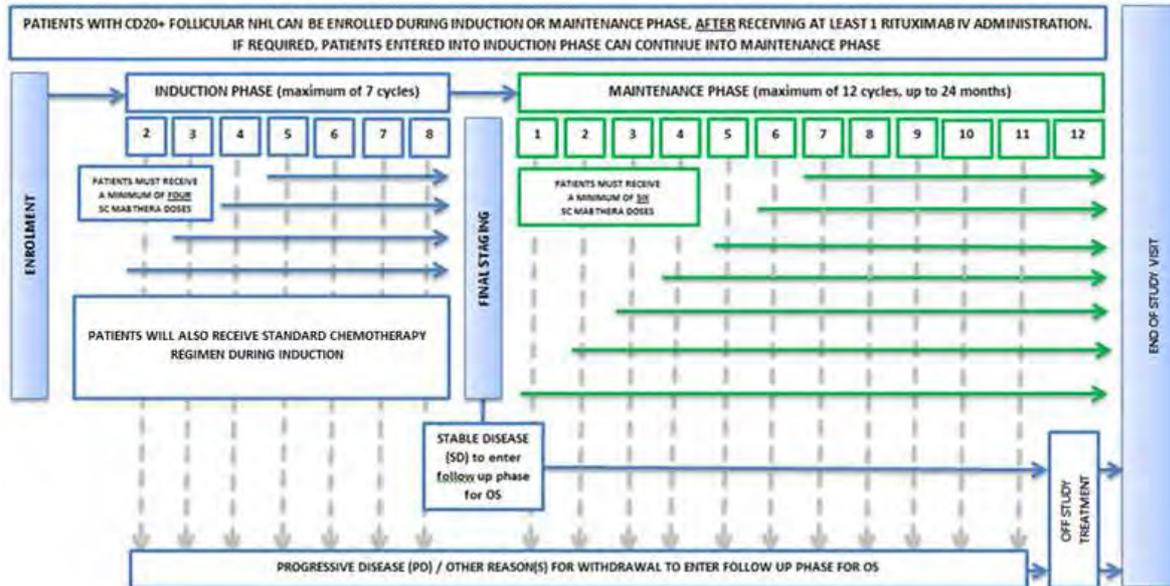
For those patients who finish the induction therapy and start the maintenance therapy, the first dose of maintenance rituximab SC will be given within 8-12 weeks after the last dose of induction rituximab SC.

Maintenance Therapy (patients with follicular NHL):

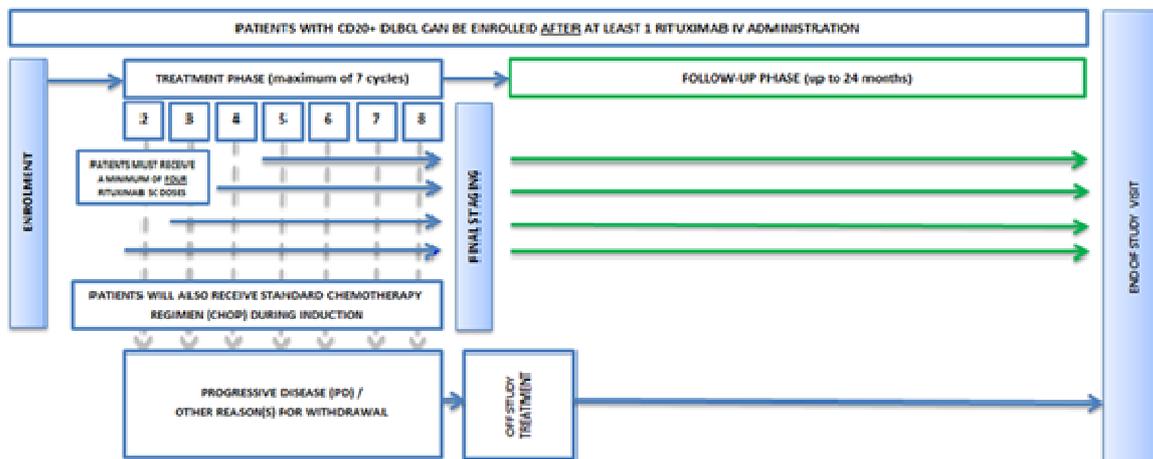
Patients receiving Maintenance therapy prior to entry into the study must be eligible to receive at least six further cycles of rituximab SC (i.e. 12 additional months of Maintenance treatment). Patients who are continuing into Maintenance therapy following at least four cycles of rituximab SC during Induction Therapy must also be eligible to receive at least six cycles of rituximab SC (i.e. 12 additional months of Maintenance treatment).

Figure 1: enrollment conditions

a) Patients with CD20+ Follicular NHL



b) Patients with CD20+ DLBCL



Number of Patients

A total of 139 patients will be recruited into this study.

Target Population

The target population will consist of adults with CD20+ DLBCL or CD20+ follicular NHL grade 1, 2 or 3a, according to the World Health Organization (WHO) classification system, undergoing first line treatment with intravenous rituximab treatment as per local clinical practice.

Inclusion Criteria

Patients must meet the following criteria for study entry:

Subject related criteria

1. Signed, written informed consent form
2. Age \geq 18 and \leq 80 years at time of enrolment
3. Eastern Cooperative Oncology Group (ECOG) performance status \leq 3 (see [Appendix 4](#)).

Disease related criteria

4. Histologically confirmed, CD20+ DLBCL or CD20+ follicular NHL grade 1, 2 or 3a, according to the WHO classification system.
5. Induction only:
 - a. For DLBCL: An International Prognostic Index (IPI) score of 1-4 or IPI score of 0 with bulky disease, defined as one lesion \geq 7.5 cm (see [Appendix 4](#)).
 - b. For FL: Follicular Lymphoma International Prognostic Index (FLIPI) (low, intermediate or high risk). Patients with FL should also meet GELF criteria to initiate treatment (see [Appendix 4](#))
6. Induction only: At least one bi-dimensionally measurable lesion defined as \geq 1.5 cm in its largest dimension on computed tomography (CT) scan

NHL Treatment related criteria

7. Currently being treated with rituximab IV as first line Induction or Maintenance therapy, having received at least one full dose of rituximab IV, defined as standard full dose of rituximab IV 375 mg/m² administered without interruption or early discontinuation because of tolerability issues
8. Expectation and current ability for the patient to receive at least four additional cycles of treatment during the Induction phase or six additional cycles of treatment during the Maintenance phase (patients with follicular NHL)

Exclusion Criteria

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

Cancer-Related Criteria

1. Transformed lymphoma or follicular lymphoma (FL) 3b
2. Primary central nervous system lymphoma, , primary effusion lymphoma, primary mediastinal DLBCL, DLBCL of the testis, primary cutaneous DLBCL or histologic evidence of transformation to a Burkitt lymphoma
3. History of other malignancy that could affect compliance with the protocol or interpretation of results. This includes a malignancy that has been treated but not with curative intent, unless the malignancy has been in remission without treatment for \geq 5 years prior to dosing. Note: 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 for the study.

Prior or Concomitant Treatments

4. Ongoing corticosteroid use > 30 mg/day of prednisone or equivalent. Note: patients receiving corticosteroid treatment with ≤ 30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to start of dosing

Laboratory Assessments at Screening

5. Inadequate renal function, defined as:
 - Creatinine > 1.5 times the upper limit of normal (ULN) (unless normal creatinine clearance), or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)
6. Inadequate hematologic function, defined as:
 - Haemoglobin < 9 g/dL
 - Absolute neutrophil count < $1.5 \times 10^9/L$
 - Platelet count < $75 \times 10^9/L$ (Note: abnormalities outside this range are allowed if related with involvement of bone marrow by the underlying disease)
7. Inadequate hepatic function, defined as:
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN
 - Total bilirubin ≥ 1.5 x ULN. Note: patients with documented Gilbert disease may be enrolled if total bilirubin is ≤ 3.0 x ULN

Other Prior or Current Medical Conditions or Treatments

8. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
9. For patients with DLBCL - Contraindication to any of the individual components of CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone), including prior receipt of anthracyclines. For patients with FL – contraindication to standard chemotherapy.
10. Other serious underlying medical conditions, which, in the Investigator's judgment, could impair the ability of the patient to participate in the study (e.g., significant cardiovascular disease, uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease)
11. Recent major surgery (within 4 weeks prior to dosing), other than for diagnosis
12. Active and/or severe bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics except if for tumour fever) within 4 weeks prior to dosing.
13. Active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection (must be ruled out during Screening). [Note: Patients with hepatitis B or C positive serology testing (i.e. positive hepatitis B virus antibodies serology or positive hepatitis C virus antibodies serology) but with undetectable viral load (i.e. negative PCR for HBV RNA or HCV RNA) may be included].
14. History of human immunodeficiency virus (HIV) seropositive status

General Criteria

15. Inability to provide informed consent and comply with protocol requirements.

16. Life expectancy of less than 6 months
17. A positive serum pregnancy test in women of childbearing potential within 7 days prior dosing or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to dosing. Women of childbearing potential are defined as pre-menopausal women or women who are < 2 years after the onset of menopause and are not surgically sterile
18. Fertile men or women of childbearing potential who do not agree to use a highly effective measure of contraception (such as oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) throughout the study and for at least 12 months after the last dose of rituximab.

Length of Study

The study is estimated to take approximately 3.5 years based on an approximately 12 month recruitment period, a maximum of 32 months of study duration.

Since patients can be included in different moments of their Induction or Maintenance treatment with IV rituximab, the largest duration of the study treatment with SC rituximab could range from:

- Up to 7 months, for those undergoing Induction rituximab SC treatment only.
- Up to 32 months (i.e. 7 months of induction, 1 month after for staging and 24 months of maintenance) for those undergoing Induction rituximab SC treatment followed by Maintenance rituximab SC treatment (patients with follicular NHL)

In addition to receiving induction therapy (up to 7 months duration), at least 24 months of follow-up will be required for patients with DLBCL. For patients with FL who complete or withdraw study treatment before the end of study, follow-up visits will be done as per clinical practice [i.e. every 3 months (\pm 2 weeks) for the first year after the last dose of rituximab SC and every 6 months (\pm 2 weeks) for the second year after the last dose of rituximab SC] until the end of study.

End of Study

The end of the study will occur up to 32 months after the last study patient has been enrolled.

Safety Outcome Measures

Safety outcomes will include AARs (defined as all related AEs occurring within 24 hours of rituximab SC administration, including IIRRs, injection-site reactions, administration site conditions and all symptoms thereof), grade \geq 3 AEs, - and SAEs. Other safety assessments include routine safety laboratory tests, vital signs measurements and changes in concomitant medications. All clinical AEs and SAEs as well as laboratory abnormalities (i.e. treatment emergent laboratory abnormalities that satisfy one or more of the following conditions for clinical significance: accompanied by clinical symptoms; leading to a change in study drug; requiring a change in concomitant therapy) will be recorded. Grading will be completed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (See [Appendix 6](#)).

Efficacy Outcome Measures

Tumour assessments will be done according to the protocol schedule of assessments (See [Appendix 1-Appendix 2](#)) based on imaging tests used as per clinical practice.

Response assessments 4-6 weeks after the last dose of Induction treatment will be based on the Investigator's assessment, completed according to the International Working Group (IWG) response criteria ([Cheson et al. 1999](#), see [Appendix 3](#)) or local standard practice.

The efficacy of rituximab SC will be evaluated during Induction and/or Maintenance in terms of EFS, PFS, OS, CR/CRu, PR, SD, PD and DFS.

EFS is defined as the time from first dose of rituximab IV to first occurrence of progression or relapse, according to the IWG response criteria (Cheson et al. 1999, see Appendix 3) or initiation of a non-protocol-specified anti-lymphoma therapy or death, whichever occurs first.

PFS is defined as the time from first dose of rituximab IV to the first occurrence of progression or relapse, according to the IWG response criteria (Cheson et al. 1999, see Appendix 3) or death from any cause.

OS is defined as the time from first dose of rituximab IV to death from any cause.

DFS will be assessed in patients achieving CR/CRu and is defined as the period from the date of the initial CR/CRu until the date of relapse or death from any cause.

CR/CRu is complete response or complete response unconfirmed and will be measured 4-6 weeks after the last dose of Induction treatment. PR (Partial Response), SD (Stable disease) and PD (Progression disease) will also be measured after last dose of induction treatment.

Exploratory Outcome Measures

- [REDACTED]

Patient-Reported Outcome Measures

- To evaluate and compare the methods of rituximab administration (SC vs IV) in terms of patients' satisfaction using the "Rituximab Administration Satisfaction Questionnaire" (RASQ) provided in Appendix 7.
- To assess patients' quality of life and utilities by EUROQoL 5D instrument.

Study Intervention and Study Drug

The term "study intervention" will be used to refer to the switching from rituximab IV to rituximab SC. The term "study drug" will be used throughout the protocol to refer to rituximab SC.

Investigational Medicinal Product

Rituximab SC - The rituximab SC dose is 1400 mg for all patients, independent of patient body surface area (BSA). This translates into an injection volume of 11.7 mL.

Each administration will consist of a single SC injection of rituximab 1400 mg independent of BSA.

Induction therapy: rituximab SC will always be administered **prior** to the selected chemotherapy regimen (with the exception of the corticosteroid component in CHOP regimens), on average of once a month for a minimum of four cycles.

Maintenance therapy (patients with follicular NHL): rituximab SC will be administered at 2-month intervals for a minimum of six cycles, according to local standards of care.

Comparator

Not applicable.

Statistical Methods

Safety will be assessed on the following safety parameters: AARs, including IRRs, AEs, AEs of grade ≥ 3 , SAEs, routine laboratory parameters, vital signs, concomitant medications, premature withdrawal from the study and from study medication due to AEs or ECOG performance status.

The incidence of AARs, AEs, AEs leading to premature discontinuation or interruption of study treatment, SAEs, grade ≥ 3 AEs will be estimated with 95%-Clopper-Pearson confidence intervals. The incidence of each AE will be summarized by the primary system-organ class and by preferred term. The incidence of deaths and cause of deaths will be listed and summarized.

Laboratory parameters will be summarized and select laboratory parameters may also be displayed graphically.

Vital signs will be summarized over time.

ECOG performance status will be summarized by frequency tables over time and percentage of patients in different categories will be presented by bar charts at different time points.

Concomitant medication will be coded according to the WHO DRUG dictionary and tabulated in summary tables.

All safety analyses will be based on the Safety population.

The analysis of this study will be exploratory and will primarily make use of descriptive statistical methods. In addition, exploratory statistical testing and modelling will be used to highlight interesting aspects of the data. All tests will be two-sided and carried out with a 5% α -error rate without correction for multiplicity.

All enrolled patients who receive at least one dose of study medication will be included in the Safety Population, which will be the primary analysis population for safety parameters. All enrolled patients will be included in the Intent-to-Treat (ITT) population. Efficacy parameters and patient reported outcome measures will be analysed separately using subsets of the ITT population for patients undergoing Induction therapy, Induction + Maintenance therapy and Maintenance therapy. Other analysis populations may be defined based on more restrictive criteria, such as fulfilment of eligibility criteria or a minimum duration of the observation period.

Endpoint and Analysis

The proportion of patients experiencing at least one AAR will be estimated with 95%-Clopper-Pearson confidence intervals.

[REDACTED]

For EQ-5D analysis, the proportion of subjects reporting problems in mobility, self-care, usual activities, pain/discomfort and anxiety/depression will be calculated

The RASQ is a 19-item questionnaire measuring the impact of the mode of treatment administration on five domains: Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. Descriptive statistics will be presented by domain and timepoint, for the total sample. Listings will present by patient data for individual responses and domain scores.

The analysis of endpoints measured as a time to event (EFS, PFS, OS and DFS) is based on the survivor function, which is the probability of remaining event-free beyond a certain point in time. The survivor function will be estimated using Kaplan-Meier methodology and summarized using the range, the 25th and 75th percentiles and median survival along with a 95% confidence interval for median survival.

Endpoints resulting in an incidence rate (e.g. CR/CRu) will be summarised with a 95% Clopper-Pearson confidence interval.

Determination of Sample Size

A total of 139 patients will be recruited into this study.

The incidence of AAR is deemed of primary interest for this study. Based on the results of a recent study, the most frequent AAR with SC rituximab is the injection site-erythema (10%) ([Davies et al. 2012](#)). If this endpoint is achieved by 10% of a sample size of 139 evaluable study patients, the two sided 95% confidence will have a maximum imprecision of $\pm 5\%$. The precision of these estimates is considered sufficient to address the main objective of the study.

Interim Analyses

Two interim analyses are planned:

- The first interim analysis will be done one year after the end of recruitment (i.e. one year after last patient first visit).
- The second interim analysis will be done at the end of study treatment (i.e. last patient end of treatment visit).

Study Procedures

See [Schedule of Assessments](#), [Appendix 1- Appendix 2](#).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
aaIPI	Age-adjusted International Prognostic Index
AAR	Administration-associated reaction
AE	adverse event
ALT (SGPT)	alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST (SGOT)	aspartate aminotransferase
BSA	body surface area
BUN	blood urea nitrogen
CEC	Clinical Events Committee
CHO	Chinese hamster ovary
CHOP	cyclophosphamide, oncovine (vincristine), doxorubicin, prednisone/prednisolone
CHOP-21	CHOP given every 21 days
CHOP-14	CHOP given every 14 days
CHVP	cyclophosphamide, doxorubicin, etoposide, prednisone/prednisolone
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CR	complete response
CRF	Case report form
CRu	complete response unconfirmed
CRO	contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	Minimal plasma concentration prior to next drug administration
CVP	cyclophosphamide, vincristine, prednisone/prednisolone
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival

Abbreviation	Definition
EGSG	East German Study Group
EU	European Union
FDA	Food and Drug Administration
FDG-PET	[18F]deoxyglucose positron emission tomography
FFS	failure-free survival
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
G-CSF	granulocyte colony-stimulating factor
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GLSG	German Low-Grade Lymphoma Study Group
HACA	human antichimeric antibody
HAMA	human anti-mouse antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSMB	Independent Data Safety Monitoring Board
IFN	interferon- α
IMP	investigational medicinal product
INR	International Normalized Ratio
IPI	International Prognostic Index
IRC	Independent Review Committee
IRF	Independent Review Facility
IRR	Infusion-related reaction
IIRR	infusion/injection-related reaction
ITT	Intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LDH	lactate dehydrogenase
LPLV	last patient, last visit
MCP	mitoxantrone, chlorambucil, prednisone/prednisolone
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MInT	MabThera international trial
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
NIMP	Non-investigational medicinal product
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
PT	Prothrombin Time
QoL	Quality of life
RBC	red blood cell count
RCR	Roche Clinical Repository
R-CHOP	rituximab plus CHOP chemotherapy
RCT	randomized controlled trial
R-CVP	rituximab plus CVP chemotherapy
R-CHVP	rituximab plus CHVP chemotherapy
rHuPH20	recombinant human hyaluronidase
R-MCP	Rituximab plus MCP chemotherapy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SPD	sum of the products of the greatest diameters
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWT	Satisfaction with Therapy

Abbreviation Definition

TLS	Tumour lysis syndrome
TNLT	time to next lymphoma treatment
TTF	time to treatment failure
TTP	time to tumour progression
ULN	upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma (NHL), a heterogeneous group of lymphoproliferative malignancies, is one of the leading causes of cancer death in the United States (US) and Europe. NHL accounted for 3.2% of new cancer cases and 2.8% of cancer deaths in Europe in 2006, making it the 8th leading cause of new cancer cases and the 10th leading cause of cancer deaths (Ferlay *et al*, 2007). NHL has been classified into two types: aggressive (i.e. fast growing) and indolent (i.e. slow growing) (Landis *et al*. 1999). Indolent NHL comprises a group of incurable, generally slow-growing lymphomas that are highly responsive to initial therapy and are characterized by a relapsing and progressive course. Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of NHL (Swerdlow S *et al*, 2008). Follicular lymphoma (FL) is the most common of the indolent NHLs (Friedberg, 2008), accounting for 20-25% of all lymphomas.

1.1.1 Current Management

The CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone) regimen, administered every 21 days (and every 14 days in some countries), has been the standard therapy for DLBCL for over three decades (Michallet and Coiffier, 2009; Niitsu 2010). However, the cure rate with CHOP is considered suboptimal, with 3-year progression-free survival (PFS) and overall survival (OS) rates of about 40% and 50%, respectively (Fisher *et al*. 1993). Rituximab, a genetically engineered chimeric monoclonal antibody that specifically binds to CD20, is the first monoclonal antibody approved for the treatment of B-cell lymphoma. The addition of rituximab to chemotherapy has improved PFS and OS of patients with DLBCL (Niitsu 2010). Based on randomized controlled trials (RCTs) demonstrating that the addition of rituximab to CHOP (R-CHOP) improved disease-free survival (DFS), event-free survival (EFS) and OS, R-CHOP has become the standard of care in DLBCL. Rituximab administration on Day 1 of each treatment cycle is also convenient (Habermann 2007).

Since approval was granted for the use of rituximab in the first-line treatment of patients with CD20+ DLBCL in combination with CHOP or other anthracycline-based chemotherapy regimens, rituximab has been recommended in relevant guidelines as standard therapy in the treatment of DLBCL (Tilly and Dreyling 2010; Keating 2010; NCCN 2011).

The scale of therapeutic options for FL is wide and ranges from a watch-and-wait policy to aggressive alternatives, such as haematopoietic stem cell transplant. There are several reports of significant improvements in the clinical course of the disease over the past decades (Swenson *et al* 2005; Fisher *et al*, 2005). However, the most striking outcome improvement has been achieved with the introduction of anti-CD20 monoclonal antibodies in combination with standard chemotherapy as demonstrated in several phase III studies (Marcus *et al*, 2005; Marcus *et al*, 2008; Hiddemann *et al*, 2005; Herold *et al*, 2007; Salles *et al*, 2008) and registry data (Pulte *et al*, 2008). The combination of rituximab with chemotherapy as first-line treatment has become the standard Induction therapy.

1.2 Background on Rituximab

Rituximab (RO 45-2294) is a chimeric murine/human monoclonal antibody that specifically binds to CD20, a hydrophobic trans-membrane protein present on the surface of B lymphocytes (Tedder and Engel, 1994).

Rituximab has had a large impact on the treatment of indolent non-Hodgkin's lymphoma (NHL). Its effectiveness as a single agent and in conjunction with known chemotherapy regimens has made it a standard of care in the treatment of NHL (Dreyling et al, 2001; Rodríguez-Abreu D et al, 2010; López-Guillermo A et al, 2011; OncoGuía LBDCG). The approved oncology indications for rituximab IV in the EU include, among others, the treatment of diffuse large B-cell (DLBCL) and follicular non-Hodgkin's lymphoma (FL).

1.2.1 Subcutaneous (SC) Rituximab

The available marketed formulation of rituximab is administered via intravenous (IV) injection. Recently a subcutaneous (SC) injection has been developed which is currently being studied for its clinical usage.

In contrast to the IV infusion, the rituximab SC injection takes only 5-6 minutes, and could thus significantly reduce the time a patient spends in the hospital and could eliminate hospital burdens associated with IV administration (e.g., nursing time for IV dosing, clinic space and utilities). It is therefore envisaged that an SC formulation of rituximab could bring significant clinically-meaningful benefits to patients and considerable economic reductions to healthcare providers.

Until now, the relatively large volume of the established rituximab IV dose has hindered the SC administration route for rituximab. By concentrating the IV rituximab formulation 12-fold and by adding recombinant human hyaluronidase (rHuPH20) as a novel excipient and a permeation enhancer, the injectable volume is no longer considered to be an issue. rHuPH20 hydrolyses hyaluronic acid fibres of the interstitial matrix allowing the installation of volumes larger than 2-3 mL and increasing the dispersion of locally injected drugs across a broad range of molecular weights without tissue distortion. rHuPH20 improves the PK profiles of large biopharmaceuticals administered via the interstitial route and drives the PK profile towards an IV administration profile. rHuPH20 was approved by the US Food and Drug Administration (FDA) in 2005. The approved indication includes 'hypodermoclysis', i.e. SC injection/infusion of fluid in large volume. Preclinical, clinical and extensive post-marketing experience with the rHuPH20 excipient used in the rituximab SC formulation has shown the component to be well-tolerated (Bookbinder et al. 2006; Frost 2007).

The results of a recently presented IV/SC pharmacokinetic/pharmacodynamic (PK/PD) cynomolgus monkey B cell depletion model study suggest that the SC versus IV dosing routes do not influence the pre-clinical efficacy of rituximab. Cynomolgus monkeys were treated twice, one week apart, with the rituximab SC formulation containing rHuPH20 or with IV rituximab. The results indicate similar rituximab trough concentrations in serum as well as similar B-cell depletion efficacy in both peripheral blood and distal secondary lymphoid tissue after IV and SC dosing (Del Nagro et al. 2010).

Study BP22333

Study BP22333 is a two-stage, randomized, open-label, multicentre phase Ib clinical study investigating the PK, safety and tolerability of SC rituximab Maintenance treatment in patients with previously treated or untreated FL (grade 1, 2 or 3a). This study was designed to determine and confirm the SC rituximab dose that yielded comparable C_{trough} to the standard IV dose (375 mg/m²) in the Maintenance setting. Results from Stage 1 have recently been reported (Salar *et al.* 2010). Based on modelling and simulation of PK data from Stage 1, a fixed dose of 1400 mg was established and considered to be non-inferior to the rituximab IV dose of 375 mg/m².

The initial results of Stage 2 of the BP22333 trial examining the rituximab levels after SC injection compared to IV injection (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 regimens and 1.12 (90% CI 0.86-1.45) for the 3-monthly treatment intervals in patients with CD20-positive indolent NHL during Maintenance. Additionally, the estimated area under the curve SC/IV ratio was 1.35 (90% CI 1.23-14.9) and 1.35 (1.23-1.48) for the two and three monthly regimens, respectively.

Preliminary safety data are available for 108 patients treated with a single SC dose in Stage 1 of study BP22333 (Cohorts B, 375 mg/m² SC, N=34; Cohort, 625 mg/m² SC, N=34; and Cohort D, 800 mg/m² SC, N=40). In addition, 16 patients had been enrolled in Cohort A (375 mg/m² IV). Overall, rituximab SC was well tolerated at all dose levels, with an adverse event (AE) profile comparable to that of rituximab IV.

A total of 65 patients experienced 157 AEs in the four cohorts combined, including 57 of the 108 patients receiving rituximab SC; see [Table 1](#). Observed AEs were mostly mild to moderate.

Table 1: Summary of Adverse Events from Stage 1 of Study BP22333

Cohort	Total Patients Enrolled	Patients with at least 1 AE	AEs	SAEs	CTC GRADE 1	CTC GRADE 2	CTC GRADE 3
A (375 mg/m ² IV)	16	8	27	1*	23	3	1
B (375 mg/m ² SC)	34	17	50	0	35	10	5
C (625 mg/m ² SC)	34	19	46	1	27	18	1
D (800 mg/m ² SC)	40	21	34	1	21	12	1

CTC: common terminology criteria; SAE: serious adverse event; SC: subcutaneous

* One additional SAE (major depression) was subsequently downgraded to a non-serious event.

Data available on clinical database as of September 28, 2010

Four serious adverse events (SAEs) were reported in four patients (appendicitis [Cohort A], hospitalization for transluminal angioplasty [Cohort C], major depression [Cohort A], subsequently downgraded to a non-serious event, and angina pectoris [Cohort D]). All were considered unrelated to study treatment. There have been no reports of serious or severe infections. There were no AEs leading to death, withdrawal or treatment discontinuation.

The most commonly documented AE was local administration-associated reactions (AARs; N = 30). AARs are defined as all AEs occurring within 24 hours of rituximab administration and considered related to study drug. AARs included IRRs, injection-site reactions, administration site conditions and all symptoms thereof. After AARs, the most common events were mild infections (N = 18) and gastrointestinal disorders (N = 17). The majority of AARs (85%) and of AEs overall (68%) were assessed as mild (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] grade 1), 27% of AEs as moderate (CTC grade 2) and the remaining 5% as severe (CTC grade 3), all of which resolved.

Safety data is now available from the comparative part of study BP22333 ([Salar et al, 2012](#)). Results showed that the incidence and intensity of AEs were generally balanced, as 79% of patients in each arm experienced AEs. Serious AEs were observed in 12% and 14% of patients in the SC and IV arms, respectively. No SAE occurred in > 1 patient in either treatment arm. Grade 3/4 AEs occurred in 18% and 17% of patients in the SC and IV arms, respectively. Neutropenia (2 patients in each arm) and arthralgia (2 patients in the IV arm) was the only grade 3/4 AE occurring in > 1 patient in either treatment arm. AARs were the most frequent AE and had a higher incidence in the SC arm (31% of SC vs 4% of IV patients). AARs consisted mostly of local reactions, and the most common in the SC arm were erythema (13%), injection site erythema (5%), and myalgia (5%).

Ongoing Clinical Studies

Two additional clinical studies with rituximab SC are ongoing . Study BO22334 (NCT01200758), investigating the PK, safety and efficacy of rituximab SC in combination with chemotherapy followed by rituximab SC Maintenance therapy in 530 patients with FL and study BO25431 (NCT01292603), investigating the PK and safety of rituximab SC in 200 patients with CLL. First interim results were presented at the American Society of Hematology (ASH) conference 2012.

Lastly, 3 phase IIIb trials have been initiated.

MO25455 will evaluate the efficacy in terms of PFS after randomization of rituximab SC in 770 patients with relapsed or refractory, indolent NHL who responded to induction and initial two years Maintenance therapy (Maintenance I), and were randomized to either prolonged rituximab maintenance until progression (Maintenance II) or observation. First interim results are expected in Q4/2013.

MO28107, study will investigate the efficacy of the combination of subcutaneous rituximab in combination with chemotherapy in patients with previously untreated diffuse large B cell lymphoma. First interim results are expected in Q4/2013.

MO28457 will evaluate patient preference with subcutaneous administration of rituximab versus intravenous rituximab in previously untreated patients with diffuse large B cell lymphoma or follicular lymphoma. First interim results are expected in Q1/2014.

Refer to the current rituximab SC IB for further details on nonclinical and clinical studies of rituximab SC.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study rationale

For safety reasons SC Rituximab should be given after at least one dose of IV Rituximab has been successfully administered ([IB for rituximab SC](#)). Therefore, in all the on-going clinical trials, SC dose is being administered after the first IV dose of Rituximab. However, in the clinical practice setting, given the fact that the SC injection could significantly reduce the burdens associated with IV administration (time, costs, patients preferences...), it is more likely that the switch to SC injection will occur at any point in time after the first dose of IV Rituximab, rather than only in the second cycle of the induction therapy. This scenario is particularly expected in patients who are undergoing long-term treatment with rituximab (i.e. maintenance for a maximum of 2 years). In this context, the aim of this pragmatic clinical trial is to evaluate the safety of switching from IV to SC Rituximab at any point in time during standard rituximab-based regimens administered to patients with previously untreated DLBCL or FL.

1.3.2 Benefits of Rituximab

The efficacy and safety of rituximab IV is well established. Rituximab IV is administered as an infusion over 3 to 4 hours. Frequently observed 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. 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 (i.e. IIRRs, long administration times, hospital facilities requirements, difficulty treating patients with poor venous access). SC administration of rituximab takes significantly less time (5-6 minutes) compared to IV infusion and this is expected to improve treatment convenience, patient satisfaction and compliance.

Based on modelling and simulation of PK data from Stage 1 of the dose-finding study BP22333 ([Salar A et al. 2010](#)), a fixed rituximab SC dose of 1400 mg has been found non-inferior to the rituximab IV dose of 375 mg/m² and selected for further investigation. BP22333 was the first-in-human adaptive two-stage study (Stage 1 and Stage 2) for selecting a rituximab SC dose that achieves non-inferior trough concentrations compared to those of rituximab IV, and comparing exposure and safety for the IV and SC formulations in patients with FL. Preliminary safety data collected for 108 patients treated with a single SC dose and 16 patients receiving standard rituximab IV in Stage 1 of study BP22333 indicate that rituximab SC was well tolerated, with an AE profile comparable to that of the IV formulation. A total of 65 patients experienced 157 AEs in the 4 cohorts combined, including 57 of the 108 patients receiving rituximab SC. Observed AEs were mostly mild to moderate and none required discontinuation of treatment. A total of 3 SAEs were reported, none of which were considered related to rituximab (SC or IV). Further details about the BP22333 study design, as well as PK and preliminary safety findings are provided in Section [1.2.1](#).

The safety profile and the efficacy of the rituximab SC formulation containing rHuPH20 are expected to be similar to those of the IV formulation. Preclinical, clinical and extensive post-marketing experience with the rHuPH20 excipient used in the SC formulation has shown the component to be well-tolerated. In addition, the SC route of administration may reduce the

risk and intensity of IIRRs compared to IV administration. For other monoclonal antibodies in other clinical settings the switch from IV to SC administration has resulted in an improved tolerability with less IIRRs, increased patient-convenience and improved cost-effectiveness (Stilgenbauer *et al.* 2009; Wynne *et al.* 2010; Moreau *et al.* 2011). For example, the administration of alemtuzumab by the IV route resulted in a significant proportion of patients experiencing IRRs; however these were rare or absent following SC administration (Stilgenbauer *et al.* 2009).

1.3.3 Mitigation of the Known Safety Risks of Rituximab

The safety of rituximab IV in patients with haematologic malignancies, including previously untreated DLBCL or follicular NHL is well characterised.

The contraindications for rituximab administration in NHL (known hypersensitivity to the active substance or to any of the excipients or to murine proteins, active, severe infections and severely immunocompromised state) are specified as exclusion criteria for the current study. The risk of hypersensitivity reaction to rituximab after SC injection is minimized by administering the rituximab SC formulation only to patients that have been previously treated with rituximab IV and who, consequently, are unlikely to have relevant quantities of circulating B-cells that may induce IIRRs, such as fever, or hypotension, upon their destruction through rituximab. In the event of an allergic reaction during administration of rituximab, standard treatment for hypersensitivity reactions (e.g. epinephrine [adrenaline], antihistamines and glucocorticoids), should be available for immediate use.

Rituximab is associated with IIRRs, which may be related to release of cytokines and/or other chemical mediators. Severe IIRRs might be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Severe IRRs with fatal outcome have been reported with rituximab IV during post-marketing use. Severe IIRRs usually manifested within 30 minutes to 2 hours after starting the first rituximab IV infusion, were characterized by pulmonary events and included, in some cases, rapid tumour lysis and features of TLS in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (Rituximab IV IB). In order to reduce the incidence and severity of IIRRs, it is recommended that all patients receive premedication with paracetamol (acetaminophen) and diphenhydramine hydrochloride (or alternative antihistamine), administered 30-60 minutes prior to each rituximab administration (see Section 4.4.1.1). Recommendations for TLS prophylaxis are also provided (see Section 4.4.1.2). Patients who were not able to receive the full dose of rituximab at Cycle 1 as a result of IIRRs will not continue in the study.

Use of rituximab may be associated with an increased risk of neurotoxicity, including PML. If PML is suspected based on any new or worsening neurological, cognitive or psychiatric symptoms or signs, further dosing will be suspended until PML has been excluded. The protocol provides guidance for management of neurotoxicity (see Section 5.1.3).

Although rituximab is not myelosuppressive when given as monotherapy, decreased red blood cell (RBC), leucocyte and platelet counts have been reported with the R-CHOP combination regimens. Therefore, only patients with adequate haematological function (defined as haemoglobin ≥ 9 g/dL, absolute neutrophil count $\geq 1.5 \times 10^9/L$ and platelet counts of $\geq 75 \times 10^9/L$), will be enrolled in the study. The protocol also provides guidance for management of haematological toxicities (see Section 5.1.3).

Angina pectoris or cardiac arrhythmia (such as atrial flutter and fibrillation), heart failure and myocardial infarction have occurred in patients treated with rituximab IV. Prospective study patients will therefore undergo an electrocardiogram (ECG) assessment at baseline, to rule out clinically significant abnormalities.

The potential risk of side effects at the injection site is minimized by instructing the study personnel and Investigators to pay special attention to the injection site and to report any findings in the case report form (CRF).

Patients treated with monoclonal antibodies may develop antibodies against these monoclonal antibodies potentially resulting in hypersensitivity reactions or attenuation of therapeutic effects. Patients with human anti-mouse antibody (HAMA) or human antichimeric antibody (HACA) titres may develop allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies (Kornbrot *et al.* 1994). The development of such antibodies is a rare event. In an integrated review of data from 356 patients, four patients developed a HACA response following treatment with rituximab IV. Two of these patients were retreated without problems. No correlation was seen between HACA response and loss of, or interference with, response to treatment.

In summary, the SC formulation is expected to bring significant and clinically meaningful benefits to patients in terms of improved tolerability with potentially fewer and less severe IIRRs. This expectation is based on the lower peak serum concentrations after administration, which are attained more slowly, as well as an improved treatment convenience due to the faster and more convenient SC administration. Therefore the overall risk-benefit assessment of this study is considered to be positive.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is as follows:

- To evaluate the incidence of AARs following multiple doses of rituximab SC during Induction and/or Maintenance therapy in patients with CD20+ follicular NHL or CD20+ DLBCL, who have previously received at least one dose of rituximab IV.

AARs are defined as all AEs occurring within 24 hours of rituximab SC administration and which are considered related to study drug. AARs include IIRRs, injection-site reactions, administration site conditions and all symptoms thereof.

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To further evaluate the safety of rituximab SC in terms of:
 - Grade \geq 3 AEs
 - Grade \geq 3 IIRRs
 - SAEs
- To evaluate the efficacy of rituximab SC in terms of:

- EFS
- PFS
- OS
- DFS
- complete response (CR) rate, unconfirmed (CRu), partial response (PR), stable disease (SD) and progressive disease (PD), 4-6 weeks after the last dose of Induction treatment (See [Appendix 3](#)).

2.3 EXPLORATORY OBJECTIVES

- [REDACTED]

2.4 PATIENT-REPORTED OUTCOME OBJECTIVES

- To evaluate and compare the methods of rituximab administration (SC vs IV) in terms of patients' satisfaction using the "Rituximab Administration Satisfaction Questionnaire" (RASQ) provided in Appendix 7.
- To assess patients' quality of life and utilities by EUROQoL 5D instrument.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview

This is an open-label, single-arm -clinical trial to evaluate the safety of switching from IV rituximab to SC rituximab administered during first line treatment for FL (Induction and or Maintenance therapy) or DLBCL(treatment plus 24 months of follow up).

This study will include adult patients with CD20+ DLBCL or CD20+ follicular NHL (grades 1, 2 or 3a; NHL), who have already received at least one full dose of IV rituximab during induction or maintenance. Patients receiving Induction therapy must be eligible to receive at least 4 cycles of rituximab SC in addition to standard chemotherapy. Patients receiving Maintenance therapy must be eligible to receive at least 6 cycles of rituximab SC.

During administration of rituximab SC, patients will be assessed for safety and efficacy as detailed in the [Schedule of Assessments](#) (see [Appendix 1- Appendix 2](#)).

Induction Therapy:

Patients receiving Induction therapy prior to entry into the study must be eligible to receive at least four further cycles of rituximab SC.

A single staging visit 4-6 weeks after the end of Induction treatment will be required for patients with follicular NHL before continuing to Maintenance treatment and as part of efficacy assessment in patients with DLBCL.

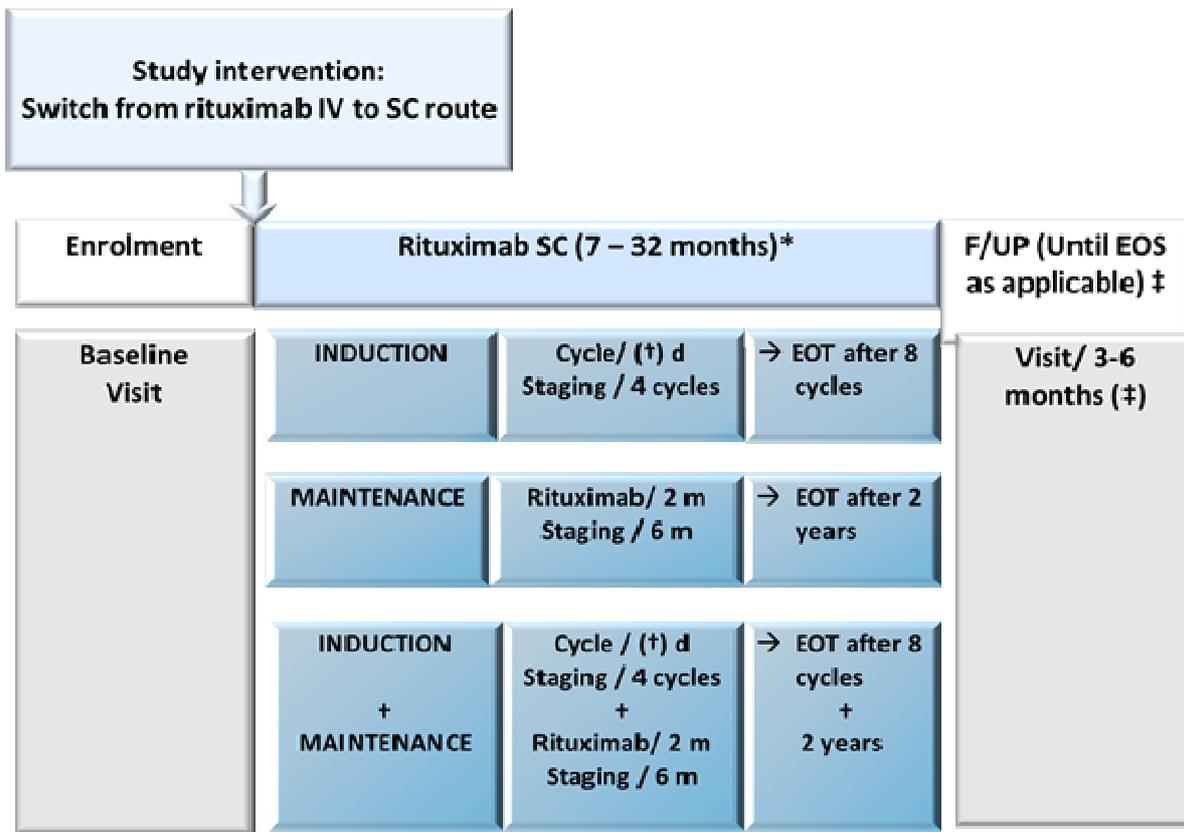
For those patients who finish the induction therapy and start the maintenance therapy, the first dose of maintenance rituximab SC will be given within 8-12 weeks after the last dose of induction rituximab SC.

Maintenance Therapy (patients with follicular NHL):

Patients receiving Maintenance therapy prior to entry into the study must be eligible to receive at least six further cycles of rituximab SC (i.e. 12 additional months of Maintenance treatment). Patients who are continuing into Maintenance therapy following at least four cycles of rituximab SC during Induction Therapy must also be eligible to receive at least six cycles of rituximab SC (i.e. 12 additional months of Maintenance treatment).

Figure 2: Study visits

Figure 2a: Patients with FL



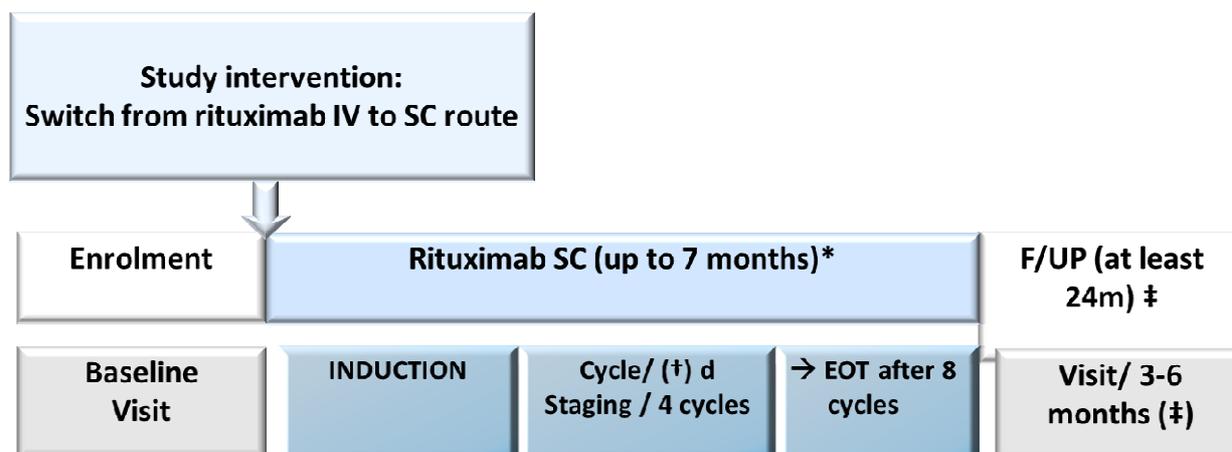
d=days; EOS=End of Study; EOT=end of treatment; IV=intravenous; m=months; SC=subcutaneous

() Study duration will depend on SC route initiation; after at least 1 rituximab IV infusion, and eligible to receive at least 4 further cycles of rituximab SC (for those undergoing Induction therapy) or 6 further administrations of rituximab SC (for those undergoing Maintenance therapy).*

(†) Induction cycles will be administered as per standard clinical practice,

(‡) For those patients who complete or withdraw study treatment before the end of study, follow-up visits will be done as per clinical practice (i.e. every 3 months (± 2 weeks) for the first year after the last dose of rituximab SC and every 6 months (± 2 weeks) for the second year after the last dose of rituximab SC) until the end of study.

Figure 2b: Patients with DLBCL



d=days; EOT=end of treatment; IV=intravenous; m=months; SC=subcutaneous

() Study duration will depend on SC route initiation: after at least 1 rituximab IV infusion, and eligible to receive at least 4 further cycles of rituximab SC*

(†) Induction cycles will be administered as per standard clinical practice,

(‡) Patients with DLBCL will be followed up for at least 24 months as per clinical practice [i.e. every 3 months (± 2 weeks) for the first year after the last dose of rituximab SC and every 6 months (± 2 weeks) for the second year after the last dose of rituximab SC].

3.2 END OF STUDY

The end of the study will occur up to 32 months after the last study patient has been enrolled.

3.3 RATIONALE FOR STUDY DESIGN

The objective of this clinical trial is to evaluate the safety of switching from IV to SC Rituximab at any point in time during standard rituximab-based regimens administered to patients with previously untreated DLBCL or FL. Given the expected change of the ARR profile after the switching to rituximab SC (Davies et al. 2012), the primary outcome of interest will be the incidence of AARs.

This will be a pragmatic clinical trial, in order to reproduce as much as possible real clinical practice conditions. Therefore, the diagnosis, the treatment and the follow up of the disease will be done as per local clinical practice (Rodríguez-Abreu D et al, 2010; López-Guillermo A et al, 2011; OncoGuía LBDCG).

3.3.1 Rationale for Test Product Dosage

Modelling and simulation of PK data from Stage 1 and initial results of Stage 2 of the aforementioned study BP22333 (NCT00930514) (Salar et al. 2010; Salar et al. 2012), indicate that the fixed dose of 1400 mg rituximab SC achieves trough levels that are non-inferior to the rituximab IV dose of 375 mg/m² in patients with previously treated or untreated FL (grade 1, 2 or 3a). Rituximab SC was well tolerated with an AE profile comparable to that

of rituximab IV. No SAEs related to rituximab SC were reported. A fixed SC dose of 1400 mg has therefore been selected for further clinical testing of rituximab SC in this study as well as ongoing registrational studies.

3.3.2 Rationale for Patient Population and Analysis Groups

The objective of this clinical trial is to evaluate the safety of switching from IV to SC Rituximab at any point in time during standard rituximab-based regimens. Given the fact that this switching could occur for patients undergoing Induction therapy or Maintenance therapy, the study population will include patients with CD20+ follicular non-Hodgkin's lymphoma (NHL) or CD20+ diffuse large B-cell lymphoma (DLBCL) who have previously received at least 1 dose of intravenous (IV) rituximab as part of a Induction or Maintenance therapy, and that are eligible to receive at least 4 further cycles of rituximab SC (for those undergoing Induction therapy) or 6 further administrations of rituximab SC (for those undergoing Maintenance therapy).

All enrolled patients who receive at least one dose of study medication will be included in the Safety Population, which will be the primary analysis population for safety parameters. Efficacy parameters and patient reported outcome measures will be analyzed separately for the population undergoing Induction therapy, Induction + Maintenance therapy and Maintenance therapy.

3.4 OUTCOME MEASURES

3.4.1 Safety Outcome Measures

Safety outcome measures will include AARs (defined as all related AEs occurring within 24 hours of rituximab SC administration, including IRRs, injection-site reactions, administration site conditions and all symptoms thereof), grade ≥ 3 AEs and SAEs. Other safety assessments include routine safety laboratory tests, vital signs measurements, and changes in concomitant medications. All clinical AEs and SAEs as well as laboratory abnormalities (i.e. treatment emergent laboratory abnormalities that satisfy one or more of the following conditions for clinical significance: accompanied by clinical symptoms; leading to a change in study drug; requiring a change in concomitant therapy) will be recorded. . Grading will be completed according to the NCI CTCAE version 4.0 (see [Appendix 6](#)).

3.4.2 Efficacy Outcome Measures

The efficacy of rituximab will be evaluated from the first dose of rituximab IV until the end of follow up, in terms of EFS, PFS, OS, CR/CRu, PR, SD, PD, DFS:

- **EFS** is defined as the time from first dose of rituximab IV to first occurrence of progression or relapse, according to the IWG response criteria ([Cheson *et al* 1999](#), see [Appendix 3](#)) or other country standards, or initiation of a non-protocol-specified anti-lymphoma therapy or death, whichever occurs first.
- **PFS** is defined as the time from first dose of rituximab IV to the first occurrence of progression or relapse, according to the IWG response criteria ([Cheson *et al* 1999](#), see [Appendix 3](#)) or other country standards, or death from any cause.
- **OS** is defined as the time from first dose of rituximab IV to until death from any cause.

- **DFS** will be assessed in patients achieving CR/CRu and is defined as the period from the date of the initial CR/CRu until the date of relapse or death from any cause.
- **CR/CRu**: Response assessments 4-6 weeks after the last dose of Induction treatment will be based on the Investigator’s assessment, completed according to the original International Working Group (IWG) response criteria for response assessment of lymphoma (Cheson et al. 1999; see [Appendix 3](#)) or local standard practice.
- **PR**: Partial response based on the Investigator’s assessment, completed according to the original International Working Group (IWG) response criteria for response assessment of lymphoma (Cheson et al. 1999; see [Appendix 3](#)) or local standard practice.
- **SD**: Stable disease based on the Investigator’s assessment, completed according to the original International Working Group (IWG) response criteria for response assessment of lymphoma (Cheson et al. 1999; see [Appendix 3](#)) or local standard practice.
- **PD**: Progressive disease based on the Investigator’s assessment, completed according to the original International Working Group (IWG) response criteria for response assessment of lymphoma (Cheson et al. 1999; see [Appendix 3](#)) or local standard practice.

3.4.3 Exploratory Outcome Measures

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

3.4.4 Patient-Reported Outcome Measures

- To evaluate and compare the methods of rituximab administration (SC vs IV) in terms of patients’ satisfaction using the “Rituximab Administration Satisfaction Questionnaire” (RASQ) provided in [Appendix 7](#).
- To assess patients’ quality of life and utilities by EUROQoL 5D instrument.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population will consist of adults with CD20+ DLBCL or CD20+ follicular NHL grade 1, 2 or 3a, according to the WHO classification system.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

Subject related criteria

1. Signed, written informed consent form
2. Age ≥ 18 and ≤ 80 years at time of enrolment
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3 (see Appendix 4)

Disease related criteria

4. Histologically confirmed, CD20+ DLBCL or CD20+ follicular NHL grade 1, 2 or 3a, according to the WHO classification system
5. Induction only
 - a. For DLBCL: An International Prognostic Index (IPI) score of 1-4 or IPI score of 0 with bulky disease, defined as one lesion ≥ 7.5 cm (see Appendix 4).
 - b. For FL: Follicular Lymphoma International Prognostic Index (FLIPI) (low, intermediate or high risk). Patients with FL should also meet GELF criteria to initiate treatment (see Appendix 4)
6. Induction only: At least one bi-dimensionally measurable lesion defined as ≥ 1.5 cm in its largest dimension on CT scan

NHL Treatment related criteria

7. Currently being treated with rituximab IV as first line Induction or Maintenance therapy, having received at least one full dose of rituximab IV, defined as standard full dose of rituximab IV 375 mg/m^2 administered without interruption or early discontinuation because of tolerability issues
8. Expectation and current ability for the patient to receive at least four additional cycles of treatment during the Induction phase or six additional cycles of treatment during the Maintenance phase (patients with follicular NHL)

4.1.2 Exclusion Criteria

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

Cancer-Related Criteria

1. Transformed lymphoma or FL3b
2. Primary central nervous system lymphoma, , primary effusion lymphoma, primary mediastinal DLBCL, DLBCL of the testis, primary cutaneous DLBCL or histologic evidence of transformation to a Burkitt lymphoma
3. History of other malignancy that could affect compliance with the protocol or interpretation of results. This includes a malignancy that has been treated but not with curative intent, unless the malignancy has been in remission without treatment for ≥ 5 years prior to dosing. Note: 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 for the study.

Prior or Concomitant Treatments

4. Ongoing corticosteroid use > 30 mg/day of prednisone or equivalent. Note: patients receiving corticosteroid treatment with ≤ 30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to dosing.

Laboratory Assessments at Screening

5. Inadequate renal function, defined as:
 - Creatinine > 1.5 times the upper limit of normal (ULN) (unless normal creatinine clearance), or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)
6. Inadequate hematologic function, defined as:
 - Haemoglobin < 9 g/dL
 - Absolute neutrophil count < $1.5 \times 10^9/L$
 - Platelet count < $75 \times 10^9/L$. (Note: abnormalities outside this range are allowed if related with involvement of bone marrow by the underlying disease)
7. Inadequate hepatic function, defined as:
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN
 - Total bilirubin ≥ 1.5 x ULN. Note: patients with documented Gilbert disease may be enrolled if total bilirubin is ≤ 3.0 x ULN

Other Prior or Current Medical Conditions or Treatments

8. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
9. For patients with DLBCL - Contraindication to any of the individual components of CHOP, including prior receipt of anthracyclines. For patients with FL – contraindication to standard chemotherapy.
10. Other serious underlying medical conditions, which, in the Investigator's judgment, could impair the ability of the patient to participate in the study (e.g., significant cardiovascular disease, uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease)
11. Recent major surgery (within 4 weeks prior to start of dosing, other than for diagnosis)
12. Active and/or severe bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics except if for tumour fever) within 4 weeks prior to dosing.
13. Active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection (must be ruled out during Screening) [Note: Patients with hepatitis B or C positive serology testing (i.e. positive hepatitis B virus antibodies serology or positive hepatitis C virus antibodies serology) but with undetectable viral load (i.e. negative PCR for HBV RNA or HCV RNA) may be included]

14. History of human immunodeficiency virus (HIV) seropositive status

General Criteria

15. Inability to provide informed consent and comply with protocol requirements.

16. Life expectancy of less than 6 months

17. A positive serum pregnancy test in women of childbearing potential within 7 days prior to dosing or within 14 days if with a confirmatory urine pregnancy test within 7 days prior dosing. Women of childbearing potential are defined as pre-menopausal women or women who are < 2 years after the onset of menopause and are not surgically sterile

18. Fertile men or women of childbearing potential who do not agree to use a highly effective measure of contraception (such as oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) throughout the study and for at least 12 months after the last dose of rituximab.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Not applicable, since it is an open label study with only one treatment group.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Rituximab SC

Rituximab for SC administration (MabThera® SC; RO 45-2294) is supplied as a ready-to-use liquid formulation with rituximab at a concentration of 120 mg/mL. Rituximab must not be diluted prior to administration. Furthermore, rituximab SC contains rHuPH20 as an excipient at a concentration of 2000 U/mL (manufactured in a Chinese Hamster Ovary [CHO] cell line) acting as a permeation enhancer, histidine/histidine-HCl (buffer), α,α -trehalose (bulking agent), methionine (stabilizer), and polysorbate 80 (surfactant) in water for injection at a pH of 5.5. The drug product is a sterile, colourless to yellowish, clear to opalescent liquid.

The rituximab SC dose is 1400 mg for all patients, independent of patient body surface area (BSA). This translates into an injection volume of 11.7 mL.

Rituximab SC will be supplied by Roche and shipped to the pharmacist of each centre by the local Roche affiliate or contract research organization (CRO) designee. Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

The recommended storage condition for rituximab SC is 2°C to 8°C, protected from light. From a microbiological point of view the product should be used immediately after first opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C. Batch specific details and information on shelf-life are given on the packaging label.

Under no circumstances the investigator should allow the study drug to be used other than as directed by the protocol.

For further details, see the rituximab SC IB.

4.3.2 Dosage, Administration and Compliance

Patients entering the study will already be receiving rituximab IV in the Induction or Maintenance setting. Where possible, rituximab SC should start in alignment with the next planned cycle start date.

Rituximab is always administered prior to chemotherapy (with the exception of the corticosteroid component). The day of rituximab administration in all cycles will be considered as 'Day 1'.

4.3.2.1 Rituximab SC

Each cycle will consist of a single SC injection of rituximab administered at a fixed dose of 1400 mg.

During induction therapy, cycles will be repeated every 14, 21 or 28 days, depending on the combination chemotherapy regimen selected, according to standard local practice.

During Maintenance therapy, rituximab SC will be administered every 2 months.

For each injection, 11.7 mL of the solution should be withdrawn from the vial. The 27 gauge 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 every patient's SC tissue. Study drug should not be injected into moles, scars, or bruises. The skin should be pinched and needle inserted before the skin is released and the pressure on the syringe can be 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 5-6 minutes. If there is a request by the patient to interrupt the injection, the pressure on the syringe should initially be eased to alleviate the pain. If the pain is not alleviated the injection should be stopped and the patient should be asked when they are comfortable to resume the injection.

Refer to [Appendix 5](#) for additional details.

Rituximab SC must be administered in outpatient setting in this study. There is no specific recommendation regarding the observation period after rituximab SC injections; medical judgment should be utilized.

No dose modification should be made for rituximab SC. If chemotherapy is delayed, rituximab administration must also be delayed. Fourteen days will be considered an acceptable delay of a cycle.

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4.3.3 Investigational Medicinal Product Accountability

The IMP (i.e. Rituximab SC) will be supplied by Roche and shipped to the pharmacist of each centre by the local Roche affiliate or contract research organization (CRO) designee. Storage temperature conditions in the label must be ensured at any time, including the shipment.

In accordance with the requirements of national regulatory agencies and of local health authorities, the Investigator or the responsible local pharmacist will be held accountable for proper storage and dispensing of the IMP. All drug supplies that will be used in the study

must be maintained securely. The study drug shall be dispensed in accordance with the Investigator's prescription. The site pharmacy must not release rituximab if the patient's enrolment number is not on the prescription received. Under no circumstances will the Investigator supply study drug to a third party, or allow the study drug to be used, destroyed or disposed in other ways than as directed by this protocol. Adequate records for the disposition of the study drug (e.g. Drug Dispensing Log) must be maintained. Accountability will be assessed by monitoring drug dispensing and return records and the IMP stored on-site. All records and drug supplies must be available for inspection by the Monitor at every monitoring visit.

All supplies, including partially used or empty containers and copies of the dispensing and inventory logs, must be returned to the Monitor at the end of the study, unless alternate destruction has been authorized by Roche before any IMP has been destroyed, or is required by local or institutional regulations.

The electronic case report form (eCRF) and clinic records will be checked for consistency with site-administered chemotherapy agents used during Induction treatment.

4.3.4 Post-Trial Access to Rituximab

The Sponsor does not intend to provide rituximab SC or other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g. prescription drugs, over the counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to Screening to the end of treatment/early termination visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

Background therapy (standard chemotherapy) should also be recorded on the eCRF.

4.4.1 Permitted Therapy

Patients should receive full supportive care, such as granulocyte colony-stimulating factor (G-CSF) support, transfusions of blood and blood products, prophylactic antiviral medication, antibiotics, anti-emetics, or local application of radiotherapy for consolidation after induction, as applicable and according to institutional standards. Regular application of G-CSF is not generally recommended. However, it should be applied according to the American Society of Clinical Oncology guidelines especially in case of infections and prolonged neutropenia in previous cycles ([Smith et al. 2006](#)). Mesna (2-Mercapto Ethane Sulfonate sodium) may be used as prophylaxis of haemorrhagic cystitis. The reason(s) for treatment, dosage and dates of treatment must be recorded in the eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.1.1 Premedication

In order to reduce the incidence and severity of IIRRs, it is recommended that all patients receive the following premedication administered 30-60 minutes prior to each rituximab administration:

- paracetamol (acetaminophen)

- diphenhydramine hydrochloride or alternative antihistamine.

Institutions should follow their standard premedication procedures regarding other supportive care, including transfusions of blood and blood products, or G-CSF.

If given, these medications must be documented on the Concomitant Medications eCRF.

4.4.1.2 Tumour Lysis Syndrome Prophylaxis

TLS describes the metabolic derangements that occur with tumour breakdown following the initiation of cytotoxic therapy. The metabolites released in TLS can overwhelm the body's normal homeostatic mechanisms, cause hyperuricaemia, hyperkalaemia, hypophosphatemia, hypocalcaemia and uraemia, and lead to acute renal failure. Prophylaxis against TLS may be given as per institutional practice and should be documented on the Concomitant Medications eCRF accordingly.

The mainstays of TLS prevention include hydration and prophylactic rasburicase (recombinant urate oxidase) in high-risk patients, hydration plus allopurinol or rasburicase for intermediate-risk patients, and close monitoring of electrolyte abnormalities for low-risk patients. Primary management of established TLS involves similar recommendations, with the addition of aggressive hydration and diuresis, plus allopurinol or rasburicase for hyperuricemia. Alkalinization is not recommended ([Cairo and Bishop, 2004](#); [Coiffier *et al.* 2008](#)).

4.4.2 Prohibited Therapy

The following treatments are prohibited during study treatment:

- Investigational or unlicensed/unapproved agents of any type
- Other concomitant anti-tumour agents not defined in this protocol as study treatment, including lymphoma-therapeutic doses of glucocorticosteroids.

Patients receiving any of the prohibited therapies will be discontinued and followed for survival.

Patients should not receive long-term treatment (> 1 month) with corticosteroids other than intermittent dexamethasone to control or prevent nausea or vomiting, or corticosteroids for non-infective exacerbations of asthma or respiratory disease.

Non-steroidal hormones administered for non-lymphoma-related conditions (e.g. insulin for diabetes) are permitted.

It is recommended that any course of immunization for patients should be completed at least 4 weeks before starting rituximab and patients should not receive any vaccinations that contain live or attenuated organisms during the study.

4.4.3 Initiation of New Anti-lymphoma Treatment

New anti-lymphoma treatment is defined as start of any radiation therapy (even focal radiation), chemotherapy or immunotherapy, alone or in any combination of them, which is instituted for lymphoma treatment and is not planned in the protocol.

New anti-lymphoma treatment should be started at any time of documented disease progression if this progression is symptomatic and/or if the Investigator considers that a new

treatment is necessary for the patient's benefit. Disease progression should be documented. If the new anti-lymphoma treatment was initiated during the rituximab-based Induction treatment, the patient will undergo end-of-study assessment and subsequently only be followed for survival until the end of the study.

Data on treatment at progression will be recorded in the eCRF. If a new anti-lymphoma treatment has been started, the therapy used and the response to therapy should be documented in the eCRF.

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

Study-mandated assessments are summarised in the [Schedule of Assessments](#) (see [Appendix 1-2](#)).

For details on the timing of each assessment listed in this section, refer to Section [4.5.2](#).

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) happened to the patient within 28 days prior to the Screening visit.

Also concomitant therapy includes any medication (e.g. prescription drugs, over the counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to Screening to the end of treatment/early termination visit

Demographic data will include age, sex and ethnicity.

4.5.1.2 Vital Signs

Vital signs measurements will include resting (sitting) heart rate, systolic and diastolic blood pressure, and body temperature and will be performed at every study visit.

4.5.1.3 Physical Examinations

A complete Screening/Baseline physical examination should include an evaluation of the head, eye, ear, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at Screening/Baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent study visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF. As part of physical exams, SC injection sites will also be checked at every applicable treatment visit.

Patients should be assessed at every visit for presence of active infections throughout the treatment period.

4.5.1.4 Tumour and Response Evaluations

Tumour assessments will be done according the protocol schedule of assessments ([Appendix 1-2](#)) based on imaging tests used as per clinical practice.

Response assessments 4-6 weeks after the last dose of Induction treatment will be based on the Investigator's assessment, completed according to the International Working Group (IWG) response criteria (Cheson et al. 1999, see Appendix 3) or local standard practice.

Patients with stable disease (SD) or PD at staging will be withdrawn from study treatment and will only be followed for resolution of SAEs related to rituximab therapy (as applicable) and for survival until the end of the study, **according to the Schedule of Assessments (see Appendixes 1 and 2).**

4.5.1.5 Disease-Specific Screening/Baseline Assessments

Screening and pre-treatment (Baseline) evaluations will include the following:

- DLBCL or follicular NHL diagnosis (Note: the diagnosis of DLBCL or follicular NHL before rituximab SC treatment must have included histological diagnosis and initial CD20 expression confirmation.)
- ECOG performance status; see [Appendix 4](#) for details. (Note: ECOG performance status needs to be ≤ 3 for inclusion of the patient into the study.)
- IPI score (according to Shipp et al. 1993) and/or FLIPI score ([Solal-Celigny et al, 2004](#); see [Appendix 4](#)) determined at Baseline (prior to Cycle 1). The IPI score (according to [Shipp et al. 1993](#)) is able to differentiate patients into four prognostic groups (low risk, low intermediate risk, high intermediate risk, and high risk). Where possible, the baseline IPI and/or FLIPI score should be calculated from the patient notes. Missing IPI / FLIPI scores will not preclude enrolment.
- GELF criteria will be considered to initiate treatment in patients with FL (see [Appendix 4](#)).

4.5.1.6 Laboratory Assessments

Samples for the laboratory tests listed below will be analysed. The results from the safety laboratory assessments must be available on treatment days, prior to the rituximab administrations.

All laboratory assessments will be performed locally according to local standards. Normal ranges for the study laboratory parameters must be supplied to Roche before the study starts.

- Haematology parameters will include haemoglobin, RBC count, white blood cell (WBC) count, and platelet count.
- Biochemistry parameters at Screening will include sodium, potassium, ALT/SGPT, AST/SGOT, total bilirubin, serum creatinine, alkaline phosphatase, albumin, blood urea nitrogen (BUN), C-reactive protein and LDH. Biochemistry parameters at any further timepoint during the study will include sodium, potassium, ALT/SGPT, AST/SGOT, total bilirubin, and serum creatinine.
- Coagulation tests will include: International Normalized Ratio (INR), Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT).
- Pregnancy test: women of childbearing potential (defined as pre-menopausal women or women who are < 2 years after the onset of menopause and not surgically sterile) must undergo serum pregnancy test within 7 days prior to dosing or within 14 days if with a

confirmatory urine pregnancy test within 7 days prior to dosing.. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- Viral serology and detection should be performed before the first study drug administration according to clinical judgment and may include the following tests:
 - HBV: hepatitis B surface antigen and total hepatitis B core antibody
 - HCV: HCV antibody
 - HIV antibody testing.

Patients known or found to have HIV, HCV or active HBV infection must not be included in the study. Local guidelines for patient consent to viral testing must be adhered to.

4.5.1.7 Electrocardiograms

A standard resting 12-lead ECG needs to be performed at Screening/Baseline as part of the eligibility assessments. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. ECGs should be performed prior to vital sign measurements and blood draws.

The Investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site.

4.5.1.8 Patient Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterise the clinical profile of rituximab SC (add any other objectives as appropriate).The PRO instrument(s), RASQ and EuroQol's EQ-5D questionnaires , translated as required in the local language, will be distributed by the Investigator or his/her staff and completed in their entirety by the patient. To ensure instrument validity and that the data collected meet health authority requirements and data standards, PRO questionnaires should be self-administered at the investigational site. The PRO questionnaires will be administered at the following time points:

- EuroQoL: at the end of the induction treatment and/or at the end of the maintenance treatment (for those patients undergoing maintenance treatment).
- RASQ will be administered as follows:
 - o RASQ-IV : at baseline, before switching to SC Rituximab.
 - o RASQ-SC: at the end of induction treatment (for those patients undergoing induction treatment).
 - o RASQ-SC: at end of maintenance treatment (for those patients undergoing maintenance treatment).

EuroQol's EQ-5D Questionnaire is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. The EQ-5D Questionnaire will be utilised in this study for further economic modelling.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for enrolled patients and for patients who were screened but not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 28 days prior to start of treatment with rituximab SC, unless otherwise specified. Standard-of-care tests or examinations performed prior to obtaining informed consent and within 35 days prior to start of treatment with rituximab IV do not need to be repeated for Screening. All sites of known disease should be documented at Screening/Baseline in order to provide an accurate basis for future assessments. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before study enrolment. Patients who are suspected of progressing between their Screening/Baseline tumour assessments and first dose should be re-screened and re-assessed for their suitability for the trial. The Investigator will maintain a screening log in accordance with local study file documentation requirements to record details of all patients screened and to confirm eligibility or record reasons for screening failures.

RASQ-IV will be administered at baseline before switching to SC Rituximab (see [Appendix 7](#)).

Please see [Appendix 1-2](#) for the schedule of Screening and pre-treatment assessments.

4.5.2.2 Assessments during Treatment Visits

All assessments must be performed on the day of the specified visit, unless a time window is specified in the **Schedule of Assessments** (see [Appendix 1-2](#)). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the **Schedule of Assessments**. PRO assessments should be performed prior to the completion of other study assessments.

The same imaging modalities should be used for tumour assessments throughout the study unless new disease sites are indicated. The frequency of tumour assessments should be as consistent as possible. Tumour assessments should be continued in patients who discontinue study treatment for reasons other than disease progression until progression is documented.

Please see [Appendix 1-2](#) for the **Schedule of Assessments** performed during the treatment period.

During induction, patients with SD or PD at staging will be withdrawn from Study treatment and will only be followed for all AEs and SAEs and for survival until the end of the Study.

Patients who do not complete the study treatment per protocol will undergo end-of-study assessment within 4-6 weeks after the last dose of study treatment and will be followed until the end of the whole study according to local practice for safety assessment [i.e. resolution of SAEs related to rituximab SC therapy (as applicable)] and efficacy assessment [i.e. tumour response / progression (if PD not yet documented), survival, or documentation of any new anti-lymphoma treatment, whatever happens first].

EuroQoL will be administered:

- At the end of the induction treatment (for those patient undergoing induction treatment).
- At the end of the maintenance treatment (for those patient undergoing maintenance treatment).

RASQ-SC will be administered:

- At the end of induction treatment (for those patients undergoing induction treatment).
- At the end of maintenance treatment (for those patients undergoing maintenance treatment).

4.5.2.3 Post-Treatment Follow-up (Observation) Period

After the end of study treatment/early termination visit, AEs should be followed as outlined in Sections 5.5 and 5.6.

Please see [Appendix 1-2](#) for the schedule of follow-up assessments.

All patients who complete the Study treatment will then enter the post-treatment follow-up phase until the end of Study. Patients with SD at staging during induction will be permanently discontinued from Study treatment and will enter the post-treatment follow-up phase. Patients with PD at staging (or at any time during treatment) during induction will be permanently discontinued from Study treatment and will be followed only for survival and AEs / SAEs until the end of Study. Patients who receive at least one dose of Study drug but do not complete the Study as per protocol will undergo the early treatment termination assessments within 4 weeks after the last dose of (Induction or Maintenance) treatment and will enter the post-treatment follow-up phase until the end of Study for safety assessment [i.e. resolution of SAEs related to rituximab SC therapy (as applicable)] and efficacy assessment [i.e. tumour response / progression (if PD not yet documented), survival, or documentation of any new anti-lymphoma treatment, whatever happens first].

Follow-up of patients after last dose of SC rituximab will occur every 3 months for the first year and then every 6 months (\pm 2 weeks) for the second year, as detailed in [Appendix 1-2 \(Schedule of Assessments\)](#). In sites where it is not feasible to perform a CT scan every 3 months (\pm 1 week) for 2 years, it is acceptable to perform a CT scan every 6 months (\pm 1 week) for 2 years instead or as per clinical practice.

4.5.2.4 Assessments at the End of Study Treatment/Early Termination Visit

Patients who complete the study treatment (i.e. as described in figure 2) or discontinue from the study early will be asked to return to the clinic 4-6 weeks after the last dose of study drug for the end of treatment study visit.

Please see [Appendix 1-2](#) for the [Schedule of Assessments](#) performed at the study completion/early termination visit.

4.5.2.5 Unplanned Visits

Assessments other than those specified in [Appendix 1-2, Schedule of Assessments](#), may be performed as clinically indicated. These assessments should be adequately documented.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The Investigator has the right to discontinue a patient from study treatment or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason. Reasons for discontinuation of study treatment may include, but are not limited to, the following:

- Any medical condition that the Investigator or Sponsor determines may jeopardise the patient's safety if he or she continues study treatment.
- Pregnancy
- Major protocol violation
- Patient withdrawal of consent at any time. In instances where consent is withdrawn, the Investigator must clarify and document whether the patient is willing to continue to be followed (i.e. for survival).
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient lost to follow-up
- Trial termination by the Sponsor, Regulatory Authorities
- Trial termination at site by Investigator or EC

4.6.1.1 Discontinuation from Study Drug

Patients who discontinue rituximab SC prematurely will be asked to return to the clinic for the end of treatment visit/early termination visit (see Section 4.5.2.4) and may undergo follow-up assessments (see Section 4.5.2.3). The primary reason for premature study drug treatment discontinuation should be documented on the appropriate eCRF.

Patients who discontinue rituximab SC prematurely will not be replaced.

4.6.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after informed consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study and Site 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 AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrolment is unsatisfactory.

The Sponsor will notify the Investigator if the patient enrolment is placed on hold, or if the Sponsor decides to discontinue the study or development program.

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

- Excessively slow recruitment
- Poor protocol adherence and/or repeated protocol violations
- Repetitive late/inaccurate or incomplete data recording or failure to resolve data queries in the eCRF.
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Patients will be assessed by prior medical history, vital signs (including resting blood pressure, heart rate, and body temperature), weight and height, physical examination, AEs and concomitant medications. A complete medical history (including prior treatments for cancer) will be documented at Screening/Baseline. A general physical exam with infection assessment will be performed at Screening/Baseline, and at every treatment and post-treatment follow-up visit; see [Appendix 1-2, Schedule of Assessments](#)). As part of physical exams, SC injection sites will be checked at every treatment visit. All patients will undergo routine safety laboratory tests.

AEs will be monitored and documented continuously during the study (at each on-treatment visit and during the post-treatment follow-up, as detailed in Section 5.3.1) refer to Sections 5.4.2 and 5.5 for details on SAE reporting and follow-up requirements, respectively. All AEs and SAEs (including patients' symptoms and signs of toxicity and clinically significant haematological and biochemical parameters) will be graded according to NCI CTCAE version 4.0 (see [Appendix 6](#)).

Changes in concomitant medication will be recorded at each study visit. Recording of concomitant treatments and therapies will include any new anti-lymphoma treatment initiated after the Baseline visit.

5.1.1 Adverse Events of Special Interest

AEs of special interest include AARs, hepatotoxicity (elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6) and suspected transmission of an infectious agent by the Study drug (see Section 5.2.3).

5.1.2 Interaction with Other Medicinal Products

At present, there are limited data on possible drug interactions with rituximab. The tolerability of the simultaneous or sequential combination of rituximab SC with chemotherapy agents that are liable to cause depletion of normal B-cells is well defined.

Patients with HAMA or HACA titers may develop allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

5.1.3 Administration-Associated Reactions and their Management

AEs of special interest include AARs. AARs are defined as all AEs occurring within 24 hours of rituximab administration and considered by the investigator to be related to study drug. AARs include IIRRs, injection-site reactions, administration site conditions and all symptoms thereof. IIRRs can present with one or more of the following symptoms: allergic reaction, arthralgia, bronchospasm, chills, cough, dizziness, dyspnea, headache, hypertension, hypotension, myalgia, nausea, pruritus, pyrexia, rash, tachycardia, urticaria, vomiting.

All AARs must be recorded on the Adverse Event eCRF. Cutaneous and soft-tissue AARS will be classified in the eCRF as either localized at the injection site, or non-localized reactions (including generalized reactions). 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 individual symptoms of the AARs.

Signs and symptoms suggestive of an IIRR were reported in more than 50% of patients who received rituximab IV in clinical trials, and were predominantly seen during the first infusion. Severe IIRRs occurred in up to 12% of all patients at the time of the first treatment cycle with rituximab in combination with chemotherapy. These included cases of cytokine release syndrome accompanied by hypotension and bronchospasm. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is <1% of patients by the eighth cycle. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with an anti-pyretic (e.g. acetaminophen), an antihistaminic (such as diphenhydramine) is recommended. Additional treatment with bronchodilators, oxygen or IV saline may be indicated.

Patients who develop severe cytokine release syndrome or severe pulmonary events should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until TLS and pulmonary infiltration have been resolved or ruled out.

Hypersensitivity reactions typically occur within minutes after starting rituximab infusion. Medicinal products for the treatment of hypersensitivity reactions (e.g. epinephrine (adrenaline), antihistamines and glucocorticoids), should be available for immediate use in the event of an allergic reaction during administration of rituximab.

If PML is suspected based on any new or worsening neurological, cognitive or psychiatric symptoms or signs, further dosing must be suspended until PML has been excluded. The Investigator should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML.

Guidelines for managing of specific haematologic and non-haematologic AEs associated with R-CHOP treatment are summarized in [Appendix 8](#).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious adverse events of special interest; measurement of protocol-specified safety

laboratory assessments; measurement of protocol-specified vital signs; and 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 AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavourable 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), except as described in Section 5.3.5.9
- 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
- AEs 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 SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death)
- The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 AE (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3 and Appendix 6); 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 AE recorded on the eCRF.

SAEs are required to be reported by the Investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

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

Non-serious AEs of special interest are required to be reported by the Investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions). AEs of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- Suspected transmission of an infectious agent by the study drug
- AARs.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

For each AE recorded on the AE 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 AEs at each patient contact. All AEs, 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 SAEs caused by a protocol-mandated intervention should be reported (e.g. SAEs related to invasive procedures such as biopsies). SAEs must be reported to Roche (or designee) within 24 hours of the Investigator becoming aware of the event.

After initiation of study drug, all SAEs/AEs, regardless of relationship to study drug, will be reported until study closure. The Investigator does not need to actively monitor subjects for adverse events once the trial has ended. However, if becoming aware of any death serious adverse events and non-serious adverse events of special interest which are considered to be related to study-drug, occurring to a subject, the Investigator should report those to the Sponsor (see Section 5.6).

Resolution of AEs and SAEs including dates should be documented on the AE/SAE eCRF and in the patient's medical record to facilitate source data verification. For SAEs, non-serious AEs of special interest, and pregnancies, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE (e.g., hospital discharge summary, consultant report, or autopsy report).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation time-points. 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 NCI CTCAE (version 4.0; see [Appendix 6](#)) will be used for assessing AE severity. [Table 2](#) will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 2: Adverse Event Severity Grading Scale

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

- 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 one's self, 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 an SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.
- d. Grade 4 and 5 events must be reported as SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE 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 or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where 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

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 AEs on the Adverse Event eCRF. Colloquialisms and abbreviations should be avoided.

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Reactions Temporally Associated with the Rituximab Injections

AEs that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For AEs other than IIRRs, 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 AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring 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. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment, 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 haemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation time-points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

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

- 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
- Clinically significant in the Investigator's judgment.

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 AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g. alkaline phosphatase and bilirubin five times the ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 if 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 AE. 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 not be repeatedly recorded on the Adverse Event eCRF, unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- 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
- 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 AE.

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 not be repeatedly recorded on the Adverse Event eCRF, unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ baseline value) 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. Therefore, Investigators must report the occurrence of either of the following as an AE:

- Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST $> 3 \times$ baseline value 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 5.3.5.1) and reported to the Sponsor immediately (i.e. no more than 24 hours after learning of the event), either as an SAE or a non-serious adverse events of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths (see Section 5.3.1) that are attributed by the Investigator solely to progression of the underlying condition (DLBCL or follicular NHL) should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and reported to the Sponsor within 24 hours (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. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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.

During study survival follow-up, deaths attributed to progression of the underlying condition should be recorded on the Study Completion/Early Discontinuation eCRF.

For any deaths occurring after study closure, refer to Section 5.6.

5.3.5.8 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the Screening/Baseline visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an AE 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 pre-existing condition has changed by including applicable descriptors (e.g. “more frequent headaches”).

5.3.5.9 Lack of Efficacy or Worsening of the Underlying Condition

Events that are clearly consistent with the expected pattern of progression of the underlying condition (DLBCL or follicular NHL) should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the original IWG for response assessment of lymphoma (Cheson *et al*, 1999; [Appendix 3](#)) or other country standards. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of an SAE in [Section 5.2.2](#)), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g. for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a pre-existing 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 suffered an AE
- Hospitalization due solely to progression of the underlying condition (DLBCL or follicular NHL).

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfils serious 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 reporting instructions).

5.3.5.12 Patient-Reported Outcomes as Safety Data

AE reports will not be derived from PRO data. However, if any patient responses suggestive of a possible AE are identified during site review of the PRO questionnaires, site staff will alert the Investigator, who will determine if the criteria for an AE have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an AE, it will be reported on the Adverse Event eCRF.

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:

- SAEs
- Non-serious AEs of special interest
- Pregnancies

The Investigator must report new significant follow-up information for these events to the Sponsor within 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.

All participating Investigators and the respective EC will be notified of all Suspected Unexpected Serious Adverse Reactions (SUSARs) that are reported during the study; see Section 5.7.

5.4.1 Emergency Medical Contacts

The primary emergency contact for each country will be assigned by the local Roche affiliate.

To ensure the safety of study patients, an Emergency Medical Call Centre 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 Monitor, and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all Investigators (please contact local monitor for further information).

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

For reports of SAEs and non-serious AEs of special interest, Investigators should record all case details that can be gathered **within 24 hours** 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, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the event, using the fax numbers provided to Investigators (please contact local monitor for further information). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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 last dose of study drug. A Pregnancy Report eCRF should be completed by the Investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. Details of the course and outcome of any pregnancy will be collected and reported. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. 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 foetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to Investigators (please contact local monitor for further information).

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 90 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the Investigator **within 24 hours** after learning of the pregnancy and submitted via the EDC system. 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. The pregnant partner will need to sign an *Authorization for Use and Disclosure of Pregnancy Health Information* to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. 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 foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, the reporting instructions provided in Section [5.4.3.1](#) should be followed.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.4 Congenital Anomalies / Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor within 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 AE 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 SAEs until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range or baseline state and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For SAEs, non-serious AEs of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, 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 POST-STUDY ADVERSE EVENTS

At the End of Study / Early Treatment Termination visit, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events. After the study has ended, the Sponsor should be notified if the investigator becomes aware of any death, serious adverse event, or other non-serious adverse event of special interest which are considered to be related to the study drug, occurring at any time after a patient has

discontinued study participation. The Investigator is not required to actively monitor patients after the study has ended.

The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management via telephone (please contact local monitor for further information).

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

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using

- the Mabthera® Rituximab SC IB

The Sponsor will summarize 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.

All participating Investigators and the respective EC will be notified of all SUSARs that are reported during the study. An AE only qualifies as a SUSAR when all of the following conditions are met:

- The event is serious (SAE);
- The event is deemed related to the study drug, according to the criteria provided in Section 5.3.4. (Note: any suspicion of a causal relationship should lead to an assessment of 'related');
- When assessed against the known safety profile of rituximab (as described in the IB for rituximab SC), the event is considered unexpected (i.e. not foreseen in the IB).

Individual SUSAR reports originating in this trial, including SUSARs considered being a significant safety issue and/or which result in Roche recommending a change to the ICF, will be forwarded to all participating Investigators and the EC associated with their sites, on an expedited basis. SUSAR reports originating from other trials using the same IMP will be provided as six-monthly SUSAR Reports to all Investigators and EC.

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6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A total of 139 patients will be recruited into this study.

The incidence of AAR is deemed of primary interest for this study. Based on the results of a recent study, the most frequent AAR with SC rituximab is the injection site-erythema (10%) (Davies *et al.* 2012). If this endpoint is achieved by 10% of a sample size of 139 evaluable study patients, the two sided 95% confidence will have a maximum imprecision of +5%. The precision of these estimates is considered sufficient to address the main objective of the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

This is a prospective, open-label, single-arm study to evaluate the safety of rituximab SC administered as Induction and/or Maintenance therapy. The study will include at least 139 adult patients with CD20+ DLBCL or CD20+ follicular NHL (grades 1, 2 or 3a; NHL), who are currently undergoing Induction and/or Maintenance therapy with rituximab IV. Patients receiving Induction therapy must be eligible to receive at least 4 cycles of rituximab SC in addition to standard chemotherapy. Patients with follicular NHL receiving Maintenance therapy must be eligible to receive at least 6 cycles of rituximab SC.

Induction Therapy:

Patients receiving Induction therapy prior to entry into the study must be eligible to receive at least four further cycles of rituximab SC. Patients with follicular NHL who will continue into Maintenance therapy (after staging at the end of Induction) can continue to receive rituximab SC during Maintenance (see below).

Maintenance Therapy (patients with follicular NHL):

Patients receiving Maintenance therapy prior to entry into the study must be eligible to receive at least six further cycles of rituximab SC (i.e. 12 additional months of Maintenance treatment). Patients who are continuing into Maintenance therapy following at least four cycles of rituximab SC during Induction therapy must also be eligible to receive at least six cycles of rituximab SC (i.e. 12 additional months of Maintenance treatment).

6.3 SUMMARIES OF PATIENT POPULATION

Baseline characteristics will be summarized, as well as the demographic profile, medical history, IPI score (according to Shipp *et al.* 1993) or GELF criteria (see [Appendix 4](#)), concomitant medication use and serum pregnancy test at Screening/Baseline using appropriate descriptive statistics: mean, standard deviation, median and range (minimum and maximum) for the continuous variables, and number/percentage of patients for the categorical variables.

Exposure to study treatment (rituximab), including the number of cycles administered, duration of treatment exposure (calculated from date of first treatment date to the last treatment date) and dosing information (e.g. dose interruptions, modifications and delays) will be summarized.

The number of patients who prematurely discontinue study treatment and the number of patients who withdrew from the study will be summarized and reasons for withdrawal will be displayed.

Further details about the planned analyses will be presented in the Statistical Analysis Plan (SAP).

6.3.1 Analysis Populations

All enrolled patients who receive at least one dose of study medication will be included in the Safety Population, which will be the primary analysis population for safety parameters.

All enrolled patients will be included in the Intent-to-Treat (ITT) population. Efficacy parameters and patient reported outcome measures will be analysed separately using subsets of the for the ITT population for patients undergoing Induction therapy, Induction + Maintenance therapy and Maintenance therapy.

Other analysis populations may be defined based on more restrictive criteria, such as fulfilment of eligibility criteria or a minimum duration of the observation period.

6.4 SAFETY ANALYSES

Safety will be assessed by AEs, AEs of grade ≥ 3 , SAEs, IIRRs / AARs, AEs within the MedDRA SMQ 'Anaphylactic reactions' (wide), safety laboratory parameters, vital signs, concomitant medications, premature withdrawal from the study and from study medication due to AEs and ECOG performance status. All clinical AEs and SAEs as well as laboratory abnormalities will be recorded and graded according to the NCI-CTCAE version 4.0.

The analysis of AEs will focus on treatment-emergent adverse events, i.e. AEs occurring on the day of or after the first administration of study drug and up to 28 days after the last dose. Non-treatment emergent AEs (i.e. those occurring before commencement of study medication) will only be listed. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The incidence of AARs, AEs, AEs leading to premature discontinuation or interruption of study treatment, SAEs, grade ≥ 3 AEs, will be computed with 95% Confidence Interval. The incidence of each AE will be summarized according to the primary system-organ class and by preferred term. The incidence of cutaneous and soft tissue AARs will additionally be summarised for those that are defined as localized and those that are defined as non-localized. The incidence of deaths and cause of deaths will be listed and summarized.

Safety laboratory parameters (haematology, biochemistry, coagulation tests, as defined in Section 4.5.1.6), will be presented in shift tables of NCI CTCAE grade at baseline against worst grade recorded during the treatment period. Laboratory parameters will be summarized and select laboratory parameters may also be displayed graphically.

Vital signs will be summarized over time.

ECOG performance status will be summarized by frequency tables and percentage of patients in different categories will be presented by bar charts at baseline.

Concomitant medication will be coded according to the WHO DRUG dictionary and tabulated in summary tables. New anti-lymphoma treatment (chemotherapy, radiotherapy, immunotherapy), initiated after the Baseline visit will be presented in summary tables.

All safety analyses will be based on the Safety population.

Primary safety endpoint will be summarized as incidence proportion together with its 95% confidence interval. Since AARs could occur more than once in one patient, only the first event will be considered to estimate the incidence proportion of AARs (i.e. proportion of

patients with at least 1 AAR of interest over the total number of patients included in the safety population).

Secondary safety endpoints will be also summarized as incidence proportions together with their 95% confidence interval.

Further details about the planned safety analyses will be presented in the SAP.

6.5 EFFICACY ANALYSES

The analyses will include all enrolled patients.

Efficacy endpoints include EFS, PFS, OS, DFS, CR/CRu proportion, PR, SD, PD and will be analysed separately for the population undergoing Induction therapy, Induction + Maintenance therapy and Maintenance therapy.

Response assessments will be based on the Investigator's assessment, completed according to the IWG response criteria ([Cheson *et al* 1999](#), see [Appendix 3](#)) or other country standards.

EFS is defined as the time from first dose of rituximab IV to first occurrence of progression or relapse, according to the IWG response criteria ([Cheson *et al* 1999](#), see [Appendix 3](#)) or other country standards, or initiation of a non-protocol-specified anti-lymphoma therapy or death, whichever occurs first.

PFS is defined as the time from first dose of rituximab IV to the first occurrence of progression or relapse, according to the IWG response criteria ([Cheson *et al* 1999](#), see [Appendix 3](#)) or other country standards, or death from any cause.

OS is defined as the time from first dose of rituximab IV to until death from any cause.

DFS will be assessed in patients achieving CR/CRu and is defined as the period from the date of the initial CR/CRu until the date of relapse or death from any cause.

CR/CRu proportion at 4-6 weeks after the last dose of Induction treatment will be summarized and presented with the corresponding 95% two-sided Pearson-Clopper CI by treatment group and overall. The same estimation will be done for PR, SD and PD proportions, after the last dose of induction treatment.

Endpoints will be summarized with a 95% confidence interval.

The analysis of endpoints measured as a time to event (e.g. EFS, PFS, OS and DFS) is based on the survivor function, which is the probability of remaining event free beyond a certain point in time. The survivor function will be estimated using Kaplan-Meier methodology and summarized using the range, the 25th and 75th percentiles and median survival along with a 95% confidence interval for median survival. Patients who have experienced none of these events at the time of analysis (clinical-cut off) and patients who are lost to follow up will be censored at their last clinical assessment date. Patients without post-baseline tumour assessments will be censored at the time of their baseline visit except if death occurs prior to their first scheduled tumour assessment.

6.6 EXPLORATORY ANALYSES



6.7 PATIENT-REPORTED OUTCOME ANALYSES

For EQ-5D analysis, the proportion of subjects reporting problems in mobility, self-care, usual activities, pain/discomfort and anxiety/depression will be calculated

The RASQ is a 19-item questionnaire measuring the impact of the mode of treatment administration on five domains: Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. The Physical Impact domain comprises of 3 items (Pain, swelling, and redness, Pain experience, Side effects as expected), the Psychological Impact domain contains 5 items (Anxious about injection/IV, Worry condition will get worse, Anxious thinking about disease, Confidence the injection/IV treating disease, Feeling restricted by injection/IV), the Convenience domain contains 3 items (Is it convenient to get injection/IV, Length of time to get injection/IV as expected, Bothered by the amount of time to get injection/IV) and the Satisfaction domain includes 2 items (How satisfied or dissatisfied are you with the injection/IV, Would you recommend the way you received the treatment). All 15 RASQ items included in the above domains have five response options. Reverse-coded response values will be created for eight of the RASQ items (Q2, Q3, Q5, Q6, Q7, Q9, Q14a, and Q14b). In addition, there are 4 descriptive questions that are not part of the above domains and scored separately. For each domain, if the number of completed items is greater than or equal to the pre-specified minimum number, the domain will be scored using the formula:

- Domain score = [(Sum of completed item responses / Number of completed items) - 1] x 100 / (Maximum possible item response value – Minimum possible item response value)

However, if fewer items are completed than the minimum number indicated above, then the domain will not be scored (i.e. a missing value is assigned).

Since the maximum possible item response value is 5 and the minimum possible response value is 1 for all RASQ items, a simpler way to represent the above formula for the RASQ domains is:

- RASQ domain score = (Mean of completed item responses – 1) x 25

Descriptive statistics will be presented by domain and timepoint, for the total sample. Listings will present by patient data for individual responses and domain scores.

6.8 INTERIM ANALYSES

Two interim analyses are planned:

- The first interim analysis will be done one year after the end of recruitment (i.e. one year after last patient first visit).

- The second interim analysis will be done at the end of study treatment (i.e. last patient end of treatment visit).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply electronic eCRF specifications for this Study. A CRO will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

Electronic CRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Roche and records retention for the study data will be consistent with Roche's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using 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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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, PROs, 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 7.6.

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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, ePRO data (if applicable), ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 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) and the EU Clinical Trial Directive (2001/20/EC).

This study will be conducted in the European Union (EU)/European Economic Area, so it will comply with the EU Clinical Trial Directive (2001/20/EC), in addition to the local Spanish Royal Decree 223/2004, of February 6th, regulating clinical tests with medicines and subsequent orders SCO/256/2007 and SCO/362/2008.

Roche Farma S.A. has taken out civil responsibility insurance with the company [REDACTED], branch in Spain, that is in accordance with the Spanish Royal Decree 223/2004 of February 6th that establishes the requirements for the conduct of Clinical Trials with drugs and covers any damage to you that may occur as a consequence of the Clinical Trial.

8.2 INFORMED CONSENT

Roche's sample ICF (and any applicable ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, if applicable) will be provided to each site. It will be provided in a certified translation of the local language. Roche or its designee must review and approve any proposed deviations from Roche's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before EC submission. The final EC-approved Consent Forms must be provided to Roche for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorised 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 EC-approved Consent Forms must be provided to Roche for health authority submission purposes.

Patients must be re-consented to the most current EC-approved version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and EC policy) during their participation in the study. 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 authorised 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 HEALTH AUTHORITY, INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the, EC/IRB and the Agencia Española de Medicamento y

Productos Sanitarios (AEMPS), and reviewed and approved by both of them before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC and the AEMPS.

Written summaries of the status of the study will be provided to the EC/IRB and the AEMPS annually or more frequently in accordance with the requirements, policies, and procedures established by the EC/IRB and AEMPS. Investigators or, as applicable, the Country Study Manager are/is also responsible for promptly informing the EC of any protocol amendments (see Section 9.5).

Investigators may receive written safety reports or other safety-related communications from Roche. 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 EC.

8.4 CONFIDENTIALITY

Roche 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 Roche location.

Additionally, the study will be conducted in observance of the the Ley Orgánica 15/1999, from December 13th, for Personal Data Protection and its development through the Royal Decree 1720/2007.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorisation 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 the US FDA and other national and local health authorities, Roche monitors, representatives, and collaborators, and the EC for each study site, as appropriate.

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.

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,

ICFs, and documentation of EC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

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

9.3 ADMINISTRATIVE STRUCTURE

The Reference Ethics Committee will be the Ethics Committee of "██████████".

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. 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.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre trials only in their entirety and not as individual centre 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.

9.5 PROTOCOL AMENDMENTS

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

Approval must be obtained from the 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).

10. REFERENCES

- Badin F, Hayslip J. Rituximab in the treatment of B-cell non-Hodgkin lymphoma, focus on outcomes and comparative effectiveness. *Clinicoecon Outcomes Res* 2010;2:37-45.
- Bookbinder LH, Hofer A, Haller MF *et al.* A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J Control Release* 2006;114(2):230-41.
- Bordeleau L, Berinstein NL. Molecular diagnostics in follicular non-Hodgkin's lymphoma: a review. *Semin Oncol* 2000;27(Suppl 12):42-52.
- Boye J, Elter T, Engert A. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. *Ann Oncol* 2003;14:520-35.
- Cairo M, Bishop M. Tumor lysis syndrome: new strategies and classification. *Br J Hematol* 2004;127(1):3-11.
- Cartwright RA. Time trends in incidence of haematological malignancies and related conditions. *Br J Haematol* 1999;106:281-95.
- Cheson BD, Horning SJ, Coiffier B, *et al.* Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999;17(4):1244.
- Clarke CA, Glaser SL. Changing incidence of non-Hodgkin's lymphomas in the United States. *Cancer* 2002;94:2015-23.
- Coiffier B, Altman A, Pui CH *et al.* Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol.* 2008 Jun 1;26(16):2767-78.
- Coiffier B, Lepage E, Briere J *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346(4):235-42.
- Coiffier B, Thieblemont C, Van Den Neste E *et al.* Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood* 2010;116(12):2040-5.
- Cunningham D, Smith P, Mouncey P *et al.* R-CHOP14 versus R-CHOP21: Result of a randomized phase III trial for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma. *J Clin Oncol* 2011;29(15, suppl):abstr 8000Davies A, Merli F, Mihaljevic B, Siritanaratkul N, Solal-Céligny P, Boehnke A, Berge C, McIntyre C, Barrett M, MacDonald D. Pharmacokinetics, Safety, and Overall Response Rate Achieved With Subcutaneous Administration of Rituximab in Combination With Chemotherapy Were Comparable With Those Achieved With Intravenous Administration in Patients With Follicular Lymphoma in the First-Line Setting: Stage 1 Results of the Phase 3 SABRINA Study (BO22334). 54th American Society of Hematology Annual Meeting; December 8–11, 2012; Atlanta, Georgia [Abstract 3708].
- Davis TA, Grillo-Lopez AJ, White CA *et al.* Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. *J Clin Oncol* 2000;18(17):3135-43.

Davis TA, White CA, Grillo-Lopez AJ *et al.* Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a phase II trial of rituximab. *J Clin Oncol* 1999;17(6):1851-7.

Delarue R, Tilly H, Salles G *et al.* R-CHOP-14 compared to R-CHOP-21 in elderly patients with diffuse large B-cell lymphoma (DLBCL): Results of the second interim analysis of the LNH03-6B GELA study. *Ann Oncol* 2011;22(suppl 4):117 abstract 106.

Del Nagro CJ, Mao CP, Brovarney M *et al.* Comparison of B cell depletion mediated by intravenous (IV) Rituxan(R) and Rituxan given subcutaneous (SC) in cynomolgus monkeys. *Blood (ASH Annual Meeting Abstracts)* 2010;116(21): abstract 3980.

Demidem A, Lam T, Alan S *et al.* Chimeric anti-CD20 (IDEC-C2B8) monoclonal antibody sensitizes a B cell lymphoma cell line to cell killing by cytotoxic drugs. *Cancer Biother Radiopharm* 1997;12:177-86.

Dreyling M, Ghielmini M, Marcus R, Salles G, Vitolo U. ESMO Guidelines Working Group. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2011 Sep;22 Suppl 6:vi59-63.

Eltom MA, Jemal A, Mbulaiteye SM *et al*. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. *J Natl Cancer Inst*. 2002;94:1204-10.

Ferlay J, Autier P, Boniol M *et al*. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;18:581-92.

Feugier P, Van Hoof A, Sebban C *et al*. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2005;23:4117-26.

Fisher RI, Gaynor ER, Dahlborg S *et al*. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *New Engl J Med* 1993;328:1002-6.

Fisher RI, LeBlanc M, Press OW *et al*: New treatment options have changed the survival of patients with follicular lymphoma. *J Clin Oncol* 2005;23:8447-52.

Friedberg JW. Treatment of follicular non-Hodgkin's lymphoma: the old and the new. *Semin Hematol* 2008;45(3 suppl 2):S2-6.

Friedberg JW, Taylor MD, Cerhan JR *et al*. Follicular lymphoma in the United States: first report of the national LymphoCare study. *J Clin Oncol* 2009;27(8):1202-8.

Frost GI. Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. *Expert Opin Drug Deliv* 2007;4(4):427-40.

Habermann TM. Antibody therapy in aggressive lymphomas. *Hematology Am Soc Hematol Educ Program* 2007:257-64.

Habermann TM, Weller EA, Morrison VA *et al*. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 2006;24(19):3121-7.

Herold M, Dölken G, Fiedler F *et al*. Ongoing clinical studies – randomized phase III study for the treatment of advanced indolent NHL and MCL: chemotherapy versus chemotherapy plus Rituximab. *Ann Hematol* 2003;82:77-9.

Herold M, Haas A, Srock S *et al*. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: An East German study group hematology and oncology study. *J Clin Oncol* 2007;25(15):1986-92.

Hiddemann W, Kneba M, Dreyling M *et al*: Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German low-grade lymphoma study group. *Blood* 2005;106:3725-32.

Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. *Semin Oncol* 1993;20(Suppl 5):75-88.

Howlader N, Noone AM, Krapcho M *et al.* (eds). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2009_pops09/, based on November 2011 SEER data submission, posted to the SEER web site, 2012.

[ILSG] The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* 1997;89:3909-18.

Investigator Brochure MabThera®, Rituxan®, Fifteenth Edition, July 2010 (Rituximab IV), and Second Edition, October 2010 (Rituximab SC).

Jaffe ES, Harris NL, Stein H *et al.* (eds). World Health Organization classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2001.

Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma. *Drugs* 2010;70(11):1445-76.

Kornbrot B, Kobayashi RH, Singer A *et al.* Hypersensitivity to therapeutic murine monoclonal antibodies. *Nebr Med J* 1994;79(12):393-8.

Landis SH, Murray T, Bolden S *et al.* Cancer Statistics, 1999. *CA Cancer J Clin* 1999;49(1):8-31.

Lenz G, Dreyling M, Hoster E *et al.* Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: Results of a prospective randomized trial of the German low grade lymphoma study group (GLSG). *J Clin Oncol* 2005;23(9):1984-92.

López-Guillermo A, Caballero D, Canales M, Provencio M, Rueda A, Salar A; Spanish Hematology and Hemotherapy Association; Oncological Group for the Treatment of Lymphatic Diseases; Spanish Lymphomas/Autologous Bone Marrow Transplant Group. Clinical practice guidelines for first-line/after-relapse treatment of patients with follicular lymphoma. *Leuk Lymphoma*. 2011 Dec;52 Suppl 3:1-14

Lossos IS. Higher-grade transformation of follicular lymphoma - a continuous enigma. *Leukemia* 2005;19(8):1331-3.

Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J Pharmacokinet Pharmacodyn*. 2001;28(6):507-32.

Maloney D, Smith B, Appelbaum F. The anti-tumor effect of monoclonal anti-CD20 antibody (MAB) therapy includes direct anti-proliferative activity and induction of apoptosis in CD20 positive non-Hodgkin's lymphoma (NHL) cell lines. *Blood* 1996;88:637a.

Marcus R, Imrie K, Belch A *et al.* CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005;105:1417-23.

Marcus R, Imrie K, Solal-Celigny P *et al.* Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol* 2008;26(28):4579-86.

McLaughlin P, Grillo-López AJ, Link BK *et al.* Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998;16:2825-33.

Michallet AS, Coiffier B. Recent developments in the treatment of aggressive non-Hodgkin lymphoma. *Blood Rev* 2009;23(1):11-23.

Moreau P, Pylypenko H, Grosicki S *et al.* Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol* 2011;12(5):431-40.

Morton LM, Wang SS, Devesa SS *et al.* Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood* 2006;107(1):265–76.

Nathwani BN, Harris NL, Weisenburger D *et al.* Follicular lymphoma. In Jaffe ES, Harris NL, Stein H *et al.* (eds). *World Health Organization classification of tumors. Pathology and genetics of tumors of haematopoietic and lymphoid tissues.* IARC Press: Lyon 2001;162-7.

National Cancer Center Network Guidelines, v3 2011 (www.nccn.org)

Niitsu N. Current treatment strategy of diffuse large B-cell lymphomas. *Int J Hematol* 2010;92(2):231-7.

“OncoGuía de linfoma B difuso de células grandes” [22nd October 2012]; Available from: <http://www.gencat.cat/salut/depsan/units/aatrm/pdf/og0301es.pdf>

Pettengell R, Linch D. Position paper on the therapeutic use of rituximab in CD20-positive diffuse large B-cell non-Hodgkin’s lymphoma. *Br J Haematol* 2003;121(1):44-8.

Pfreundschuh M, Schubert J, Ziepert M *et al.* German high-grade non-Hodgkin lymphoma study group (DSHNHL). Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol* 2008;9(2):105-16.

Pfreundschuh M, Trümper L, Osterborg A *et al.* MabThera international trial group. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera international trial (MInT) group. *Lancet Oncol* 2006;7(5):379-91.

Pulte D, Gondos A, Brenner H. Ongoing improvement in outcomes for patients diagnosed as having non-Hodgkin’s lymphoma from the 1990s to the early 21st century. *Arch Intern Med* 2008;168:469-76.

Reff ME, Carner K, Chambers KS *et al.* Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994;83:435-45.

Rituximab Summary of Product Characteristics

Rodríguez-Abreu D, Llanos Muñoz M, Provencio Pulla M, Rueda Domínguez A, Isla Casado D; SEOM (Spanish Society for Medical Oncology). SEOM clinical guidelines for the treatment of follicular non-Hodgkin's lymphoma. *Clin Transl Oncol.* 2010 Nov;12(11):760-4

Salar A, Bouabdallah R, McIntyre C *et al.* A two-stage phase Ib study to investigate the pharmacokinetics, safety and tolerability of subcutaneous rituximab in patients with follicular lymphoma as part of maintenance treatment. *Blood (ASH Annual Meeting Abstracts)* 2010;116(21): abstract 2858.

Salar A, *et al.* Final Results of the BP22333 Study Demonstrate Non-Inferior Pharmacokinetics and Safety of Subcutaneous Administration of Rituximab Compared with Intravenous Administration As Maintenance Therapy in Patients with Follicular Lymphoma (ASH Annual Meeting Abstracts) 2012. Abstract 1641. Full citation pending.

Salles G, Mounier N, de Guibert S *et al.*: Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: Results of the GELA-GOELAMS FL2000 study. *Blood* 2008;112:4824-31.

Shipp MA, Harrington DP *et al.* A predictive model for aggressive non-Hodgkin's lymphoma. The international non-Hodgkin's lymphoma prognostic factors project. *N Engl J Med* 1993;329(14):987-94.

[REDACTED]

Smith TJ, Khatcheressian J, Lyman GH *et al.* 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24(19):3187-205.

Solal-Celigny P, Roy P, Colombat P *et al.* Follicular lymphoma international prognostic index. *Blood* 2004;104(5):1258-65.

Sousou T, Friedberg J. Rituximab in indolent lymphomas. *Semin Hematol* 2010;47(2):133-42.

Stilgenbauer S, Zenz T, Winkler D *et al.*; German chronic lymphocytic leukemia study group. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: Clinical results and prognostic marker analyses from the CLL2H study of the German chronic lymphocytic leukemia study group. *J Clin Oncol* 2009;27(24):3994-4001.

Swenson WT, Wooldridge JE, Lynch CF *et al.* Improved survival of follicular lymphoma patients in the United States. *J Clin Oncol* 2005;23:5019-26.

Swerdlow SH, Campo E, Harris NL *et al.* WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edition, IARC Press, 2008.

Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. *Immunol Today* 1994;15:450-4.

Tilly H, Dreyling M; ESMO guidelines working group. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(suppl 5):v172-4.

Wynne C, Harvey V, Schwabe C *et al.* The development of a formulation of trastuzumab for subcutaneous administration. *Ann Oncol* 2010;21(8):viii78–viii95, abstract 218PD.

Yin A, Li J, Hurst D *et al.* Population pharmacokinetics (PK) and association of PK and clinical outcomes of rituximab in patients with non-Hodgkin's lymphoma. *J Clin Oncol*

2010;28:(suppl; abstract e13108) [*Published in conjunction with the ASCO 2010 Annual Meeting*].

11. APPENDICES

11.1 APPENDIX 1 SCHEDULE OF ASSESSMENTS FOR PATIENTS WITH CD20+ FOLLICULAR NHL

Study Period	Screening / Baseline	Induction (cycles)								Final Staging	Maintenance (cycles)												EOT	F/UP	EOS		
Timing / Assessments		Every 21+28d depending on standard chemotherapy								4-6w after last dose of SC Rit.	Every 8 w (± 7 days)												4-6w after last dose of SC Rit	Every 3m (year 1) Every 6m (year 2)	End of Study Visit		
Visit	D -28 to D -1	1[a]	2	3	4	5	6	7	8		1	2	3	4	5	6	7	8	9	10	11	12					
Written informed consent [b]	X																										
Demographic data	X																										
Medical history	X																										
Documentation of Follicular NHL diagnosis and WHO Classification [c]	X																										
Documentation of/testing for HIV, active hepatitis and other infections [d]	X																										
Tumour evaluation [e.1]	X									X															X[e.2]	X[e.2]	X[e.2]
Physical examination, infection assessment, vital signs [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height and weight	X									X																	
12-lead ECG	X																										
FLIPI score; GELF criteria [g]	X																										
ECOG performance status [h]	X																										
Serum pregnancy test [i]	X																										

Study Period	Screening / Baseline	Induction (cycles)								Final Staging	Maintenance (cycles)												EOT	F/UP	EOS		
Timing / Assessments		Every 21+28d depending on standard chemotherapy								4-6w after last dose of SC Rit.	Every 8 w (± 7 days)												4-6w after last dose of SC Rit	Every 3m (year 1) Every 6m (year 2)	End of Study Visit		
Visit	D -28 to D -1	1[a]	2	3	4	5	6	7	8		1	2	3	4	5	6	7	8	9	10	11	12					
Laboratory: Haematology, Biochemistry, Coagulation tests [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion/ Exclusion criteria review	X																										
Study Treatment (minimum doses) [k]					X	X	X	X									X	X	X	X	X	X					
Adverse event recording [l.1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatments & therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival	X									X														X	X	X	
RASQ [n]	X									X														X			
EuroQoL										X														X			

- Patients must have received at least one full dose of rituximab IV (defined as standard full dose of rituximab IV 375 mg/m² administered without interruption or early discontinuation because of tolerability issues) before enrolment. All Screening/Baseline assessments could have been performed at the IV cycle visit.
- Signed informed consent must be obtained prior to any study-required Screening/Baseline assessments.
- Diagnosis of follicular NHL before treatment must have included histological diagnosis and initial CD20 expression confirmation.
- Patients known to have active hepatitis C, active hepatitis B, history of HIV seropositive status, 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. Local guidelines for patient consent to viral testing must be adhered to. Patients with hepatitis B or C positive serology testing (i.e. positive hepatitis B virus antibodies serology or positive hepatitis C virus antibodies serology) but with undetectable viral load (i.e. negative PCR for HBV RNA or HCV RNA) may be included.
- e.1) CT and MRI are currently the best available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT or MRI should be performed according to institutional standards. Tumour assessment will be based on CT scans of the neck, chest, abdomen and pelvis, as applicable. CT scan with contrast is the recommended technique. However, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Owing to the global nature of this study, and due to limited availability of

FDG-PET scanners, an FDG-PET scan cannot be mandated. The CT scan used for eligibility assessment may be performed up to 35 days before first dose of IV rituximab. The end-of-treatment response assessment including radiology/imaging report must be obtained 4-6 weeks after the last dose of Induction treatment. Response should be determined on the basis of radiographic and clinical evidence of disease according to the IWG guidelines ([Cheson et al. 1999](#); see [Appendix 3](#)), or if not applicable, institutional standards should be used for tumour evaluation. Disease progression will be evaluated by the Investigator according to the IWG response criteria for NHL ([Cheson et al. 1999](#); see [Appendix 3](#)) or other country standards until PD. Screening/Baseline bone marrow examinations should include biopsy and aspirate for morphology (flow studies are optional) for staging purposes unless it has been performed within 4 months prior to first dose of rituximab IV and was done for the purpose of diagnosis and staging of FL. Subsequent bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline.

e.2) Patients who do not complete the study treatment per protocol will undergo end-of-study assessment within 4-6 weeks after the last dose of study treatment and will be followed until the end of the whole study according to local practice efficacy assessment [i.e. tumour response / progression (if PD not yet documented), survival, or documentation of any new anti-lymphoma treatment, whatever happens first].

- f. As part of physical exam, SC injection sites will be checked at every treatment visit. As part of tumour assessments, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Patients should be assessed for presence of active infections throughout the treatment periods. Vital signs assessment includes resting heart rate, body temperature and blood pressure.
- g. FLIPI score determined at Baseline (prior to Cycle 1). Where possible, the baseline FLIPI score should be calculated from the patient notes. Missing FLIPI scores will not preclude enrolment. GELF Criteria to initiate treatment. See [Appendix 4](#).
- h. ECOG performance status needs to be ≤ 3 for inclusion of the patient into the study. See [Appendix 4](#).
- i. Women of childbearing potential (defined as pre-menopausal women or women who are < 2 years after the onset of menopause and not surgically sterile) must undergo serum pregnancy test within 7 days prior to first dose or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to dosing.
- j. Haematology parameters will include haemoglobin, RBC, WBC, and platelet count. Biochemistry parameters at Screening will include sodium, potassium, ALT/SGPT, AST/SGOT, total bilirubin, serum creatinine, alkaline phosphatase, albumin, BUN, C-reactive protein and LDH. Biochemistry parameters at any further timepoint during the study will include sodium, potassium, ALT/SGPT, AST/SGOT, total bilirubin, and serum creatinine. Coagulation tests will include: INR, PT, and aPTT. The results from the safety laboratory assessments must be available on treatment days, prior to the rituximab administrations. For laboratory assessments it will be allowed a time window of 5 days.
- k. Patients undergoing induction therapy must be eligible to receive at least 4 cycles of rituximab SC in addition to standard chemotherapy. Patients undergoing Maintenance therapy must be eligible to receive at least 6 cycles of rituximab SC. For those patients who finish the induction therapy and start the maintenance therapy, the first dose of maintenance rituximab SC will be given within 8-12 weeks after the last dose of induction rituximab SC.
- l. l.1) After informed consent has been obtained but prior to dosing, only SAEs caused by a protocol-mandated intervention should be reported (e.g. SAEs related to invasive procedures such as biopsies). All clinical and laboratory AEs reported during the study will be documented and graded using the NCI CTCAE criteria, version 4.0. Special attention should be given to any acute infusion-related toxicities. [l.2](#)). After initiation of study drug, all AEs/SAEs, regardless of relationship to study drug, will be reported until study closure.
- m. During post-treatment follow-up concomitant medication will be recorded only if required for post-treatment safety assessment (i.e. SAEs related to rituximab therapy and/or adverse events of special interest starting up until 6 months after the last dose of study medication).

- n. Treatment satisfaction will be assessed using the Rituximab Administration Satisfaction Questionnaire (RASQ): n1) RASQ – IV will be done after last dose of rituximab IV prior to switching to the SC route; n2) RASQ-SC will be done at the end of induction therapy (i.e. after last induction dose of rituximab SC, prior to chemotherapy) and at the end of maintenance therapy (i.e. after last maintenance dose of rituximab SC, prior to chemotherapy). .

11.2

APPENDIX 2 SCHEDULE OF ASSESSMENTS FOR PATIENTS WITH CD20+ DLBCL

Study Period	Screening / Baseline	Induction (cycles)							EOT	F/UP	EOS
Timing / Assessments		Every 21+28d depending on standard chemotherapy							4-6w after last dose of SC Rit.	Post-Treatment Follow-Up Every 3m (year 1) Every 6m (year 2)	End of Study Visit
Visit	D -28 to D -1	[a]	2	3	4	5	6	7			
Written informed consent [b]	X										
Demographic data	X										
Medical history	X										
Documentation DLBCL diagnosis and WHO Classification [c]	X										
Documentation of/testing for HIV, active hepatitis and other infections [d]	X										
Tumour evaluation [e.1]	X									X	X [e.2]
Physical examination, infection assessment, vital signs [f]	X	X	X	X	X	X	X	X	X	X	X
Height and weight	X									X	
12-lead ECG	X										
IPI score [g]	X										
ECOG performance status [h]	X									X	
Serum pregnancy test [i]	X										
Laboratory: Haematology,	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening / Baseline	Induction (cycles)							EOT	F/UP	EOS
Timing / Assessments		Every 21+28d depending on standard chemotherapy							4-6w after last dose of SC Rit.	Post-Treatment Follow-Up Every 3m (year 1) Every 6m (year 2)	End of Study Visit
Visit	D -28 to D -1	1[a]	2	3	4	5	6	7			
Biochemistry, Coagulation tests [j]											
Inclusion/Exclusion criteria review	X										
Study Treatment [k]					X	X	X	X			
Adverse event recording [l.1]	X	X	X	X	X	X	X	X	X	X[l.2]	X[l.2]
Concomitant treatments & therapies	X	X	X	X	X	X	X	X	X	X[m]	X[m]
Survival									X	X	X
RASQ[n]	X								X		X
EuroQoL									X		X

- a. Patients must have received at least one full dose of rituximab IV (defined as standard full dose of rituximab IV 375 mg/m² administered without interruption or early discontinuation because of tolerability issues) before enrolment. All Screening/Baseline assessments could have been performed at the IV cycle visit.
- b. Signed informed consent must be obtained prior to any study-required Screening/Baseline assessments.
- c. Diagnosis of DLBCL before treatment must have included histological diagnosis and initial CD20 expression confirmation.
- d. Patients known to have active hepatitis C, active hepatitis B, history of HIV seropositive status, 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. Local guidelines for patient consent to viral testing must be adhered to. Patients with hepatitis B or C positive serology testing (i.e. positive hepatitis B virus antibodies serology or positive hepatitis C virus antibodies serology) but with undetectable viral load (i.e. negative PCR for HBV RNA or HCV RNA) may be included.
- e. e.1) CT and MRI are currently the best available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT or MRI should be performed according to institutional standards. Tumour assessment will be based on CT scans of the neck, chest, abdomen and pelvis, as applicable. CT scan with contrast is the recommended technique. However, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Owing to the global nature of this study, and due to limited availability of FDG-PET scanners, an FDG-PET scan cannot be mandated (for those sites using PET/CT, the response will need to be based on the CT result of the PET/CT). The CT scan used for eligibility assessment may be performed up to 35 days before first dose of IV rituximab. The end-of-treatment response assessment including

radiology/imaging report must be obtained 4-6 weeks after the last dose of Induction treatment. Response should be determined on the basis of radiographic and clinical evidence of disease according to the IWG guidelines (Cheson *et al.* 1999; see [Appendix 3](#)), or if not applicable, institutional standards should be used for tumour evaluation. Screening/Baseline bone marrow examinations should include biopsy and aspirate for morphology (flow studies are optional) for staging purposes unless it has been performed within 4 months prior to first dose of rituximab IV and was done for the purpose of diagnosis and staging of DLBCL. Subsequent bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline. e.2) Patients who do not complete the study treatment per protocol will undergo end-of-study assessment within 4-6 weeks after the last dose of study treatment and will be followed until the end of the whole study according to local practice efficacy assessment [i.e. tumour response / progression (if PD not yet documented), survival, or documentation of any new anti-lymphoma treatment, whatever happens first].

- f. As part of physical exam, SC injection sites will be checked at every treatment visit. As part of tumour assessments, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Patients should be assessed for presence of active infections throughout the treatment periods. Vital signs assessment includes resting heart rate, body temperature and blood pressure.
- g. IPI (according to Shipp *et al.* 1993) score determined at Baseline (prior to Cycle 1). Where possible, the baseline IPI score should be calculated from the patient notes. Missing IPI scores will not preclude enrolment. See [Appendix 4](#).
- h. ECOG performance status needs to be ≤ 3 for inclusion of the patient into the study. See [Appendix 4](#).
- i. Women of childbearing potential (defined as pre-menopausal women or women who are < 2 years after the onset of menopause and not surgically sterile) must undergo serum pregnancy test within 7 days prior to first dose or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to dosing.
- j. Haematology parameters will include haemoglobin, RBC, WBC, and platelet count. Biochemistry parameters at Screening will include sodium, potassium, ALT/SGPT, AST/SGOT, total bilirubin, serum creatinine, alkaline phosphatase, albumin, BUN, C-reactive protein and LDH. Biochemistry parameters at any further timepoint during the study will include sodium, potassium, ALT/SGPT, AST/SGOT, total bilirubin, and serum creatinine. Coagulation tests will include: INR, PT, and aPTT. The results from the safety laboratory assessments must be available on treatment days, prior to the rituximab administrations. For laboratory assessments it will be allowed a time window of 5 days.
- k. Patients undergoing induction therapy must be eligible to receive at least 4 cycles of rituximab SC in addition to standard chemotherapy.
 - l. l.1) After informed consent has been obtained but prior to dosing, only SAEs caused by a protocol-mandated intervention should be reported (e.g. SAEs related to invasive procedures such as biopsies). All clinical and laboratory AEs reported during the study will be documented and graded using the NCI CTCAE criteria, version 4.0. Special attention should be given to any acute infusion-related toxicities. During post-treatment follow-up, only SAEs related to rituximab therapy will be followed. Adverse events of special interest, regardless of relationship to study treatment or whether or not they are SAEs, will be reported if they start up until 6 months after the last dose of study medication. l.2). After initiation of study drug, all AEs/SAEs, regardless of relationship to study drug, will be reported until study closure
- m. During post-treatment follow-up concomitant medication will be recorded only if required for post-treatment safety assessment (i.e. SAEs related to rituximab therapy and/or adverse events of special interest starting up until 6 months after the last dose of study medication).
- n. Treatment satisfaction will be assessed using the Rituximab Administration Satisfaction Questionnaire. RASQ: n1) RASQ – IV will be done after last dose of rituximab IV prior to switching to the SC route; n2) RASQ-SC will be done at the end of induction therapy (i.e. after last induction dose of rituximab SC, prior to chemotherapy) and at the end of maintenance therapy (i.e. after last maintenance dose of rituximab SC, prior to chemotherapy).

11.3 APPENDIX 3 RESPONSE ASSESSMENT ACCORDING TO THE INTERNATIONAL WORKING GROUP RESPONSE CRITERIA

Complete response (CR) requires the following:

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

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

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

Partial response (PR) requires the following:

1. $\geq 50\%$ decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from

as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, e.g., large-cell lymphoma or low-grade lymphoma (i.e., small, lymphocytic small cleaved, or mixed small and large cells).
6. No new sites of disease.

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

Progressive disease (PD, nonresponders) requires the following:

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

Table summary

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	$\geq 50\%$ decrease	$\geq 50\%$ decrease	Irrelevant
	Decrease in liver / spleen	$\geq 50\%$ decrease	$\geq 50\%$ decrease	Irrelevant
SD		< 50% decrease	< 50% decrease	Irrelevant
Progression	Enlarging liver / spleen; new sites	New or increased	New or increased	Reappearance

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

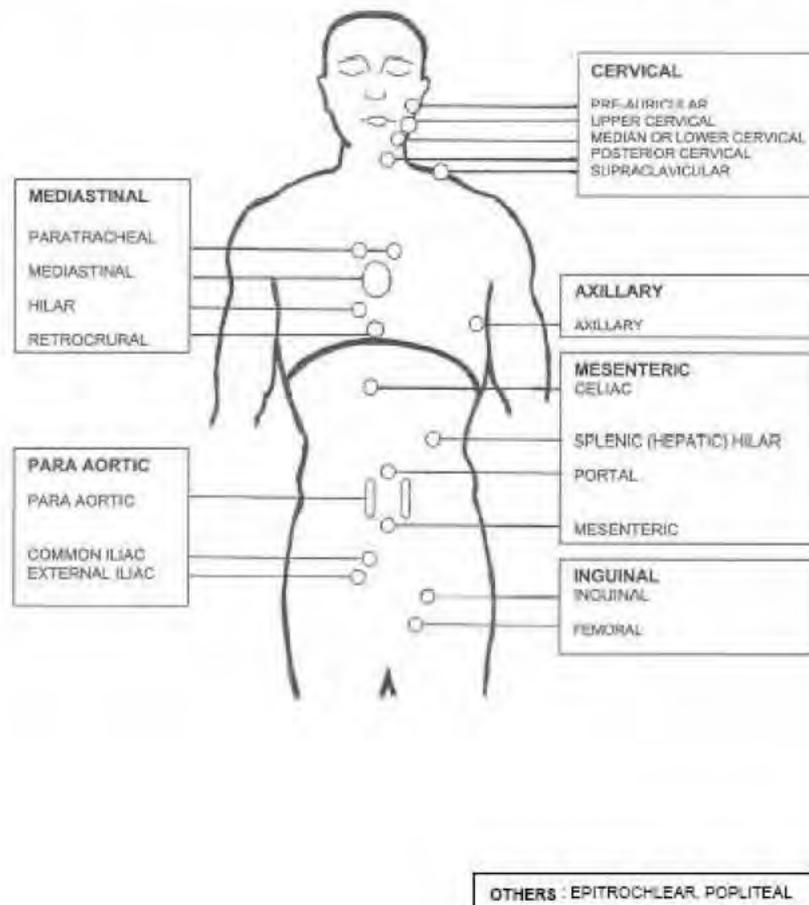
11.4 APPENDIX 4 GRADING SYSTEMS AND SCALES

11.4.1 ECOG Performance status

Grade	ECOG Status
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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, *et al.* Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.

11.4.2 Follicular Lymphoma International Prognostic Index (FLIPI)



Five adverse prognostic factors were selected:

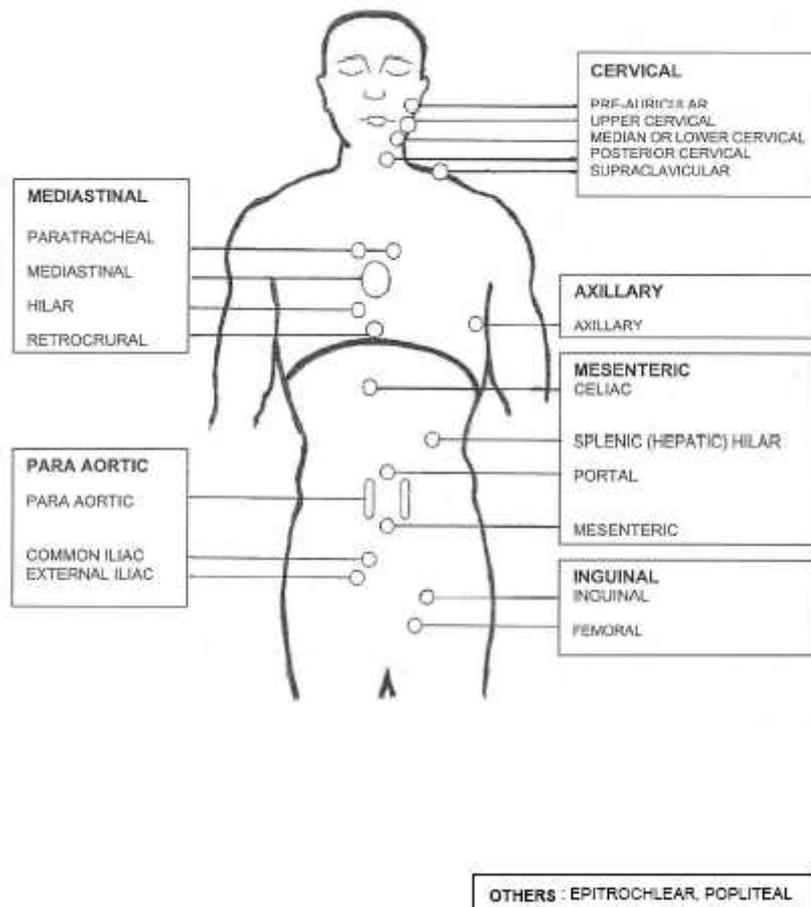
1. Age (> 60 vs. ≤ 60)
2. Ann Arbor Stage (III-IV vs. I-II)
3. Haemoglobin level (< 12 g/dl vs. ≥ 12 d/dl)
4. Number of nodal areas (> 4 vs. ≤ 4)
5. Serum LDH level ($>$ normal vs. \leq normal)

Three risk groups were defined:

1. LOW RISK (0-1 adverse factor)
2. INTERMEDIATE RISK (2 adverse factors)
3. POOR RISK (≥ 3 adverse factors)

Source: Solal-Celigny P, Roy P, Colombat P *et al.* Follicular lymphoma international prognostic index. *Blood* 2004;104(5):1258-65.

11.4.3 Prognosis in Diffuse Large B-cell Lymphoma: International Prognostic Index (IPI) and Revised International Prognostic Index (R-IPI).



International Prognosis Index (IPI):

Five adverse prognostic factors are considered:

- Age older than 60
- Lactate dehydrogenase level higher than normal
- Poor general health status (ECOG performance status score of 2 or greater)
- Stage III or IV disease
- More than one involved extranodal disease site

The International Prognostic Index (IPI), gives one point for each of the above characteristics, for a total score ranging from zero to five, representing the following risk groups:

- Low risk — IPI score of 0 or 1
- Low to intermediate risk — IPI score of 2
- High to intermediate risk — IPI score of 3
- High risk — IPI score of 4 or more

Revised International Prognostic Index (R-IPI)

The Revised International Prognostic Index (R-IPI), gives one point for each of the above characteristics, for a total score ranging from zero to five, representing the following risk groups:

- Low risk — IPI score of 0
- Intermediate risk — IPI score of 1 or 2
- High risk — IPI score of 3 or more

Source: The original IPI was developed by Shipp et al. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. NEJM 329:987-994. (1993). The newer prognostic index was revised and developed by Sehn et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 109:1857-1861. (2007)

11.4.4 GELF Criteria

Initiate treatment in patients meeting one or more of the following:

- High tumor bulk (see definition below)
- Presence of systemic symptoms
- Eastern Cooperative Oncology Group (ECOG) performance status > 1
- Serum lactate dehydrogenase (LDH) or B2-microglobulin level above normal values

High tumor bulk is defined with the following parameters:

- A tumor > 7 cm in diameter
- 3 nodes in 3 distinct areas each > 3 cm in diameter
- Symptomatic spleen enlargement
- Organ compression
- Ascites or pleura effusion

Source: Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. J Clin Oncol. 1997;15:1110-7

11.5 APPENDIX 5 GUIDELINES FOR STANDARD RITUXIMAB SC PREPARATION AND ADMINISTRATION

HOW SUPPLIED

Rituximab SC for the subcutaneous administration (MabThera SC; Ro 045-2294) is supplied as a ready to use liquid formulation with a nominal content of 120 mg/mL rituximab in an 11.7 mL vial and must not be diluted prior to administration. The drug product contains 2,000 U/mL rHuPH20 (manufactured in a CHO cell line) 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. The drug product is a sterile, colourless to yellowish, clear to opalescent liquid in colourless 11.7 mL vials.

STABILITY AND STORAGE

The recommended storage condition for rituximab SC is 2°C to 8°C, protected from light. Once transferred from the vial to the syringe, the solution of Mabthera SC formulation is physically and chemically stable for 48 hours at 2°C to 8°C, and subsequently 8 hours at 30°C in diffuse daylight. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid any potential needle clogging. From a microbiological point of view the product should be used immediately after first opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The product should be handled gently and foaming avoided. It should not be shaken. Batch specific details and information on shelf-life are given on the packaging label.

PREPARATION OF RITUXIMAB FOR SC ADMINISTRATION

Patients receiving SC rituximab will be administered at a dose of 1400 mg.

1. Withdraw 11.7 mL of solution from the vial.
2. Insert the injection needle (25 or 27 gauge) using sterile technique in the subcutaneous tissue of the abdomen.

Note: 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 every patient's subcutaneous tissue. Study drug should not be injected into moles, scars, or bruises. The skin should be pinched and needle inserted before the skin is released and the pressure on the syringe can be applied.

3. Push the injection manually at a flow rate of approximately 2 mL/min; administration of the 11.7 mL volume should take approximately 5 to 6 minutes.
4. If there is a request by the patient to interrupt the injection, initially ease the pressure on the syringe to alleviate the pain. If the pain is not alleviated, stop the injection and ask the patient when he/she is comfortable to resume the injection. The remaining content of the syringe should be administered at the same injection site.

11.6 APPENDIX 6 NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

In the present study, toxicities will be recorded according to the NCI CTCAE, version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI site, at the following address: <http://ctep.cancer.gov>

Investigators who do not have access to Internet can contact the Data Centre to receive a hard copy of this document by mail.

11.7 APPENDIX 7 RASQ

Rituximab Administration Satisfaction Questionnaire-IV (RASQ-IV): will be done after last dose of Rituximab IV prior to switching to rituximab SC.

Instructions: Please complete the following questions based on your Rituximab treatment. Your Rituximab was given through a thin plastic tube and a needle that was put directly into a vein in your arm, called an intravenous or IV infusion. Your Rituximab treatment was given BEFORE your chemotherapy medicine. Please answer the questions **based on your most recent Rituximab IV infusion.**

1. Thinking about the Rituximab IV infusion, how satisfied or dissatisfied are you with the IV infusion?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied
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2. Thinking about the Rituximab IV infusion, how do you rate the pain, swelling, or redness you experienced at the site of the drug injection?

None	Mild	Moderate	Severe	Very Severe
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3. Thinking about the Rituximab IV infusion, how do you rate the pain you experience with the IV infusion process?

None	Mild	Moderate	Severe	Very Severe
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4. Thinking about the Rituximab IV infusion, are the side effects of the IV infusion as you expected?

Much better than expected	Somewhat better than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations
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5. Before you receive the Rituximab IV infusion do you feel anxious about having the infusion?

Not at all	A little bit	Somewhat	Quite a bit	Very much
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6. When you receive the Rituximab IV infusion do you worry that your condition would get worse?

Not at all	A little bit	Somewhat	Quite a bit	Very much
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7. When you receive the Rituximab IV infusion do you feel anxious thinking about your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much
8. Thinking about the Rituximab IV infusion, how confident are you that the Rituximab IV infusion is treating your disease?				
Not at all	A little bit	Somewhat	Quite a bit	Very much
9. When you receive the Rituximab treatment do you feel restricted by the IV infusion?				
Not at all	A little bit	Somewhat	Quite a bit	Very much
10. Thinking about the Rituximab IV infusion, how convenient is it for you to get your IV infusion?				
Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient
11. Thinking about the Rituximab IV infusion, how do you feel about the amount of time it takes to get your IV infusion?				
	Too short	Just right	Too long	
12. Thinking about the Rituximab IV infusion, do you feel that the length of time to get your IV infusion was as you expected?				
Much shorter than expected	Somewhat shorter than expected	As expected	Somewhat longer than expected	Much longer than expected
13. Thinking about the Rituximab IV infusion, how bothered are you by the amount of time it takes to get the infusion?				
Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered
14. How much does the Rituximab IV infusion:				
a) Interfere with your usual or daily activities?				
Not at all	A little bit	Somewhat	Quite a bit	Very much
b) Limit your daily activities?				
Never	Rarely	Sometimes	Most of the time	Always
15. Because of the length of time to apply the Rituximab IV infusion do you feel that you have lost or gained time for other things?				

Rituximab Administration Satisfaction Questionnaire-SC (RASQ-SC): will be done at the end of induction therapy (i.e. after last induction dose of rituximab SC, prior to chemotherapy) and, if applicable, at the end of maintenance therapy (i.e. after last maintenance dose of rituximab SC, prior to chemotherapy).

Instructions: Please complete the following questions based on your Rituximab treatment. Your Rituximab was given through a needle injected into your abdomen (or belly) area, called a subcutaneous or SC injection. Your Rituximab treatment was given BEFORE your chemotherapy medicine. Please answer the questions **based on your most recent Rituximab SC injection.**

1. Thinking about the Rituximab SC injection, how satisfied or dissatisfied are you with the SC injection?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied
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2. Thinking about the Rituximab SC injection, how do you rate the pain, swelling, or redness you experienced at the site of the drug injection?

None	Mild	Moderate	Severe	Very Severe
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3. Thinking about the Rituximab SC injection, how do you rate the pain you experience with the SC injection process?

None	Mild	Moderate	Severe	Very Severe
------	------	----------	--------	-------------

4. Thinking about the Rituximab SC injection, are the side effects of the SC injection as you expected?

Much than expected better	Somewhat better than expected	Met my expectations	Somewhat worse than my expectations	Much than expectations worse my
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5. Before you receive the SC injection do you feel anxious about having the injection?

Not at all	A little bit	Somewhat	Quite a bit	Very much
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6. When you receive the SC injection do you worry that your condition would get worse?

Not at all	A little bit	Somewhat	Quite a bit	Very much
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7. When you receive the SC injection do you feel anxious thinking about your disease?

Not at all	A little bit	Somewhat	Quite a bit	Very much
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8. Thinking about the Rituximab SC injection, how confident are you that Rituximab SC injection is treating your disease?

Not at all A little bit Somewhat Quite a bit Very much

9. When you receive the Rituximab treatment do you feel restricted by the SC injection?

Not at all A little bit Somewhat Quite a bit Very much

10. Thinking about the Rituximab SC injection, how convenient is it for you to get your SC injection?

Very convenient Convenient Neither convenient nor inconvenient Inconvenient Very inconvenient

11. Thinking about the Rituximab SC injection, how do you feel about the amount of time it takes to get your SC injection?

Too short Just right Too long

12. Thinking about the Rituximab SC injection, do you feel that the length of time to get your SC injection is as you expected?

Much shorter than expected Somewhat shorter than expected As expected Somewhat longer than expected Much longer than expected

13. Thinking about the Rituximab SC injection, how bothered are you by the amount of time it takes to get the injection?

Not at all bothered A little bothered Moderately bothered Quite bothered Very bothered

14. How much does the Rituximab SC injection:

a) Interfere with your usual or daily activities?

Not at all A little bit Somewhat Quite a bit Very much

b) Limit your daily activities?

Never Rarely Sometimes Most of the time Always

15. Because of the length of time to apply the Rituximab SC injection do you feel that you have lost or gained time for other things?

Lost a lot of time Lost some time Neither lost nor gained time Gained some time Gained a lot of time

16. When you receive the Rituximab treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

- Yes, I had more than enough time to talk to my nurse and/or doctor.
- Yes, but I would have liked more time to talk to my nurse and/or doctor.
- It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.
- No, I did not have enough time to talk to my nurse and/or doctor.
- No, I did not talk to my nurse and/or doctor at all.

17. Does the Rituximab SC injection impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes No

18. Thinking about the Rituximab treatment, if given the option, which would you prefer (both options treat your disease in the same way)? Please check one.

- Prefer intravenous (IV) infusion given through a thin plastic tube and a needle into your vein (IV drip). This treatment option usually takes 1.5 to 3 hours.
- Prefer subcutaneous (SC) injection, applied with a syringe and needle into the skin of the abdomen (or belly). This treatment option is usually takes 5 to 7 minutes.
- No preference for treatment option.

19. Thinking about the Rituximab treatment, would you recommend the way you received the treatment (SC injection) to another patient?

Definitely yes Probably yes I don't know Probably not Definitely not

11.8

APPENDIX 8: GUIDELINES FOR MANAGING SPECIFIC AE RELATED TO R-CHOP TREATMENT

Event	Action to Be Taken
<ul style="list-style-type: none"> Haematologic toxicity: Grade 4 	<ul style="list-style-type: none"> Hold all study treatment for a maximum of 3 weeks. Give supportive treatment. If improvement to grade ≤ 2 does not occur within 3 weeks, discontinue all study treatment. First episode: If improvement to grade ≤ 2, decrease cyclophosphamide dose to 500 mg/m² and doxorubicin dose to 35 mg/m² for subsequent cycles. Second episode: If improvement to grade ≤ 2, decrease cyclophosphamide dose to 375 mg/m² and doxorubicin dose to 25 mg/m² for subsequent cycles. Third episode: Discontinue CHOP. If improvement to grade ≤ 2, continue rituximab at full dose. Fourth episode: Discontinue all study treatment.
<ul style="list-style-type: none"> Haematologic toxicity: Grade 3 	<ul style="list-style-type: none"> Hold all study treatment for a maximum of 3 weeks. Give supportive treatment. If improvement to grade ≤ 2 does not occur within 3 weeks, discontinue all study treatment. If improvement to grade ≤ 2, continue CHOP at current dose and continue rituximab at full dose.
<ul style="list-style-type: none"> Haematologic toxicity: Grade 1 or 2 	<ul style="list-style-type: none"> No action required.
<ul style="list-style-type: none"> Neurotoxicity: Grade 4 	<ul style="list-style-type: none"> Discontinue CHOP. Hold rituximab for a maximum of 3 weeks. If improvement to grade ≤ 1 does not occur within 3 weeks, discontinue all study treatment. If improvement to grade ≤ 1, continue rituximab at full dose.
<ul style="list-style-type: none"> Neurotoxicity: Grade 2 or 3 	<ul style="list-style-type: none"> Hold all study treatment for a maximum of 2 weeks. If improvement to grade ≤ 1 does not occur within 2 weeks, discontinue all study treatment. If improvement to grade ≤ 1, reduce vincristine dose by 50% for subsequent cycles, continue cyclophosphamide, doxorubicin, and prednisone at current dose, and continue rituximab at full dose.
<ul style="list-style-type: none"> Neurotoxicity: Grade 1 	<ul style="list-style-type: none"> No action required.

Event	Action to Be Taken
<ul style="list-style-type: none"> Other non-haematologic toxicities: Grade 3 or 4 	<ul style="list-style-type: none"> Hold all study treatment for a maximum of 3 weeks. If improvement to grade ≤ 1 or baseline does not occur within 3 weeks, discontinue all study treatment. First episode: If improvement to grade ≤ 1 or baseline, decrease cyclophosphamide dose to 500 mg/m² and doxorubicin dose to 35 mg/m² for subsequent cycles. Second episode: If improvement to grade ≤ 1 or baseline, decrease cyclophosphamide dose to 375 mg/m² and doxorubicin dose to 25 mg/m² for subsequent cycles. Third episode: Discontinue CHOP. If improvement to grade ≤ 1 or baseline, continue rituximab at full dose. Fourth episode: Discontinue all study treatment.
<ul style="list-style-type: none"> Other non-haematologic toxicities: Grade 2 	<ul style="list-style-type: none"> Hold all study treatment for a maximum of 3 weeks. If improvement to grade ≤ 1 or baseline does not occur within 3 weeks, discontinue all study treatment. If improvement to grade ≤ 1 or baseline, continue CHOP at current dose and continue rituximab at full dose.
<ul style="list-style-type: none"> Other non-haematologic toxicities: Grade 1 	<ul style="list-style-type: none"> No action required.

Note: A haematologic toxicity is defined as neutropenia, anaemia, or thrombocytopenia