Official Title: A Single Arm, Multicentre, Phase IIIB Study to Evaluate Safety, Efficacy and Pharmacokinetic (PK) of Subcutaneous (SC) Rituximab Administered During Induction Phase or Maintenance in Previously Untreated Patients With CD20+ Diffuse Large B Cell Lymphoma (DLBCL) or Follicular Lymphoma (FL)

NCT Number: NCT01889069

Document Date: Protocol Version 4: 08-Sep-2016

PROTOCOL

TITLE:	**A SINGLE ARM, MULTICENTRE, PHASE IIIB STUDY TO EVALUATE SAFETY, EFFICACY AND PHARMACOKINETIC (PK) OF SUBCUTANEOUS (SC) RITUXIMAB ADMINISTERED DURING INDUCTION PHASE OR MAINTENANCE IN PREVIOUSLY UNTREATED PATIENTS WITH CD20+ DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) OR FOLLICULAR LYMPHOMA (FL)**
PROTOCOL NUMBER:	ML28881
VERSION:	4
EUDRACT NUMBER:	2013-000647-12
IND NUMBER:	N/A
TEST PRODUCT:	Rituximab (RO 45-2294)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Roche S.p.A., 20900 Monza, Italy
DATE FINAL :	05-Jul-2016

PROTOCOL APPROVAL:

PROTOCOL APPROVED BY:

Dr. [redacted] *(Roche S.p.A)* Date: 6/9/2016

[redacted] ***M.Phil.***

Date:

Prof. [redacted] *Italy*

Date: [redacted]

Dr. [redacted] *Italy*

[redacted]

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PROTOCOL

TITLE:	**A SINGLE ARM, MULTICENTRE, PHASE IIIB STUDY TO EVALUATE SAFETY, EFFICACY AND PHARMACOKINETIC (PK) OF SUBCUTANEOUS (SC) RITUXIMAB ADMINISTERED DURING INDUCTION PHASE OR MAINTENANCE IN PREVIOUSLY UNTREATED PATIENTS WITH CD20+ DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) OR FOLLICULAR LYMPHOMA (FL)**
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DATE FINAL :	05-Jul-2016

PROTOCOL APPROVAL:

PROTOCOL APPROVED BY:	Dr. [redacted] *(Roche S.p.A)*	Date:
	[redacted] ***M.Phil.***	Date: 08SEP2016
	Prof. [redacted] *Italy*	Date:
	Dr. [redacted] *Italy*	Date:

PROTOCOL AMENDMENT, VERSION 4:
I. RATIONALE

Protocol ML28881 has been amended to add an intermediate analysis and to specify the end of treatment visit in the schedule of assessment.

The detailed rationales for amending this protocol are described below:

- an intermediate analysis was considered necessary to analyze all patients who concluded the induction phase regarding the safety and PK endpoints.
- due to inconsistencies between the core text and schedule of assessment, the “Early termination/End of Treatment visit” was added in the appendix 11.1 and 11.1.1.
- amendment to section 4.3.4 in agreement with new requirements

Impacted Sections of the Protocol:

- Protocol Synopsis
- 4.3.4 Post-Trial Access to Rituximab SC
- 4.5.1.8 Patient Reported Outcomes
- 6.1 Determination of Sample Size
- 6.8 Intermediate Analyses
- 11.1 Appendix 1 Schedule Of Assessments For Patients With Cd20+ Follicular NHL
- 11.1.1 Appendix 2 Schedule of Assessments for patients with CD20+ DLBCL

Please refer to the **Section II** of this document for the changes implemented in each section of the protocol.

PROTOCOL AMENDMENT, VERSION 4:
II. SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

Statistical Methods

Statistical Methods

The analysis of this Study will be exploratory and will primarily make use of descriptive statistical methods. Survivor functions will be estimated using Kaplan-Meier methodology and the effect of time on PK parameters will be explored using longitudinal data analysis.

[…] All enrolled patients who receive at least one dose of study medication and who have at least one post-baseline efficacy evaluation will be included in the Intent-to-Treat Population, which will be the primary analysis population for efficacy parameters. PK analysis population will include all recruited patients who receive the investigational treatment and have at least one PK sample collected and analyzed

Endpoint and Analysis In FL patients:

[…]

The effects over time of subject characteristics (age, weight, body surface area) on the above mentioned rituximab population PK parameter will be analyzed descriptively by computing a mixed model for repeated measures. ~~a non parametric analysis of covariance model~~.
The effects of gender and of covariates related to disease at baseline in different risk categories (FLIPI 0-1/2/≥3;) on the above mentioned rituximab PK population parameter will be analysed by means of ~~Wilcoxon t test and a non parametric analysis of variance model respectively~~ T test or Mann-Whitney U test, when appropriate.

Endpoint and Analysis In DLBCL patients:

[…]

The effects over time of subject characteristics (age, weight, BSA) on the above mentioned rituximab population PK parameters will be analysed descriptively by computing a mixed model for repeated measures~~a non parametric analysis of covariance model~~.

The effects of gender and of covariates related to disease at baseline in different risk categories (IPI 0 bulky/2/3/4) on the above mentioned rituximab PK population parameters will be analysed by means of Student's T test or Mann-Whitney U test, when appropriate ~~of Wilcoxon t test and a non parametric analysis of variance model respectively~~.

Determination of Sample Size

[…] In addition it will be relevant to show differences between gender in the systemic exposition (C_{trough}). An intermediate PK analysis will be conducted once all patients completed the Final Staging Visit at the End of Induction period.

The final PK analysis will be conducted once all scheduled PK samples are collected

Intermediate Analyses

One intermediate analyses is planned:
- The intermediate analysis will be done once all patients completed the Final Staging Visit at the End of Induction period.

The final analysis will be done at the end of study (i.e. last patient end of study visit).

4.3.4 POST-TRIAL ACCESS TO RITUXIMAB SC

~~Currently, Roche does not have any plans to provide rituximab SC to patients after conclusion of the Study. Roche will evaluate the appropriateness of continuing to provide rituximab SC to Study patients depending on the commercial availability of the drug at the time of Study completion.~~
Currently, Roche does not have any plans to provide rituximab SC to patients after conclusion of the study or any earlier patient withdrawal. Roche will evaluate the appropriateness of continuing to provide rituximab SC to study patients after evaluating the safety data gathered in the study. These analyses may be conducted prior to completion of the study. If these data are medically significant, Roche may amend the protocol to continue to provide rituximab SC in an open-label extension study to patients who have shown a demonstrable benefit from rituximab SC treatment during this study as measured by primary and secondary endpoints. This open-label extension study will continue until rituximab SC is commercially available to the participating patients in their countries or until Roche ceases producing or studying rituximab SC.

4.5.1.8 PATIENT REPORTED OUTCOMES

[…] Induction:
- pre-dose at 2nd rituximab SC administration
- cycle 8 (post-dose)

Manteinance:
- pre-dose at 2nd rituximab SC administration
- pre-dose at 7th rituximab SC administration
- cycle 12 (post-dose)

In case of Early Termination/End of Treatment visit PRO questionnaire should be administered to the patient if not already completed on Cycle 8 (DLBCL/FL) or Cycle 12 Post Dose (FL).

6.1 DETERMINATION OF SAMPLE SIZE

[…] As to PK outcomes evaluation, the sample size of 100 patients will assure the possibility to evaluate the following inter-individual variability's factors:

- gender
- age (≤ 70 years and > 70 years)
- weights and BSA (median, > 25% than median, < 25% than median)
- FLIPI (0-1/ 2 / ≥3)
- IPI (0-1/ 2 / 3/ > 3)

In addition it will be relevant to show differences between gender in the systemic exposition (C_{trough}).
An intermediate PK analysis will be conducted once all patients completed the Final Staging Visit at the End of Induction period.
The final PK analysis will be conducted once all scheduled PK samples are collected.

6.3.1 Analysis Populations

[...]
The Intention-to-Treat (ITT) population will include all enrolled patients ~~and,~~ who receive at least one dose of study medication and who have at least one post-baseline efficacy evaluation, and will be used for the efficacy outcomes analysis.
An additional Per Protocol (PP) set […]

6.6 PHARMACOKINETIC ANALYSES

[…] FL patients: […]
The effects over time of subject characteristics (age, weight, body surface area) on the above mentioned rituximab population PK parameter will be analyzed descriptively by computing a mixed model for repeated measures. ~~a non parametric analysis of covariance model~~.

The effects of gender and of covariates related to disease at baseline in different risk categories (FLIPI 0-1/2/≥3;) on the above mentioned rituximab PK population parameter will be analysed by means of ~~Wilcoxon t test and a non parametric analysis of variance model respectively~~ T test or Mann-Whitney U test, when appropriate.

[…] In DLBCL patients: […]
Descriptive statistics (mean, standard deviation, median and minimum and maximum values), will be computed for all PK parameters: C_{trough}, AUC, C_{max}, and CL/F (clearance/fraction of absorbed drug). The effects over time of subject characteristics (age, weight, BSA) on the above mentioned rituximab population PK parameters will be analysed descriptively by computing a mixed model for repeated measures ~~a non parametric analysis of covariance model~~.

The effects of gender and of covariates related to disease at baseline in different risk categories (IPI 0 bulky/2/3/4) on the above mentioned rituximab PK population parameters will be analysed by means of Student's T test or Mann-Whitney U test, when appropriate ~~of Wilcoxon t test and a non parametric analysis of variance model respectively~~.

6.8: INTERMEDIATE ANALYSES

One intermediate analyses is planned:
The intermediate analysis will be done once all patients completed the Final Staging Visit at the End of Induction period.

The final analysis will be done at the end of study (i.e. last patient end of study visit).

SECTION 11- APPENDICES

11.1 appendix 1 Schedule Of Assessments For Patients With CD20+ Follicular NHL

Study Period	Screening / Baseline		Specify assessments required for each time point in the Study. Example, Induction Treatment (including staging), Maintenance Treatment, Post-Treatment Follow-up, Early Treatment Termination / End of Study																									
Visit		Induction (cycles)									Final Staging	Maintenance (cycles)												Early Termination/End of Treatment	Post-treatment Follow-Up				End of Study Visit
Timing / Assessments	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		1-6	6-12	12-18	18-24	
RASQ [k]				(X)†	(X)	(X)	(X)		X			(X)	(X)	(X)	(X)	(X)	(X)	(X)				x	X*					

d. 1) CT and MRI …[..] 2) Patients who do not complete the study treatment per protocol will undergo end-of-study assessment within 4-8 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].

k. RASQ will be collected at the following timepoints: patient enrolment (please refer to note †), at the end of induction (Cycle 8) and at the End of Maintenance (Maintenance Visit 12). If the patient prematurely terminates the study the RASQ Questionnaire will be completed at the Early Termination/End of Treatment Visit.

Early termination/End of treatment visit was added in the schedule of assessment.

11.1.1 appendix 2 Schedule Of Assessments For Patients With CD20+ DLBCL

Study Period	Screening / Baseline									Specify assessments required for each time point in the Study. Example, Induction Treatment (including staging), Maintenance Treatment, Post-Treatment Follow-up, Early Treatment Termination / End of Study					
Visit		Treatment (cycles)								Final Staging		Post-Treatment Follow-Up			/End of Study Visit
Timing / Assessments	D -28 to D -1	1*	2	3	4	5	6	7	8		Early Termination/End of Treatment	1-6	6-12	12-18	18-24

d. 1) CT and MRI …[..] 2) Patients who do not complete the study treatment per protocol will undergo ~~end of study~~ early termination/end of treatment assessment within 4-8 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].

k. RASQ will be collected at the following time points: patient enrolment (please refer to note †), at the end of induction (Cycle 8). If the patient prematurely terminates the study the RASQ Questionnaire will be completed at the Early Termination/End of Treatment Visit.

Early termination/End of treatment visit was added in the schedule of assessment

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised .

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A SINGLE ARM, MULTICENTRE, PHASE IIIB STUDY TO EVALUATE SAFETY, EFFICACY AND PHARMACOKINETIC (PK) OF SUBCUTANEOUS (SC) RITUXIMAB ADMINISTERED DURING INDUCTION PHASE OR MAINTENANCE IN PREVIOUSLY UNTREATED PATIENTS WITH CD20+ DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) OR FOLLICULAR LYMPHOMA (FL)**
PROTOCOL NUMBER:	ML28881
VERSION:	4
EUDRACT NUMBER:	2013-000647-12
IND NUMBER:	N/A
TEST PRODUCT:	Rituximab (RO 45-2294)
MEDICAL MONITOR:	[redacted]
SPONSOR:	Roche S.p.A., 20900 Monza, Italy

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

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PROTOCOL SYNOPSIS

TITLE:	A single arm, multicentre, phase IIIb study to evaluate safety, efficacy and pharmacokinetic (PK) of subcutaneous (SC) rituximab administered during induction phase or maintenance in previously untreated patients with CD20+ diffuse large B cell lymphoma (DLBCL) or follicular lymphoma (FL)
PROTOCOL NUMBER:	ML28881
VERSION NUMBER:	4
EUDRACT NUMBER:	2013-000647-12
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 S.p.A., 20900 Monza, Italy

Objectives

Primary Objective

The primary objective for this Study is as follows:

- To evaluate the proportion of AARs following multiple doses of rituximab SC during Induction and/or Maintenance therapy in patients with CD20+ DLBCL or CD20+ follicular NHL, 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.

Secondary Objective

The secondary objectives for this Study are as follows:

- To further evaluate the safety of rituximab SC in terms of:
  - Grade ≥ 3 AEs
  - Grade ≥ 3 IIRRs
  - 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)
- complete response (CR) rate, including complete response unconfirmed (CRu), 4-8 weeks after the last dose of Induction treatment

Pharmacokinetic Objective

To evaluate the following:

1. In FL patients:

- population PK parameter: C_{trough}
- effects of subject characteristics (age, gender, weight, BSA) on the above mentioned rituximab population PK parameter
- effects of the covariates related to disease at baseline:
    - FLIPI 0-1/ 2/ ≥ 3;
- interindividual variability
- relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial)

2. In DLBCL patients:

- population PK parameters: C_{trough}, AUC, C_{max} and CL/F (clearance/fraction of absorbed drug)
- effects of subject characteristics (age, gender, weight, BSA) on the above mentioned rituximab population PK parameters
- effects of the covariates related to disease at baseline:
    - IPI 0 bulky-1/ 2/ 3/ 4 on the above mentioned rituximab PK population parameters
- interindividual variability
- relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial)
- rituximab exposures (concentration over time) during the 2 different scheduling of rituximab SC R-CHOP14 or R-CHOP 21

Patient-reported outcome objectives

The patient-reported outcome (PRO) measure for this Study is as follows:

- Patient-assessed satisfaction using Rituximab Administration Satisfaction Questionnaire (RASQ).

Study Design

This is a multicentre, single arm Study to evaluate safety, efficacy and PK of rituximab SC 1400 mg fixed dose, administered as part of Induction and/or Maintenance therapy.

This Study will include 160 adult patients with CD20+ DLBCL or FL (grades 1, 2 or 3a) previously untreated, who have already received at least one full dose of rituximab IV during Induction or Maintenance. Patients receiving Induction therapy must be able to receive at least 4 cycles of rituximab SC in addition to standard chemotherapy or patients receiving Maintenance therapy must be able to receive at least 6 cycles of rituximab SC.

During the Study, all 160 patients will be assessed for safety and efficacy.

During the administration period with rituximab SC, patients satisfaction data will be collected for all 160 patients using Rituximab Administration Satisfaction Questionnaire (RASQ).

During the administration period with rituximab SC, only the first 100 enrolled patients will be evaluated for PK parameters as detailed in the Section Pharmacokinetic Outcome Measures.

Induction Therapy:

Patients receiving Induction therapy prior to entry into the Study must be eligible to receive at least four cycles of rituximab SC (i.e. 4 additional months of treatment) (Fig.1 for FL and Fig.2 for DLBCL). Patients who will continue into Maintenance therapy after final staging during the Study can continue to receive rituximab SC up to 12 cycles.

Maintenance Therapy:

Patients receiving Maintenance therapy prior to entry into the Study must be eligible to receive at least six cycles of rituximab SC (i.e. 12 months of 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 treatment - Fig.1 for FL). Patients who completed Induction Therapy with rituximab IV, as per clinical practice, can be enrolled in the Maintenance Therapy of the study starting from cycle 1 with rituximab SC.

Post-treatment Follow Up:

All patients will continue the Study with further 2 years post-treatment follow up.

Figure 1– Study Design Scheme for FL patients

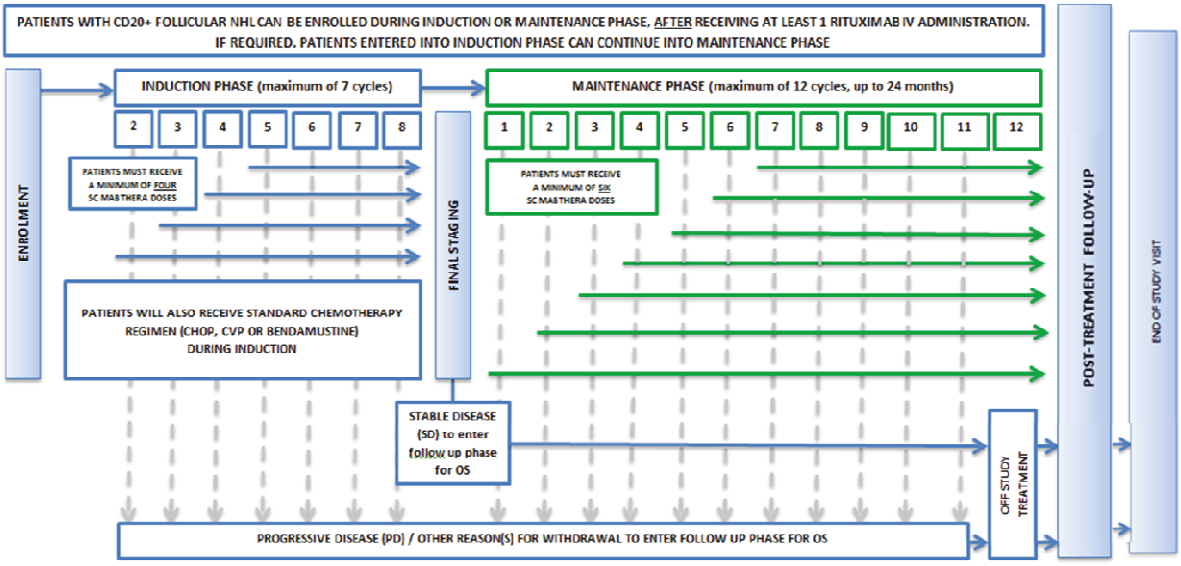
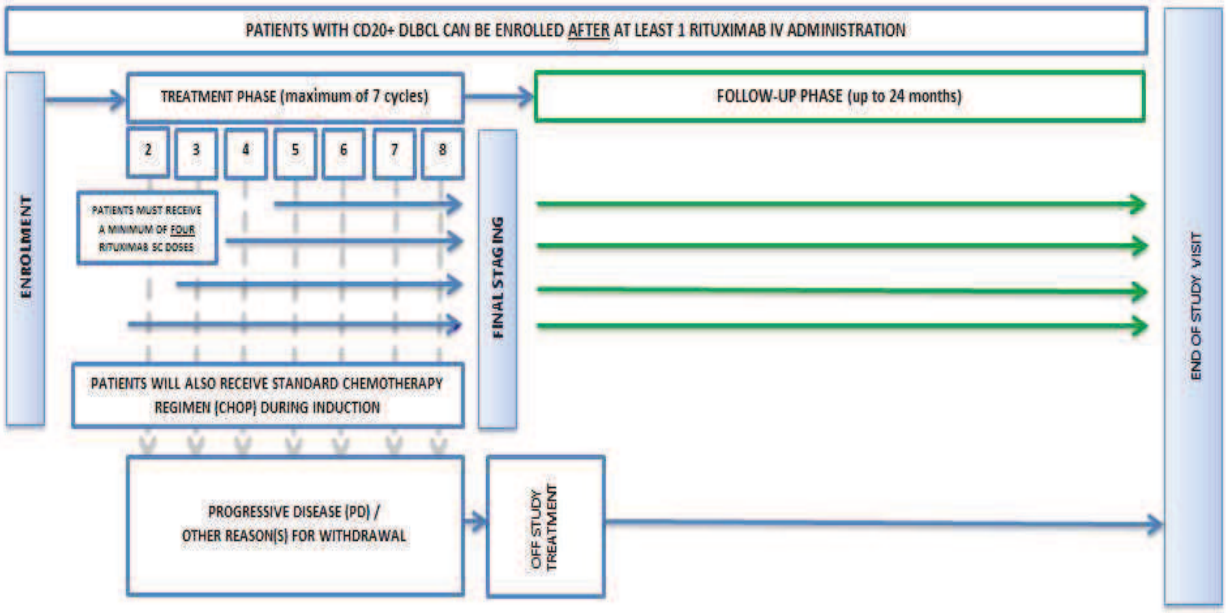


Figure 2– Study Design Scheme for DLBCL patients



Number of Patients

Overall, 160 patients will be enrolled in the Study, out of whom only the first 100 enrolled patients will be evaluated for PK parameters.

Target Population

The target population will consist of adults patients with CD20+ DLBCL or FL grade 1, 2 or 3a, according to the World Health Organization (WHO) classification system, previously untreated, who have already received at least one full dose of rituximab IV during Induction or Maintenance.

Inclusion Criteria

Patients must meet the following criteria for Study entry:

1. Signed, written informed consent form
2. Age ≥ 18 and ≤ 80 years at time of enrolment
3. Histologically confirmed, CD20+ DLBCL or CD20+ follicular NHL grade 1, 2 or 3a, according to the WHO classification system
4. Currently being treated with rituximab IV in the Induction or Maintenance setting, 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 (i.e. tolerability issues)
5. 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)
6. An International Prognostic Index (IPI) score of 1-4 or IPI score of 0 with bulky disease, defined as one lesion ≥ 7.5 cm, or Follicular Lymphoma International Prognostic Index (FLIPI) (low, intermediate or high risk) assessed before the first rituximab IV administration in Induction setting (see **Appendix 4**)
7. At least one bi-dimensionally measurable lesion defined as ≥ 1.5 cm in its largest dimension on computed tomography (CT) scan assessed up to 45 days the first rituximab IV administration in Induction setting
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3 (see **Appendix 4**)

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) IIIB
2. Primary central nervous system lymphoma, histologic evidence of transformation to a Burkitt lymphoma, primary effusion lymphoma, primary mediastinal DLBCL, DLBCL of the testis, or primary cutaneous DLBCL
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: (i) patients receiving corticosteroid treatment with ≤ 30 mg/day of prednisone dosing or equivalent must be on a documented stable dose of at least 4 weeks duration prior to randomization; (ii) a pre-phase of high dose prednisolone (e.g. 100 mg/day for 3 to 5 days) is acceptable for patients with aggressive NHL.

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 x 10^9/L
- Platelet count < 75 x 10^9/L

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 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):

✓ Positive test results for chronic hepatitis B infection (defined as positive HBsAg serology)

Patients with occult or prior hepatitis B infection (defined as positive total hepatitis B core antibody [HBcAb] and negative or positive HBsAg with HBV DNA undetectable) may be included. These patients must be followed closely according to the European Association for the Study of the Liver (EASL, Practice Guideline 2012).

Patients need to receive antiviral therapy according to the local clinical practice.

✓ Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)

Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

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. Pregnant or breastfeeding patients. A negative serum pregnancy test is required for 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 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 maximum 6 years based on an approximately 18 month recruitment period, maximum 30 months of Study treatment and 24 months of post-treatment follow-up.

End of Study

The end of the Study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur maximum 54 months after the last patient is enrolled.

Safety Outcome Measures

Safety outcome measures 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 ≥ 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 will be recorded regardless of their intensity / grading. Grading will be completed according to the NCI CTCAE version 4.0.

Efficacy Outcome Measures

Tumour assessments will be based on computed tomography (CT) scans of the neck, chest, abdomen and/or pelvis (if detectable by these techniques) or other diagnostic means (e.g. magnetic resonance imaging [MRI]) where applicable. Other methods (e.g. MRI) are acceptable for patients in whom CT scans are contraindicated. The CT scan used for eligibility assessments may be performed up to 45 days the first rituximab IV administration in Induction setting.

Response assessments after 4 cycles (interim staging) and 4-8 weeks after the completed Induction period will be based on the Investigator's assessment, completed according to the International Working Group (IWG) response criteria (Cheson *et al* 1999) or local standard practice.

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

CR/CRu is complete response or complete response unconfirmed and is measured 4 to 8 weeks after the end of Induction treatment.

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

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.

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

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

Pharmacokinetic Outcome Measures

To evaluate the following:

1. In FL patients:
   - population PK parameter: C_{trough}

- effects of subject characteristics (age, gender, weight, BSA) on the above mentioned rituximab population PK parameter
- effects of the covariates related to disease at baseline:
    - FLIPI 0-1/ 2/ ≥ 3;
- interindividual variability
- relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial)

2. In DLBCL patients:

- population PK parameters: C_{trough}, AUC, C_{max} and CL/F (clearance/fraction of absorbed drug)
- effects of subject characteristics (age, gender, weight, BSA) on the above mentioned rituximab population PK parameters
- effects of the covariates related to disease at baseline:
    - IPI 0 bulky-1/ 2/ 3/ 4 on the above mentioned rituximab PK population parameters
- interindividual variability
- relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial)
- rituximab exposures (concentration over time) during the 2 different scheduling of rituximab SC R-CHOP14 or R-CHOP 21

Patient-Reported Outcome Measures

The patient-reported outcome (PRO) measure for this Study is as follows:

- Patient-assessed satisfaction using Rituximab Administration Satisfaction Questionnaire (RASQ).

Study Drug and Study Treatment

The term "Study drug" will be used throughout the protocol to refer to rituximab SC. The term "Study treatment/medication" will be used to refer to protocol-mandated treatment (also including background chemotherapy and/or other pre-medications).

Investigational Medicinal Products

Test 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: rituximab SC will be administered at 2-month intervals for a minimum of six cycles, according to local standards of care.

Comparator

Not applicable.

Non-Investigational Medicinal Products

Concomitant medications will consist of standard regimens; CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone), CVP (cyclophosphamide, vincristine and prednisone) or bendamustine, as per standard local practice.

Statistical Methods

The analysis of this Study will be exploratory and will primarily make use of descriptive statistical methods. Survivor functions will be estimated using Kaplan-Meier methodology and the effect of time on PK parameters will be explored using longitudinal data analysis. In addition, other

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 who receive at least one dose of study medication and who have at least one post-baseline efficacy evaluation will be included in the Intent-to-Treat Population, which will be the primary analysis population for efficacy parameters. PK analysis population will include all recruited patients who receive the investigational treatment and have at least one PK sample collected and analyzed 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

Safety will be assessed on the following safety parameters: AARs, including IIRRs, 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 and ECOG performance status.

The proportion of AARs, AEs, AEs leading to premature discontinuation or interruption of Study treatment, SAEs, grade ≥ 3 AEs, will be computed with 95% Clopper-Pearson Confidence Interval. The proportion of each AE will be summarized by the primary system-organ class and by preferred term. The proportion 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 efficacy of rituximab SC will be evaluated during Induction and/or Maintenance in terms of EFS, PFS, CR/Cru, DFS and OS and will be analysed for the FAS and for the Per Protocol populations.

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 by subgroup of diagnosis and overall 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.

Endpoint and Analysis In FL patients:

Descriptive statistics (mean, standard deviation, median and minimum and maximum values), will be computed for the PK parameter C_{trough}.

The effects over time of subject characteristics (age, weight, body surface area) on the above mentioned rituximab population PK parameter will be analyzed descriptively by computing a mixed model for repeated measures. .

The effects of gender and of covariates related to disease at baseline in different risk categories (FLIPI 0-1/2/≥3;) on the above mentioned rituximab PK population parameter will be analysed by means of T test or Mann-Whitney U test, when appropriate.
The relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial) will be summarized by means of descriptive statistics.

Endpoint and Analysis In DLBCL patients:

Descriptive statistics (mean, standard deviation, median and minimum and maximum values), will be computed for all PK parameters: C_{trough}, AUC, C_{max}, and CL/F (clearance/fraction of absorbed drug). The effects over time of subject characteristics (age, weight, BSA) on the above mentioned rituximab population PK parameters will be analysed descriptively by computing a mixed model for repeated measures.

The effects of gender and of covariates related to disease at baseline in different risk categories (IPI 0 bulky/2/3/4) on the above mentioned rituximab PK population parameters will be analysed by means of Student's T test or Mann-Whitney U test, when appropriate.

Relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial) will be described.

The rituximab exposures (concentration over time) will be compared descriptively during the 2 different scheduling of rituximab SC R-CHOP14 or R-CHOP 21.

Patient-assessed satisfaction will be evaluated using the Rituximab Administration Satisfaction Questionnaire (RASQ).

PRO data will be summarized and presented by subgroup of diagnosis and overall.

Descriptive statistics will be computed for the questions assessing patient responses regarding convenience and satisfaction for rituximab SC.

Determination of Sample Size

A total of 160 patients will be recruited into this Study, with first 100 patients evaluated for PK analysis. From data of the previous Study (BP22333) the expected proportion of AARs after rituximab SC was approximately 30%: the sample size of 160 patients will assure that the precision of estimate will be ±7.2%, so the confidence interval will range from 22.8% to 37.2%.
As to PK outcomes evaluation, the sample size of 100 patients will assure the possibility to evaluate the following inter-individual variability's factors:

- gender
- age (≤ 70 years and > 70 years)
- weights and BSA (median, > 25% than median, < 25% than median)
- FLIPI (0-1/ 2 / ≥3)
- IPI (0-1/ 2 / 3/ > 3)

In addition it will be relevant to show differences between gender in the systemic exposition (C_{trough}).An intermediate PK analysis will be conducted once all patients completed the Final Staging Visit at the End of Induction period.

The final PK analysis will be conducted once all scheduled PK samples are collected

Intermediate Analyses

One intermediate analyses is planned:

- The intermediate analysis will be done once all patients completed the Final Staging Visit at the End of Induction period.

The final analysis will be done at the end of study (i.e. last patient end of study visit).

Study Procedures

See **Schedule of Assessments**, **Appendix 1** and **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
AUC	area under the plasma concentration-time curve
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
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
CL/F	apparent total clearance of the drug plasma after SC administration
C_{max}	maximum plasma concentration after drug administration
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

Abbreviation	Definition
EDC	electronic data capture
EFS	event-free survival
EGSG	East German Study Group
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
FU	follow up
G-CSF	granulocyte colony-stimulating factor
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GLSG	German Low-Grade Lymphoma Study Group
GOELAMS	Groupe Ouest Est d'Etude des Leucemies et autres Maladies du Sang
HACA	human antichimeric antibody
HAMA	human anti-mouse antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN	interferon-α
IMP	investigational medicinal product
INR	International Normalized Ratio
IPI	International Prognostic Index
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
MCL	Mantle Cell Lymphoma
MCP	mitoxantrone, chlorambucil, prednisone/prednisolone

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
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
NR	not reported/not reached
OL	open label
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
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

Abbreviation	Definition
SUSAR	Suspected Unexpected Serious Adverse Reactions
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
aaIPI	Age-adjusted International Prognostic Index
AAR	Administration-associated reaction

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). As with other lymphoid neoplasms, its aetiology remains largely unknown, although risk factors include certain infections as well as treatments and diseases that cause severe immunosuppression. NHL has been classified into two types: aggressive (i.e. fast growing) and indolent (i.e. slow growing) (Landis *et al*. 1999). Categorizing the various lymphoid neoplasms has proven to be enormously challenging and has resulted in the evolution of numerous classification schemes over the past 50 years. In 2001, the World Health Organization (WHO) introduced a new system for classifying haematopoietic neoplasms, which, in addition to morphology, incorporates immunophenotype, cytogenetic and molecular features, clinical behaviour, and some known aspects of aetiology and pathogenesis into the definition of each disease subtype (Jaffe *et al*. 2001). 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. The disease generally manifests with hypertrophy of peripheral and deep lymph nodes and splenomegaly, together with bone marrow infiltration. FL is characterized by initial responsiveness to therapy followed by repeated relapses and sometimes with histological progression into high-grade NHL (Horning, 1993). In the WHO classification the histology is further classified into grade 1, 2 or 3 FL, depending on the percentage of large cells seen on high-power field microscopy (Nathwani *et al*, 2001). Grade 3 FL is further subdivided into 3a and 3b, where 3b may represent a distinct biological entity more similar to DLBCL (Nathwani *et al*, 2001). Biologically, FL has been associated with the translocation of chromosomes 14 and 18 [t(14;18)], which results in constitutive activation of the bcl-2 oncogene and the subsequent inhibition of apoptosis of lymphoid cancer cells (Bordeleau and Berinstein, 2000). Given that FL is currently incurable with standard treatment options, there is a need to improve the clinical outcomes.

1.1.1 Epidemiology

NHLs account for almost 5% of all cancers occurring in the US, with an estimated 70,130 new diagnoses (38,160 men and 31,970 women) in the year 2012. Based on cases diagnosed in 2005-2009 from 18 Surveillance, Epidemiology and End Results (SEER) geographic areas, the age-adjusted incidence rate for NHL was 19.6 per 100,000 men and women per year and the age-adjusted death rate was 6.6 per 100,000 men and women per year (Howlander *et al*. 2012). The incidence and mortality rates for NHL were reported to have risen steadily in the US (with an estimated 50% increase in age-adjusted incidence of NHL from 1970 to 1990) and in other populations over several decades. Although further reports suggested that the steep rise in incidence may have slowed in the late 1990s, this group of closely related diseases is still an important contributor to the overall cancer burden (Morton *et al*. 2006; Cartwright 1999; Eltorn *et al*. 2002; Clarke and Glazer 2002).

Among the NHL cases included in the SEER database, B-cell NHL accounted for 90.4%, T-cell NHL accounted for 6.8%, and NHL of unknown cell lineage accounted for 2.8%.

Based on other reports, FL accounts for 20-25% of all cases of NHL (ILSG 1997). Its incidence is rapidly increasing in Western countries and has nearly doubled within the past three decades. Like many lymphomas, it is increasing in incidence with over 24,000 new cases diagnosed each year. It remains incurable with standard treatment options.

DLBCL constitutes 25-30% of NHL cases, and its incidence increases with advancing age, such that the disease represents 54% of NHL cases among patients older than 75 years (Michallet and Coiffier,

2009; Niitsu 2010). A crude incidence of 3-4 cases/100,000/year was reported in the European Union, increasing from 0.3 cases/100,000/year in patients aged 35-39 years to 26.6 cases/100,000/year in patients aged 80-84 years (Tilly and Dreyling, 2010). In the US, the incidence of DLBCL is approximately 7 cases per 100,000 person years and varies by ethnicity, with Caucasian Americans having higher rates than African Americans, Asians, and American Indian or Alaska Natives, in order of decreasing incidence (Morton *et al*, 2006).

Patients with DLBCL typically present with a rapidly enlarging symptomatic mass, most usually nodal enlargement in the neck or abdomen. The median age at presentation is approximately 65 years, and it is slightly more common in males than females. In appreciation of rapid lymph node enlargement, systemic "B" symptoms (i.e. fever, weight loss, drenching night sweats) are present in approximately 30% of patients. About 40% of DLBCLs occur from extranodal sites, most commonly the gastrointestinal canal. Among DLBCL cases, 11-27% have bone marrow infiltration, approximately 50% have elevated serum lactate dehydrogenase (LDH), and about half have advanced stage (stage III/IV) disease (Niitsu N, 2010). Bone marrow involvement in DLBCL can also be detected after histologic transformation from most other types of B-cell lymphoma. In general, patients who have undergone histologic transformation have a poorer response to therapy and prognosis than those with a de novo appearance (Swerdlow S *et al*, 2008; Niitsu N, 2010).

1.1.2 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.

Initial treatment of NHL with chemotherapy (such as alkylating agents, prednisone/prednisolone, anthracyclines, vinca alkaloids, purine analogues), combined with interferon or monoclonal antibodies such as rituximab is associated with a high rate of clinical response, although typically followed by relapse. Patients with aggressive B-cell lymphoma are potentially curable when treated with multi-agent chemotherapy such as CHOP (Fisher *et al*, 1993). In 30-70% of the FL cases, the disease eventually transforms to aggressive lymphoma, responding only to combination chemotherapies usually employed for aggressive disease, such as anthracyclines or cytosine arabinoside-containing regimens or high-dose chemotherapy with autologous stem cell transplantation (Lossos 2005). The standard of care for patients with aggressive lymphoma has changed recently with the implementation

of therapy with the chimeric anti-CD20 monoclonal antibody rituximab (Boye *et al*, 2003). Combination treatment with R-CHOP or similar regimens has resulted in superior treatment outcomes compared with multi-agent chemotherapy alone, making combined immunochemotherapy with rituximab the new standard of care for this group of patients (Feugier *et al*, 2005). The combination of cyclophosphamide, vincristine, and prednisone/prednisolone (CVP) is one of several standard treatment options for advanced FL. Similar to other chemotherapeutic regimens; this combination induces response rates of 60-80%, with median response duration of under 2 years (Marcus *et al*, 2005).

A recently published large, prospective, longitudinal, observational Study to identify current patterns of care of FL in the US (conducted between 2004 and 2007) found that amongst the 2728 patients enrolled, the most common initial therapeutic strategy was chemotherapy plus rituximab (51.9%), followed by observation (17.7%), rituximab monotherapy (13.9%), clinical trial-related interventions (6.1%), radiation therapy (5.6%) and chemotherapy alone (3.2%). Chemotherapy plus rituximab regimens were R-CHOP (55.0%), rituximab plus CVP (R-CVP, 23.1%), rituximab plus fludarabine based-chemotherapy (15.5%), and other (6.4%). The choice to initiate therapy rather than observation only was associated with age, Follicular Lymphoma International Prognostic Index (FLIPI), stage, and grade ($p < 0.01$) (Friedberg *et al*, 2009).

Toxicity of rituximab is mild and occurs most frequently during the first infusion. Importantly, it does not produce treatment-related cytopenias or severe cumulative toxicity (Sousou and Friedberg, 2010). Compared to single-agent cytotoxic therapy, single-agent rituximab was better tolerated and had similar efficacy (McLaughlin *et al*, 1998). Several Phase II and Phase III multicentre RCTs demonstrated that the addition of rituximab to various chemotherapy regimens in patients with FL significantly improves outcomes when compared with standard chemotherapy regimens, without adding significant toxicity (Sousou and Friedberg, 2010). In clinical trials with rituximab monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During rituximab Maintenance treatment for up to 2 years, grade 3/4 leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. In studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia, neutropenia, and pancytopenia were reported higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone and the neutropenia was not prolonged in the rituximab group. There were no differences reported for the incidence of thrombocytopenia or anaemia (Rituximab Summary of Product Characteristics).

Rituximab, an anti-CD20 antibody, has had a large impact on the treatment of indolent 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. Analysis of data obtained from NHL clinical trials, as well as data from the National Cancer Institute (NCI), indicate that the OS of patients with indolent NHL has improved with the use of rituximab and that given its effectiveness and tolerability, rituximab is currently being investigated as a maintenance agent with encouraging results (Sousou and Friedberg, 2010).

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). In preclinical studies, rituximab was shown to induce both complement-mediated and antibody-dependent cell mediated lyses of CD20+ cells (Reff *et al*. 1994). Rituximab has also been reported to have direct anti-tumour activity independent of the host immune system, as indicated by the induction of apoptosis of human B-cell lines. In addition, it sensitizes drug-resistant human B-cell lymphoma cell lines to the cytotoxic effects of some chemotherapeutic agents (Maloney *et al*, 1996; Demidem *et al*. 1997).

The mode of action of rituximab is mediated through binding to CD20. The specific and saturable interaction of antibodies with their receptor influences the pharmacokinetic (PK) disposition. Once target sites are saturated, linear pharmacokinetics are observed (Mager 2001). PK of the currently approved intravenous (IV) dose indicates that target sites are saturated. It is expected that maximal clinical benefit is achieved at these concentration levels (Yin *et al*. 2010, ASCO).

Several RCTs have established the efficacy and safety of rituximab IV, administered as monotherapy or in combination with chemotherapy, in NHL (FL and DLBCL) and chronic lymphocytic leukaemia (CLL), leading to marketing approvals in more than 100 countries. Importantly, the addition of rituximab to CHOP resulted in an approximately 10% absolute increase in survival beginning at one year from initiation of therapy in patients of all ages with minimal clinically relevant increases in toxicity (Pettengell and Linch, 2003; Badin and Hayslip, 2010). RCTs evaluating the efficacy and safety of rituximab IV in patients with untreated DLBCL are summarized in Section 1.2.1.1.

Rituximab is marketed under the brand names MabThera® and Rituxan®. Rituximab was first approved in the US under the brand name Rituxan® in 1997 for the treatment of relapsed or refractory indolent B-cell lymphomas. Currently, rituximab is approved for treatment of relapsed or chemo-resistant, low-grade or follicular, CD20+, B-cell NHL in over 120 countries including the European Union (EU) and the US, and for treatment of rheumatoid arthritis in the US and EU.

The approved oncology indications for rituximab in the EU include the treatment of NHL (FL and DLBCL) and CLL, as follows:

- For previously untreated patients with stage III-IV FL in combination with chemotherapy
- As Maintenance treatment for FL responding to Induction therapy
- For CD20+ DLBCL in combination with CHOP chemotherapy
- As monotherapy for treatment of patients with stage III-IV FL who are chemo-resistant or are in their second or subsequent relapse after chemotherapy
- For previously untreated or relapsed/refractory CLL in combination with chemotherapy.

Over the past decade, the use of rituximab has radically changed the treatment of NHL and has become standard in the management of patients suffering from various B-cell malignancies including FL, DLBCL and CLL. It has been observed that the previously described downward trend in mortality rates coincided with the introduction of rituximab in clinical practice (Keating 2010).

1.2.1 Rituximab IV

1.2.1.1 Efficacy of Rituximab IV Plus Chemotherapy in the Treatment of DLBCL

The efficacy of rituximab IV in combination with CHOP or CHOP-like chemotherapy for the first-line treatment of DLBCL is shown in **Table 1**. Overall, rituximab-based treatments resulted in complete remission in 58-86% of patients with previously untreated DLBCL. All studies evaluating rituximab in combination with chemotherapy demonstrated significant improvements of their respective primary endpoints.

Table 1 Efficacy Summary of Phase III Randomized Controlled Trials of R-CHOP in Previously Untreated DLBCL

Study / Reference(s)	Patient Number, Age	IPI	Treatment Arms	CR/CRu	PFS/FFS/EFS	OS
GELA LNH98-5 Coiffier *et al.* 2002; Feugier *et al.* 2005; Coiffier *et al.* 2010	N=399 60-80 yrs	all	R-CHOP-21, n=202	76%	PFS: 57%	Med 93 mo (10-yr FU)
			CHOP-21, n=197	63%	PFS: 38%	Med 37 mo (10-yr FU)

Study / Reference(s)	Patient Number, Age	IPI	Treatment Arms	CR/CRu	PFS/FFS/EFS	OS
US Intergroup Study E4494 Habermann *et al.* 2006	N=632 >60	all	R-CHOP, n=318	NR	3-yr FFS: 53%	3-yr OS: 67%
			CHOP, n=314	NR	3-yr FFS: 46%	3-yr OS: 58%
M39045, MInT Pfreundschuh *et al.* 2006	N=824 <60	<2	R-CHOP-like, n=413	86%	3-yr PFS: 85% 3-yr DFS: 94% 3-yr EFS: 79%	3-yr OS: 93%
			CHOP-like, n=411	68%	3-yr PFS: 68% 3-yr DFS: 86% 3-yr EFS: 59%	3-yr OS: 84%
Ricover-60 Pfreundschuh *et al.* 2008	N=1222 >60 years	all	CHOP-14 (6x), n=307	68%	3-yr PFS: 57% 3-yr EFS: 47%	3-yr OS: 68%
			CHOP-14 (8x), n=305	72%	3-yr PFS: 57% 3-yr EFS: 53%	3-yr OS: 66%
			R-CHOP-14 (6x), n=306	78%	3-yr PFS: 73% 3-yr EFS: 67%	3-yr OS: 78%
			R-CHOP-14 (8x), n=304	76%	3-yr PFS: 69% 3-yr EFS: 63%	3-yr OS: 73%
GELA LNH03-6b Delarue *et al.* 2011	N=600 >60 years	aaIPI ≥1	R-CHOP-21, n=296	75%	3-yr PFS: 62% 3-yr EFS: 60%*	3-yr OS: 73%
			R-CHOP-14, n=304	72%	3-yr PFS: 60% 3-yr EFS: 57%*	3-yr OS: 70%
NCRI Cunningham *et al.* 2011	N=1080 All ages	all	R-CHOP-21, n=540	63%	EFS: 75%	NR
			R-CHOP-14, n=540	58%	EFS: 75%	NR

Abbreviations: aaIPI: age-adjusted International Prognostic Index (score); CR: complete response; CRu: complete response unconfirmed; FU: follow-up; GELA: Groupe d'Etude des Lymphomes de l'Adulte; IPI: International Prognostic Index (score); Med: median; mo: months; MInT: MabThera International Trial; NR: not reported; yrs: years

1.2.1.2 Efficacy of Rituximab IV Plus Chemotherapy in the Treatment of FL

Several multicentre RCTs have demonstrated that the addition of rituximab to first-line therapy for FL significantly improves clinical outcomes when compared with standard chemotherapy regimens of varying intensities, without adding significant toxicity. See details in **Table 2**.

Table 2 Efficacy Summary of Phase III Randomized Controlled Trials of Rituximab Plus Chemotherapy in Previously Untreated FL

Study / Reference	Population	Interventions	PFS/TTP/ EFS/DFS	OS	Other Endpoints	AEs
GLSG Study Hiddemann *et al* 2005, Lenz *et al* 2005 OL RCT	N=630 (428 evaluable) 1st line FL, immunocytomas, MCL	Induction: 6-8 cycles Q3W: R-CHOP, n=223 CHOP, n=205	*At median 28 mo:* Treatment failure: **R-CHOP:** 28 **CHOP:** 61 TTF: **R-CHOP:** NR **CHOP:** 2.6 years P<0.001 DR: P=0.001	3-yr OS: R-CHOP: 95% CHOP: 90% P=0.016	ORR: **R-CHOP:** 96% **CHOP:** 90% P=0.011	Grade 3/4 granulocytopenia: **R-CHOP:** 63% **CHOP:** 53% P=0.01 Infections: **R-CHOP:** 5% **CHOP:**7% IRR (R): 7%

Study / Reference	Population	Interventions	PFS/TTP/ EFS/DFS	OS	Other Endpoints	AEs
M39021 Marcus *et al* 2005 & 2008 OL RCT	N=321 1st line advanced FL	8 cycles: R-CVP, n=162 CVP, n=159	*At median 53 mo:* Median TTF*: **R-CVP:** 27 mo **CVP:** 7 mo P<0.0001 Median TTP: **R-CVP:** 34 mo **CVP:** 15 mo P<0.0001 Median DFS: **R-CVP:** NR **CVP:** 21 mo P=0.0001 Median DR: **R-CVP:** 38 mo **CVP:** 14 mo P<0.0001	At 48 mo: R-CVP: 83% CVP: 77% P=0.03	ORR: **R-CVP:** 81% **CVP:** 57% P<0.0001 CR/CRu: **R-CVP:** 41% **CVP:** 10%	Grade 3/4 neutropenia: **R-CVP:** 24% **CVP:** 14% Any AEs: **R-CVP:** 97% **CVP:** 95% IRRs: **R-CVP:** 71% **CVP:** 51% Gr 3/4: 9%

Study / Reference	Population	Interventions	PFS/TTP/ EFS/DFS	OS	Other Endpoints	AEs
EGSG Study Herold *et al* 2003 and 2007 OL RCT	N=358 (201 in primary analysis set) Stage III-IV indolent FL (56%) or MCL	8 cycles Q4W: R-MCP, n=181 MCP, n=177 Responders: maintenance with IFN until relapse	*At median 47 mo:* Median EFS: **R-MCP:** NR (34 treatment failures) **MCP:** 26 mo (57 treatment failures) P<0.0001 Median PFS: **R-MCP:** NR (30 events) **MCP:** 28.8 mo (50 events) P<0.0001 Median DR: **R-MCP:** NR **MCP:** 35 mo P<0.0001 Median TNLT: **R-MCP:** NR **MCP:** 29.4 mo P=0.0002	4-yr OS: R-MCP: 87% MCP: 74% P=0.01 Median OS NR in either group.	ORR*: **R-MCP:** 92% **MCP:** 75% P=0.0009 CR: **R-MCP:** 50% **MCP:** 25% P=0.004	Grade 3/4 leukopenia: **R-MCP:** 72% **MCP:** 58% Grade 3/4 infections: **R-MCP:** 7% **MCP:** 8% Any AEs: **R-MCP:** 99% **MCP:** 86%

Study / Reference	Population	Interventions	PFS/TTP/ EFS/DFS	OS	Other Endpoints	AEs
GELA-GOELAMS Study FL2000 Salles *et al* 2008 OL RCT	N=358 1st line FL with high tumour burden	R-CHVP, 6 courses Q4W, + IFN for 18 mo, n=175 or CHVP+IFN, 6 courses Q4W + 6 courses Q8W, n=183 Over 18 mo	*At median 5 yrs:* Median EFS*: **R-CHVP+IFN:** 53% **CHVP+IFN:** 37% P=0.001 Median DR (4-yr): **R-CHVP+IFN:** 64% **CHVP+IFN:** 44% P=0.012	5-yr OS: R-CHVP+IFN: 84% CHVP+IFN: 79% P=0.16	ORR at 6 mo: **R-CHVP+IFN:** 94% **CHVP+IFN:** 85% CR/CRu, 6 mo: **R-CHVP+IFN:** 63% **CHVP+IFN:** 34% Global P<0.001 ORR at 18 mo: **R-CHVP+IFN:** 81% **CHVP+IFN:** 72% CR/CRu,18 mo: **R-CHVP+IFN:** 67% **CHVP+IFN:** 50% Global P=0.035	*6-mo Induction:* Grade 3/4 leukopenia: **R- CHVP+IFN:** 59% **CHVP+IFN:** 62% Grade 3/4 infections: **R- CHVP+IFN:** 2% **CHVP+IFN:** 0%

AE: adverse event; CR: Complete Response; CRu: Complete Response, unconfirmed; EGSG: East German Study Group; GELA: Groupe d'Etude des Lymphomes de l'Adulte; GLSG: German Low-Grade Lymphoma Study Group; GOELAMS: Groupe Ouest Est d'Etude des Leucemies et autres Maladies du Sang; IRR: Infusion-related reaction (within 24 hrs of the infusion); IFN: interferon-α; MCL: Mantle Cell Lymphoma; MCP: mitoxantrone, chlorambucil and prednisolone/prednisolone; NR: not reached; OL: open label; ORR: Overall Response Rate; Q3W: every 3 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; R: rituximab; R-MCP: rituximab + MCP chemotherapy; TNLT: Time to next lymphoma treatment; TTF: Time to Treatment Failure; TTP: Time to Progression

* Primary endpoint in the Study

Note: rituximab was administered at the 375 mg/m^2 dose in all trials

1.2.1.3 Safety of Rituximab IV

Safety of Rituximab IV in Patients with DLBCL

Safety data from three RCTs comparing CHOP therapy administered with or without rituximab in patients with previously untreated or newly diagnosed CD20+ DLBCL are summarized in Table 3, with focus on grade 3/4 toxicities.

Table 3 Safety Summary of Select Randomized Controlled Trials of R-CHOP in Previously Untreated DLBCL

Study / Reference	Population, Intervention	Grade 3/4 AEs			Other AEs	
GELA LNH98-5 Coiffier *et al.* 2002	N=399 60-80 years 8 cycles of R-CHOP or CHOP	**AEs, % of patients**	**R-CHOP**	**CHOP**	**R-CHOP**	**CHOP**
		Alopecia	39%	45%	97%	97%
		Infection	12%	20%	65%	65%
		Fever	2%	5%	64%	59%
		Neurologic toxicity	5%	9%	51%	54%
		Cardiac toxicity	8%	8%	47%	35%
		Liver toxicity	3%	5%	46%	46%
		Nausea / vomiting	4%	8%	42%	48%
		Constipation	2%	5%	38%	41%
		Lung toxicity	8%	11%	33%	30%
		Mucositis	3%	2%	27%	31%
		Renal toxicity	1%	2%	11%	14%
		Other toxicities*	20%	25%	84%	80%
M39045, MInT Pfreundschuh *et al.* 2006	N=824 <60 years 6 cycles of CHOP or CHOP-like chemotherapy ± rituximab	**AEs, % of patients**	**R-CHOP**	**CHOP**	**R-CHOP**	**CHOP**
		All body systems	37%	41%	NR	NR
		Infection	7%	8%		
		Leucocytopenia	7%	6%		
		Neurotoxicity	3%	3%		
		Cardiac toxicity	2%	1%		
		Vomiting	2%	2%		
		Nausea	<1%	1%		
		Anaemia	<1%	<1%		
		Thrombocytopenia	<1%	<1%		
		Lung toxicity	<1%	1%		

Study / Reference	Population, Intervention	Grade 3/4 AEs				
Ricover-60 Pfreundschuh *et al.* 2008	N=1222 >60 years 6 cycles or 8 cycles of CHOP with or without rituximab	**Gr 3/4 AEs, % of patients**	**R-CHOP-14**		**CHOP-14**	
			x6	**x8**	**x6**	**x8**
		Leucocytopenia	52%	50%	48%	48%
		Infection	28%	35%	29%	31%
		Anaemia	16%	27%	16%	23%
		Thrombocytopenia	12%	16%	10%	17%
		Neurotoxicity	7%	8%	7%	11%
		Mucositis	5%	9%	3%	6%
		Arrhythmia	4%	6%	5%	3%
		Other cardiotoxicity	3%	3%	2%	2%

GELA: Groupe d'Etude des Lymphomes de l'Adulte; MInT: MabThera International Trial
* Haematologic toxicities were not reported individually
AE: Adverse event

1.2.1.3.1 Infusion/Injection Related Reactions

Comprehensive rituximab safety information is available in the current rituximab IV Investigator's Brochure (IB).

A cluster of signs and symptoms reported during or within 24 hours of rituximab infusion, which may be related to the release of cytokines and/or other chemical mediators, has been well characterised in pivotal clinical trials of rituximab IV and also from post-marketing experience. Signs and symptoms associated with rituximab infusion/injection-related reactions (IIRRs) included hypotension, fever, chills, rigors, urticaria, bronchospasm and angioedema. In addition, some patients developed anaphylactic or hypersensitivity reactions due to IV administration of protein distinct from the cytokine release effect. In very rare cases these signs and symptoms resulted in a fatal outcome. Acute infusion reactions tend to be more frequent and more severe with the first infusion.

In the pivotal rituximab monotherapy trials (McLaughlin *et al.* 1998; Davis *et al.* 1999; Davis *et al.* 2000) in relapsed/refractory patients with follicular NHL, the incidence of infusion-related reactions (IRRs) was 77% (7% grade 3/4) with the first infusion, which decreased to approximately 30% (2% grade 3/4) with the fourth infusion and to 14% (no grade 3/4 events) with the eighth infusion. An incidence of 9% for grade 3/4 infusion-related events was also reported in patients with DLBCL, when they received their first rituximab infusion combined with CHOP chemotherapy (GELA/BO16386) (Coiffier *et al.* 2002).

1.2.1.3.2 Infection

Patients with NHL are at risk of infection because of disturbances in immune functions as a result of their underlying malignant disease. Treatment with chemotherapeutic agents leads to immunosuppression and therefore also may increase the incidence of infections. Because rituximab depletes B cells, which play an important role in the normal immune response, treatment with rituximab may further increase the risk of infection in these immunocompromised patients.

In the R-CHOP vs. CHOP alone pivotal trial in elderly patients with DLBCL (GELA/BO16386) (Coiffier *et al.* 2002) grade 3 and 4 leucopoenia and neutropenia occurred more frequently in the R-CHOP arm than in the CHOP arm (88% vs. 79% and 97% vs. 88% respectively), but the incidence of grade 2 to 4 infections was only slightly higher (46% in the R-CHOP arm compared to 42% in the CHOP arm); see **Table 3** for further details.

1.2.1.3.3 Other toxicities

Tumour Lysis Syndrome (TLS) has been reported to occur after the first rituximab infusion in patients with a high tumour burden or high numbers of circulating malignant lymphocytes during Induction treatment.

Pulmonary events were also reported. They have included hypoxia, pulmonary infiltrates, and acute respiratory failure.

In studies evaluating rituximab in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%) (Rituximab Summary of Product Characteristics).

Very rare cases of hepatitis B reactivation, including reports of fulminant hepatitis, have been reported in patients receiving rituximab, although these reports are confounded by both underlying disease and exposure to other cytotoxic chemotherapy. Patients with a history of hepatitis B infection should be carefully monitored for signs of active hepatitis B infection when rituximab is used in association with cytotoxic chemotherapy.

Use of rituximab may be associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded.

Some patients who were treated with rituximab and chemotherapy have developed gastrointestinal perforation.

Immunization following rituximab treatment in the oncology setting has been evaluated in controlled studies. Impaired response to tetanus, influenza, and the neo-antigen keyhole limpet hemocyanin were observed. It is recommended that any course of immunization for patients should be completed at least 4 weeks before starting rituximab Maintenance therapy and patients should not receive any vaccinations that contain live or attenuated organisms during the Study.

Further information concerning rituximab safety can be found in the current version of the IB for rituximab IV, Summary of Product Characteristics and local prescribing information.

1.2.1.3.4 PK of rituximab

Nowadays some PK data for rituximab have been reported for Induction and Maintenance treatment (Jager *et al.*, Haematologica 2012).). These studies have proposed a presumptive “active” level of 25,000 ng/mL in anti-lymphoma treatment.

In DLBCL pharmacokinetics of 8 doses of rituximab (375 mg/m2) given in combination CHOP-14 was determined in 20 elderly patients (Muller et al., Blood 2012). Population pharmacokinetic modeling was performed with nonlinear mixed-effect modeling software (NONMEM VI). Concentration-time data were fitted into an open 2-compartment model and total clearance, central compartment volume, intercompartment clearance, and volume of distribution at steady-state (Vdss) were investigated. Total clearance was 9.43 mL/h and Vdss was 9.61 L. Rituximab clearance was reduced (8.21 mL/h vs 12.68 mL/h; P = 0.003) and elimination half-life was prolonged in women compared to men ($t1/2\beta$ = 30.7 vs 24.7 days; P =0.003). Body weight also affected Vdss (0.1 L increase of Vdss per kilogram above median of 75 kg). A sex-dependent effect and the higher weight of males contribute to faster rituximab clearance, which might explain why elderly males benefit less than females from the addition of rituximab to CHOP.

In FL, PK was evaluated in a multi-center pivotal phase III clinical trial involving 166 patients with recurrent low-grade lymphoma who were treated with four infusions of rituximab (Berinstein *et al.,* Annals of Oncology 1998). Measurable concentrations of rituximab were detected in all patients after the first infusion and increased throughout the treatment course. The half-life of the monoclonal antibody increased from 76.3 hours after the first infusion to 205.8 hours after the fourth infusion and was concomitant with a four-fold decrease in the antibody clearance. At three months and six months post-treatment, the median rituximab serum levels were 20.3 µg/mL (range 0.0 to 96.8 µg/mL in 104 patients) and 1.3 µg/mL (range 0.0-28.7 µg/mL in 13 patients), respectively. A statistically significant

correlation was found between the median antibody concentration and response for multiple time points during the treatment and follow up. The mean serum antibody concentration was also inversely correlated with measurements of tumor bulk and with the number of circulating B cells at baseline.
Regarding to PK of rituximab in combination with chemotherapy in FL we refer to two studies:
In the first one they carried out a pilot pharmacokinetic study in 10 patients with B-cell non-Hodgkin lymphoma treated with rituximab associated with chemotherapy on a three-weekly basis. Patients received four courses of rituximab (375 mg/m2) associated with CHOP at 21-day intervals. Pharmacokinetic parameters obtained from 10 patients were similar to those described for studies in the absence of chemotherapy. They did not observe any intra-subject variation in pharmacokinetic parameters over the treatment period. The results suggest that rituximab pharmacokinetics is not affected by combination with CHOP chemotherapy. Nevertheless, the substantial intersubject variability observed in this small sample size has to be highlighted (Blasco *et al.*, Fundam Clin Pharmacol 2009).
The second study was a phase II and included 17 adult patients with previously untreated advanced follicular lymphoma grade 1 or 2 (Jager *et al.*, Haematologica 2012). Treatment consisted of 6 cycles of rituximab 375 mg/m2 i.v., mitoxantrone 10 mg/m2 i.v and fludarabine 25 mg/m2 i.v. (R-FM). Detailed PK analysis of serum samples was carried out in cycles 1 and 6 of induction. A high inter-individual variability of total area under the curve (AUC_{total}) values ranging over almost 1 log at maintenance cycle 1 (1,540-12,025 g/L*days, median 5,736) was observed. This was accompanied by a similar variation in half-life (median 23.3 days; range 5.9-54.7). Indeed, female patients had higher AUC_{total} throughout the treatment period. Overall, the median AUC_{total} in men was 81% of the values observed in women. This finding was in agreement with the observed volume of distribution in women (induction 1: 5.2 L vs. 8.6 L).
Similar findings were obtained for patients with or with- out BM infiltration (median AUC_{total} in patients with BM infiltration was 76% of that found in patients with negative BM histology).
While the differences in AUC_{total} between men and women, as well as between patients with or without BM infiltration, were not statistically significant, they may still be biologically important. No correlation was found between AUC_{total} and age.
The correlation between AUC and serum trough levels (C_{trough}) indicated that the latter could be used as surrogate for AUC_{total} in further analysis.
In FL maintenance PK was evaluated in 10 patients treated in the same previous study setting (Jager *et al.*, Haematologica 2012). Rituximab pharmacokinetic analysis showed a high variability ranging over almost 1 order of magnitude at maintenance Cycle 1 (area under the curve 1,540–12,025 g/L*days). Median area under the curve was lower in men (81%) and in patients with initial bone marrow infiltration (76%). Higher rituximab serum concentrations before next therapy (C_{trough}) were associated with female sex (P=0.04) as well as with absence of initial bone marrow infiltration (P=0.001). C_{trough} correlated with remission quality (complete vs. partial remission; P=0.005) and progression-free survival (P=0.03). A decline in rituximab C_{trough} below 25,000 ng/mL was observed from 9.5 to 62 months before clinical relapse (P=0.008).

1.2.2 Subcutaneous (SC) Rituximab

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/m^2) 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/m^2.

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/m^2 SC, N=34; Cohort C, 625 mg/m^2 SC, N=34; and Cohort D, 800 mg/m^2 SC, N=40). In addition, 16 patients had been enrolled in Cohort A (375 mg/m^2 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 4**. Observed AEs were mostly mild to moderate.

Table 4 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. ARRs were the most frequent AE and had a higher incidence in the SC arm (31% of SC vs 4% of IV patients). ARRs consisted mostly or 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 willevaluate 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, a Phase IIIB 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.

PK of rituximab SC

Rituximab efficacy depends on CD20 binding, and C_{trough} levels reflect rituximab exposure throughout the therapy cycle; therefore, achieving a non-inferior C_{trough} level with SC dosing is expected to provide comparable efficacy to IV dosing.

BP22333 is a two-stage phase Ib study assessing PK and tolerability of SC vs IV maintenance rituximab in pts with first-line or relapsed FL. Stage 1 dose-finding results (Salar et al, ASH 2010, abstract 2858) identified a fixed dose of 1400 mg for C_{trough} non-inferiority testing in Stage 2.

The Stage 2 objective was to demonstrate non-inferiority of simulated C_{trough} of rituximab SC vs IV, using a non-inferiority test with a lower boundary of 0.8 for the 90% confidence interval (CI).(Salar et

al, ASH 2012, abstract 1641, abstract 2858). Secondary endpoints include SC vs IV area under the serum concentration-time curve. Eligible pts (N=157) were aged ≥18 years with an ECOG performance status ≥2, and histologically confirmed CD20-positive grade 1, 2, or 3a FL requiring treatment. Eligible patients must have achieved a complete or partial response following IV rituximab-based induction therapy for FL and must have received ≥1 cycle of IV rituximab maintenance within 16 weeks of completing induction.

Patients (N = 154) were randomized 1:1 to receive SC rituximab (1400 mg) or IV rituximab (375 mg/m^2) for their remaining maintenance cycles, stratified by 2-monthly (q2m) vs 3-monthly (q3m) regimen. Study arms were balanced for age, sex, body surface area, FL grade at diagnosis, induction therapy and number of maintenance doses prior to study entry. Median treatment duration was 14.8 months (range, 0–19) in the SC arm and 13.8 months (range, 0–19) in the IV arm.

The primary endpoint of the study was met. Geometric mean $C_{trough,SC}$:$C_{trough,IV}$ ratios were 1.24 and 1.12, respectively, for q2m and q3m, and lower limits of the two-sided 90% CI (1.02 and 0.86, respectively) exceeded the protocol-specified non-inferiority limit ($C_{trough,SC}$:$C_{trough,IV}$ ratio of 0.8). Therefore, 1400 mg SC rituximab was concluded to be non-inferior to 375 mg/m^2 IV rituximab administration.

Induction and maintenance therapy using the 1400 mg SC rituximab dose is being assessed in the phase III BO22334 study. BO22334 is a two-stage study of SC vs IV rituximab combined with up to 8 cycles of CHOP or 8 cycles of CVP chemotherapy followed by maintenance (Davies et al, ASH 2012, Abstract 1629).The target population was patients with previously untreated FL. The primary endpoint was PK: Stage 1 aimed to confirm that the SC rituximab dose of 1400 mg (dose based on phase I study BP22333; Salar et al, ASH 2010), resulted in non-inferior C_{trough} rituximab levels compared with the 375 mg/m^2 IV dose when given as 3-weekly induction therapy combined with chemotherapy.

The stage 1 primary endpoint was non-inferiority of the $C_{trough,SC}$:$C_{trough,IV}$ ratio (limit for non-inferiority was C_{trough} ratio > 0.8) at Cycle 7 of induction. Area under the serum concentration–time curve (AUC) was secondary end-point. Previously untreated patients with histologically confirmed CD20-positive grade 1, 2, or 3a FL requiring treatment (N = 127) were randomized 1:1 to SC (n = 63) or IV (n = 64) rituximab, stratified by Follicular Lymphoma International Prognostic Index score, chemotherapy, and region. Allocation to R-CHOP or R-CVP was at the investigator's discretion; 40 patients in each arm (63%) received CHOP chemotherapy and the remaining patients (37%) received CVP chemotherapy.

The primary PK endpoint was met with a geometric mean of 134.6 µg/mL for the rituximab SC arm (n = 48) and 83.1 µg/mL for the rituximab IV arm (n = 54) resulting in an SC:IV ratio of 1.62 (90% confidence interval [CI]: 1.36, 1.94). The C_{trough} achieved with SC rituximab was therefore concluded to be non-inferior to IV administration. The geometric mean ratio of AUC_{SC}:AUC_{IV} (1.378 [90% CI: 1.241, 1.530]) was also non-inferior.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1.1 Benefits of Rituximab

As detailed in the previous sections, rituximab is a chimeric murine/human monoclonal antibody that specifically binds to CD20, a hydrophobic trans-membrane protein present on the surface of B lymphocytes. Proposed mechanisms of action of rituximab include complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. It has also been reported that rituximab demonstrates direct anti-tumour activity independent of the host immune system, through the induction of apoptosis (Coiffier et al., C R Biol 2006) and, in addition, rituximab sensitizes lymphoma cells to cell killing by cytotoxic drugs.

Rituximab was first approved in the US under the brand name Rituxan® in 1997 for the treatment of relapsed or refractory indolent B-cell lymphomas. Currently, rituximab IV is approved for treatment of relapsed or chemo-resistant, low-grade or follicular, CD20-positive, B-cell NHL in over 100 countries including the EU and the United States (US), and for treatment of rheumatoid arthritis in the US and EU. Over the past decade, the use of rituximab has radically changed the treatment of NHL and has become standard in the management of patients suffering from various B-cell malignancies including

FL, DLBCL and CLL. It has been observed that the previously described downward trend in mortality rates coincided with the introduction of rituximab in clinical practice (Keating et al., Drugs 2010).
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/m^2 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 1.2.2.
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).

1.3.1.2 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 ≥ 1.5 x 10^9/L and platelet counts of ≥ 75 x 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 electronic case report form (eCRF).

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 proportion of AARs following multiple doses of rituximab SC during Induction and/or Maintenance therapy in patients with CD20+ DLBCL or CD20+ follicular NHL, 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 ≥ 3 AEs
  - Grade ≥ 3 IIRRs
  - 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)
  - complete response (CR) rate, including complete response unconfirmed (CRu), 4-8 weeks after the last dose of Induction treatment
  -

2.3 PHARMACOKINETIC OBJECTIVES

To evaluate the following:

1. In FL patients:
   - population PK parameter: C_{trough}
   - effects of subject characteristics (age, gender, weight, BSA) on the above mentioned rituximab population PK parameter
   - effects of the covariates related to disease at baseline:
     - FLIPI 0-1/ 2/ ≥ 3;
   - interindividual variability
   - relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial)
2. In DLBCL patients:
   - population PK parameters: C_{trough}, AUC, C_{max} and CL/F (clearance/fraction of absorbed drug)
   - effects of subject characteristics (age, gender, weight, BSA) on the above mentioned rituximab population PK parameters
   - effects of the covariates related to disease at baseline:
     - IPI 0 bulky-1/ 2/ 3/ 4 on the above mentioned rituximab PK population parameters
   - interindividual variability
   - relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial)
   - rituximab exposures (concentration over time) during the 2 different scheduling of rituximab SC R-CHOP14 or R-CHOP 21

2.4 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) measure for this Study is as follows:
Patient-assessed satisfaction using Rituximab Administration Satisfaction Questionnaire (RASQ) (see **Appendix 8**).

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview

This is a multicentre, single arm Study to evaluate safety, efficacy and PK of rituximab SC 1400 mg fixed dose, administered as part of Induction and/or Maintenance therapy.

This Study will include 160 adult patients with CD20+ DLBCL or FL (grades 1, 2 or 3a) previously untreated, who have already received at least one full dose of rituximab IV during Induction or Maintenance. Patients receiving Induction therapy must be able to receive at least 4 cycles of rituximab SC in addition to standard chemotherapy or patients receiving Maintenance therapy must be able to receive at least 6 cycles of rituximab SC.

During the Study, all 160 patients will be assessed for safety and efficacy.

During the administration period with rituximab SC, patients satisfaction data will be collected for all 160 patients using Rituximab Administration Satisfaction Questionnaire (RASQ).

During the administration period with rituximab SC, only the first enrolled 100 patients will be evaluated for PK parameters as detailed in Section 3.4.3.

Induction Therapy:

Patients receiving Induction therapy prior to entry into the Study must be eligible to receive at least four cycles of rituximab SC (i.e. 4 additional months of treatment) (Fig.1 for FL and Fig.2 for DLBCL). Patients who will continue into Maintenance therapy after final staging during the Study can continue to receive rituximab SC up to 12 cycles.

Maintenance Therapy:

Patients receiving Maintenance therapy prior to entry into the Study must be eligible to receive at least six cycles of rituximab SC (i.e. 12 months of 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 treatment - Fig.1 for FL). Patients who completed Induction Therapy with rituximab IV, as per clinical practice, can be enrolled in the Maintenance Therapy of the study starting from cycle 1 with rituximab SC.

Post-treatment Follow Up:

All patients will continue the Study with further 2 years post-treatment follow up.

Figure 1– Study Design Scheme for FL patients

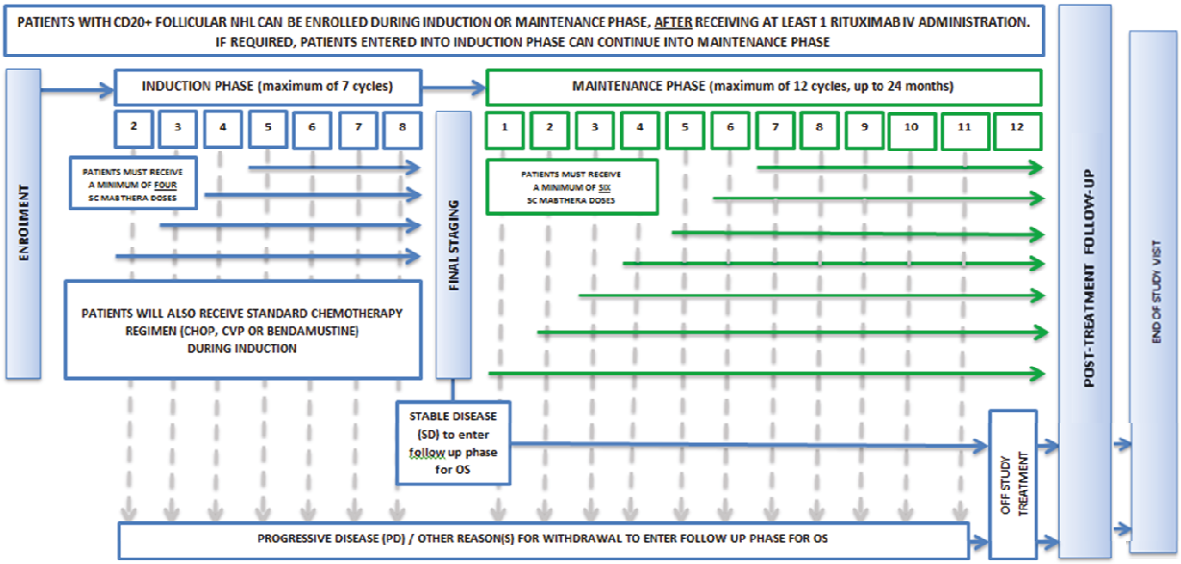
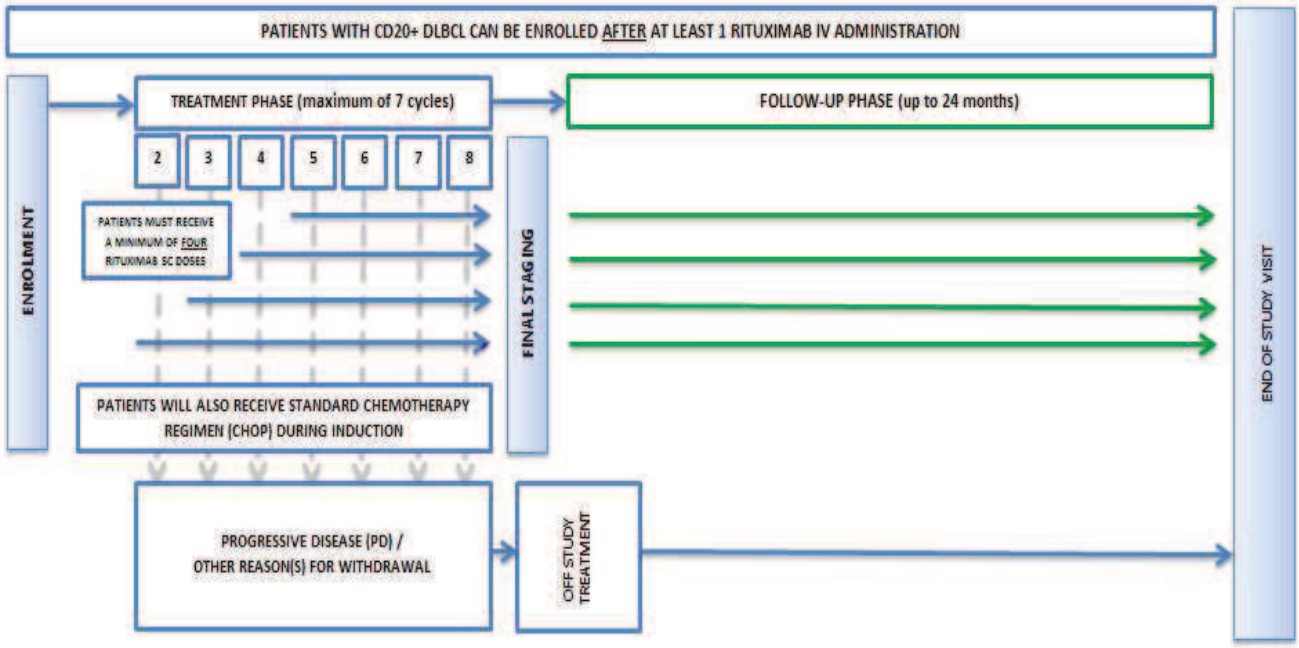


Figure 2– Study Design Scheme for DLBCL patients



3.2 END OF STUDY

The end of the Study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur maximum 54 months after the last patient is enrolled.

3.3 RATIONALE FOR STUDY DESIGN

This is a phase IIIb, multicentre, single arm Study in approximately 160 patients previously untreated with diffuse large B cell lymphoma (DLBCL) or follicular lymphoma (FL). Diagnosis of DLBCL or follicular NHL before treatment must have included histological diagnosis and initial CD20 expression confirmation.
An open label, non-comparative single arm design is considered adequate for this type of trial.
The study design includes only one treatment arm to reach the primary objective i.e. safety of a new formulation of rituximab at fixed dose. It is not requested a comparison with IV formulation or with different dosages.
The safety profile includes evaluation during Induction, Maintenance and two years post-treatment follow-up.

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/m^2 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 registration studies.

3.3.2 Rationale for Patient Population

The target population for the current ML28881 Study will consist of adults with previously untreated CD20+ DLBCL or CD20+ follicular NHL Grade 1, 2 or 3a, according to the WHO classification system. Both underlying conditions are approved indications for rituximab IV.
The population valid for the primary safety analysis will consist of Full Analysis Set defined as all recruited patients who receive at least one dose of Study medication.
The population valid for PK analysis will include all recruited patients who receive the investigational treatment (rituximab SC) and have at least one PK sample collected and analyzed.

3.3.3 Rationale for Chemotherapy

Chemotherapy regimens in the aforementioned pivotal trials in previously untreated DLBCL included CHOP-14, CHOP-21 or CHOP-like chemotherapy for six or eight cycles. Those in previously untreated follicular NHL included CVP, MCP and CHVP for six or eight cycles. In keeping with the results of the pivotal trials, as well as the approved indications for rituximab IV and current standard practices, background therapy in this Study will be the standard chemotherapy regimens, that is:

- DLBCL: R-CHOP 21 or R-CHOP-14;
- FL: R-CHOP 21 or R-CVP or R-bendamustine) (Induction only).

3.3.4 Rationale for PK of rituximab SC

In this study population PK of rituximab will be evaluated. Population PK quantify the effect of the drug on a population of patients who could use the drug. In this way it is allowed to quantify, explain and predict how the variability of the drug concentration acts on the variability of the drug effect (Concordet et al., Encyclopedia of biopharmaceutical statistics – third edition, chapter 164). Population PK enables optimization of dosage regimen.

It is now appreciated that pharmacokinetic variability is a major factor affecting clinical response to anti-CD20 antibodies (Cartron et al., Clin Cancer Res 2011). The pharmacokinetics of an mAb depends on a variety of factors, such as the dose and frequency of administration, the metabolic turnover of the Ab, its distribution in the body, and its specific and unspecific clearance. Some of these factors, such as the specific clearance by binding to CD20 cells, may be influenced by tumor bulk. In contrast, unspecific clearance, such as that caused by binding to Fc receptors, might depend on other factors such as the binding affinity of rituximab to distinct Fc receptor genotypes (Muller et al., Blood 2012).

The population PK of rituximab IV was studied in pivotal trial in patients with relapsed low-grade or follicular B-cell NHL who were treated with 4 weekly rituximab doses.(Yin et al., JCO 2010) Population PK (POP-PK) of rituximab was performed based on 1,848 serum samples from 161 patients using nonlinear mixed-effects modeling (NONMEM VI) software. The association of rituximab PK with response and time to progression (TTP) in the follicular lymphoma (FL) subgroup was evaluated by logistic and Cox regression, respectively. Rituximab clearance was best described by a two-compartment model with time varying clearance comprised of two terms—a target-independent pathway as with other endogenous IgG antibodies, which is unchanged throughout treatment, and a target-mediated pathway that decreases from its initial value following infusion at a constant decay rate related to the extent of B cell/tumor-burden at baseline. In the FL subgroup (N=111), a positive association of rituximab serum concentrations pre-second infusion with overall response rate and TTP was observed among patients with low concentrations (< 35 ug/mL): odds ratio =1.72 (95% CI: 1.14-2.60, p=0.009) for response and HR=0.75 (95% CI: 0.64-0.91, p=0.0032) for TTP (per 5 ug/mL). In contrast, no association with TTP or OR was seen for the FL patients with higher serum concentrations (≥ 35 ug/mL). Similar results were observed for time-points at 1 and 3 mo post-treatment, and the association is not qualitatively affected by baseline characteristics or disease factors. These data suggested that the lower rituximab serum levels are associated with the larger tumor burden and/or antigen load. Among FL patients, higher rituximab concentrations are associated with better clinical outcomes only on those with serum concentrations in a low range. Further studies would be necessary to identify the threshold of rituximab level sufficient to override the effects of tumor burden for FL patients.

Moreover Jager (Jager et al., Haematologica 2012) reported a unique, detailed analysis of the association between serum concentrations, prognostic factors and clinical outcome of FL during intensive immunochemotherapy induction and rituximab maintenance (see Section 1.2.1.3.3 PK of rituximab). One of the major findings of this study is the log-fold inter-individual variability in rituximab concentrations indicating that median levels are not representative. Rituximab PK depended on gender and on the presence or absence of bone marrow infiltration at diagnosis as a marker of tumor burden

Population PK was studies also in DLBCL setting in patients treated with 8 doses of rituximab in combination with CHOP-14 in 20 elderly patients (Muller et al., Blood 2012). Population pharmacokinetic modeling was performed with nonlinear mixed-effect modeling software (NONMEM VI). Concentration-time data were fitted into an open 2-compartment model and total clearance, central compartment volume, intercompartment clearance, and volume of distribution at steady-state (Vd_{ss}) were investigated.

Total clearance was 9.43 mL/h and Vd_{ss} was 9.61 L. Rituximab clearance was reduced (8.21 mL/h vs 12.68 mL/h; P = 0.003) and elimination half-life was prolonged in women compared with men ($t_{1/2\beta}$ = 30.7 vs 24.7 days; P = 0.003). Body weight also affected Vd_{ss} (0.1 L increase of Vd_{ss} per kilogram above median of 75 kg). A sex-dependent effect and the higher weight of males contribute to their faster rituximab clearance, which might explain why elderly males benefit less from the addition of rituximab to CHOP than females.

To increase understanding of rituximab SC, the Population PK parameters will be evaluated in this study.

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 IIRRs, 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 will be recorded regardless of their intensity / grading. Grading will be completed according to the NCI CTCAE version 4.0 (see **Appendix 6**).

3.4.2 Efficacy Outcome Measures

Tumour assessments will be based on computed tomography (CT) scans of the neck, chest, abdomen and/or pelvis (if detectable by these techniques) or other diagnostic means (e.g. magnetic resonance imaging [MRI]) where applicable. Other methods (e.g. MRI) are acceptable for patients in whom CT scans are contraindicated. The CT scan used for eligibility assessments may be performed up to 45 days the first rituximab IV administration in Induction setting.
Response assessments after 4 cycles (interim staging) and 4-8 weeks after the completed Induction period will be based on the Investigator's assessment, completed according to the International Working Group (IWG) response criteria (Cheson et al. 1999) or local standard practice.
The efficacy of rituximab SC will be evaluated during Induction and/or Maintenance in terms of CR/CRu, PFS, EFS, DFS and OS.
CR/CRu is complete response or complete response unconfirmed and is measured 4 to 8 weeks after the end of Induction treatment.

- **CR/CRu**: is complete response or complete response unconfirmed and is measured 4 to 8 weeks after the end of Induction treatment.
- **EFS** is defined as the time from first dose 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 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 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.

3.4.3 Pharmacokinetic Outcome Measures

To evaluate the following:

1. In FL patients:
   - population PK parameter: C_{trough}
   - effects of subject characteristics (age, gender, weight, BSA) on the above mentioned rituximab population PK parameter
   - effects of the covariates related to disease at baseline:
     - FLIPI 0-1/ 2/ ≥ 3;
   - interindividual variability
   - relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial)
2. In DLBCL patients:
   - population PK parameters: C_{trough}, AUC, C_{max} and CL/F (clearance/fraction of absorbed drug)

- effects of subject characteristics (age, gender, weight, BSA) on the above mentioned rituximab population PK parameters
- effects of the covariates related to disease at baseline:
    - IPI 0 bulky-1/ 2/ 3/ 4 on the above mentioned rituximab PK population parameters
- interindividual variability
- relationship of C_{trough} (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial)
- rituximab exposures (concentration over time) during the 2 different scheduling of rituximab SC R-CHOP14 or R-CHOP 21

3.4.4 Patient-Reported Outcome Measures

The patient-reported outcome (PRO) measure for this Study is as follows:

- Patient-assessed satisfaction using Rituximab Administration Satisfaction Questionnaire (RASQ).

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population will consist of adults patients with CD20+ DLBCL or FL grade 1, 2 or 3a, according to the World Health Organization (WHO) classification system, previously untreated, who have already received at least one full dose of rituximab IV during Induction or Maintenance.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for Study entry:

1. Signed, written informed consent form
2. Age ≥ 18 and ≤ 80 years at time of enrolment
3. Histologically confirmed, CD20+ DLBCL or CD20+ follicular NHL grade 1, 2 or 3a, according to the WHO classification system
4. Currently being treated with rituximab IV in the Induction or Maintenance setting, 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 (i.e. tolerability issues)
5. 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)
6. An International Prognostic Index (IPI) score of 1-4 or IPI score of 0 with bulky disease, defined as one lesion ≥ 7.5 cm, or Follicular Lymphoma International Prognostic Index (FLIPI) (low, intermediate or high risk) assessed before the first rituximab IV administration in Induction setting (see **Appendix 4**)
7. At least one bi-dimensionally measurable lesion defined as ≥ 1.5 cm in its largest dimension on computed tomography (CT) scan assessed up to 45 days the first rituximab IV administration in Induction setting
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3 (see **Appendix 4**)

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 follicular lymphoma (FL) IIIB

2. Primary central nervous system lymphoma, histologic evidence of transformation to a Burkitt lymphoma, primary effusion lymphoma, primary mediastinal DLBCL, DLBCL of the testis, or primary cutaneous DLBCL
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: (i) patients receiving corticosteroid treatment with ≤ 30 mg/day of prednisone dosing or equivalent must be on a documented stable dose of at least 4 weeks duration prior to randomization; (ii) a pre-phase of high dose prednisolone (e.g. 100 mg/day for 3 to 5 days) is acceptable for patients with aggressive NHL.

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 x 10^9/L
– Platelet count < 75 x 10^9/L

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 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):

✓ Positive test results for chronic hepatitis B infection (defined as positive HBsAg serology)

Patients with occult or prior hepatitis B infection (defined as positive total hepatitis B core antibody [HBcAb] and negative or positive HBsAg with HBV DNA undetectable) may be included. These patients must be followed closely according to the European Association for the Study of the Liver (EASL, Practice Guideline 2012).

Patients need to receive antiviral therapy according to the local clinical practice.

- ✓ Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)

  Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

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. Pregnant or breastfeeding patients. A negative serum pregnancy test is required for 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 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.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Not applicable.

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.

For further details, see the rituximab SC IB.

4.3.1.2 Background Treatment

Commercially available chemotherapy will be used in combination with rituximab SC, as per standard local practice.

For further details, see the local prescribing information.

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.
Rituximab for SC 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. 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.
Study drug packaging will be overseen by the Roche clinical trial supplies department and will bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labelling of the Study medication will be in accordance with Roche standards and local regulations. All the requirements of Annex 13 of the Good Manufacturing Practices guideline for labelling investigational drug will be fulfilled.
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.
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. Patient should be reserved for at least 15 minutes following rituximab SC administration. A longer period maybe appropriate in patients with an increased risk of hypersensitivity reactions.

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. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1. All Background therapy (e.g., CHOP for patients with DLBCL, or CHOP, CVP, or bendamustine for patients with follicular NHL) should be recorded on the eCRF.

Before starting a new treatment cycle, toxicity related to the previous cycle must have resolved. 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.

4.3.3 Investigational Medicinal Product Accountability

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.
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 IMPs. All drug supplies that will be used in the Study must be maintained securely. All Study drugs 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, 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 SC

Currently, Roche does not have any plans to provide rituximab SC to patients after conclusion of the study or any earlier patient withdrawal. Roche will evaluate the appropriateness of continuing to provide rituximab SC to study patients after evaluating the safety data gathered in the study. These analyses may be conducted prior to completion of the study. If these data are medically significant, Roche may amend the protocol to continue to provide rituximab SC in an open-label extension study to patients who have shown a demonstrable benefit from rituximab SC treatment during this study as measured by primary and secondary endpoints. This open-label extension study will continue until rituximab SC is commercially available to the participating patients in their countries or until Roche ceases producing or studying rituximab SC.

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 Study completion/early termination visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.
Background therapy (e.g., CHOP for patients with DLBCL, or CHOP, CVP, or bendamustine for patients with follicular NHL) 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 be withdrawn from the study and 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**). Time windows allowed are as follows:

-Assessments during treatment visits: ± 2 days

-Assessments during follow-up visits: ± 2 weeks

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), and all medications (e.g. prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the Screening 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. In addition, as part of tumour assessments, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. 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 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 assessment at Screening/Baseline and 4 weeks after the last dose of Induction treatment (staging) 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). Conventional CT or MRI should be performed according to institutional standards.

CT and MRI are currently the best available and most reproducible methods for measuring target lesions selected for response assessment. The same radiographic procedure used at Screening/Baseline must be used throughout the Study (e.g., CT with the same contrast protocol or MRI with or without a non-contrast CT). The tumour assessment may be repeated at any time, at the Investigator's discretion, if progressive disease (PD) is suspected. Due to the possible limited availability of [18F]deoxyglucose positron emission tomography (FDG-PET) scanners, an FDG-PET scan cannot be mandated, but can be performed according to local institutional standards.

The CT scan used for eligibility assessments may be performed up to 45 days the first rituximab IV administration in Induction setting. The end-of-treatment response assessment including radiology/imaging report must be obtained 4 weeks after the last dose of Induction treatment.

Response should be determined on the basis of radiographic and clinical evidence of disease according 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. 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.
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 dosing 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.

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 IV 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 assessed before the first rituximab IV administration in Induction setting (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.

4.5.1.6 Laboratory Assessments

Samples for the laboratory tests listed below will be analysed locally, except for PK analysis that will be perfomed centrally. The results from the safety laboratory assessments must be available on treatment days, prior to the rituximab administrations.
Laboratory assessments (except for PK) 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 at Screening and at any further timepoints during the Study will include haemoglobin, RBC count, total and differential white blood cell (WBC) countand 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 dosingor 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 and should include the following tests:
    1. HBV: hepatitis B surface antigen and total hepatitis B core antibody
    2. HCV: HCV antibody
    3. 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. The PRO instrument, Rituximax Administration Satisfaction Questionnaire, 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 prior to the completion of other study assessments and the administration of study treatment. See the below details of administration requirements:

Induction:

- pre-dose at 2nd rituximab SC administration
- cycle 8 (post-dose)

Manteinance:

- pre-dose at 2nd rituximab SC administration
- pre-dose at 7th rituximab SC administration
- cycle 12 (post-dose)

In case of Early Termination/End of Treatment visit PRO questionnaire should be administered to the patient if not already completed on Cycle 8 (DLBCL/FL) or Cycle 12 Post Dose (FL).

4.5.1.9 Mandatory Samples for pharmacokinetic

Serum samples for PK will be collected as follows:

- FL patients, Induction and Maintenance or Maintenance only:

Induction Collection timelines

1. Baseline: pre-dose of rituximab SC administration
2. Cycle 8 – Day 1: pre-dose of rituximab SC administration

Maintenance Collection timelines

1. Baseline = pre-dose of rituximab SC administration
2. Cycle 12 – Day 1: pre-dose of rituximab SC administration

- DLBCL patients, Induction R-CHOP-21 or Induction R-CHOP-14

Induction Collection timelines

1. Baseline: pre-dose of rituximab SC administration
2. Cycle 7 – Day 1: pre-dose of rituximab SC administration
3. Cycle 7 – Day 7 (± 3 days)
4. Cycle 7 – Day 14 (± 3 days)*
5. Cycle 8 – Day 1: pre-dose of rituximab SC administration

**In R-CHOP-14 regimen, this sampling time corresponds to sampling time of cycle 8 of R-CHOP-21 regimen (pre-dose of rituximab SC administration)*

5 mL of blood will be drawn from a peripheral vein and transferred into an EDTA/heparin-free vial. Blood samples will be centrifuged at 3000 RPM for 10 min and the serum collected into 2 vials. Samples will be stored at –20°C until shipment. Samples will be shipped in dry ice.
For serum assay for rituximab determination see **Appendix 7**.

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 Study drug treatment, unless otherwise specified. Standard-of-care tests or examinations performed prior to obtaining informed consent and within 7 days prior to start of treatment 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.
Please see **Appendix 1** for the schedule of Screening and pre-treatment assessments.

4.5.2.2 Assessments during Treatment Visits

All assessments must be performed within ±2 days of the specified treatment visit, as specified in the Schedule of Assessments (see Appendix 1). This 4-day visit window should provide flexibility for holiday schedules and patients' travel arrangements. 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 according the administration requirements detailed on section 4.5.1.8. The results from the safety laboratory assessments must be available on treatment days, prior to rituximab administration.

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.
During induction, patients with SD or PD at staging will be withdrawn from Study treatment and will be followed for all AEs and SAEs and for survival until the end of the Study.
Patients who do not complete the Induction treatment per protocol will undergo end-of-Study assessment within 4 weeks after the last dose of Induction treatment and will be followed until the end of the whole Study according to local practice for all AEs / SAEs, tumour response / progression (if PD not yet documented), survival, and documentation of any new anti-lymphoma treatment.
Please see **Appendix 1** for the **Schedule of Assessments** performed during the treatment period.

4.5.2.3 Post-Treatment Follow-up (Observation) Period

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 for survival and all 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 4-8 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 AEs / SAEs , tumour response / progression (if PD not yet documented), new treatments for lymphoma, and survival.
Follow-up of patients after Induction treatment will occur every 6 months (± 2 weeks) until the end of the Study, as detailed in **Appendix 1** (**Schedule of Assessments**).
After the Study completion/early termination visit, AEs should be followed as outlined in Sections 5.5 and 5.6.
Please see **Appendix 1** for the schedule of follow-up assessments.

4.5.2.4 Assessments at Study Completion/Early Termination Visit

Patients who complete the Study (2 years after last rituximab administration) or discontinue from the Study early will be asked to return to the clinic (specify 28 days or at least 5 half-lives of any non-rituximab IMPs, whichever longer) after the last ~~dose of Study drug~~ visit for a follow-up visit.
Please see **Appendix 1** 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**, **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

Reasons for withdrawal from the Study may include, but are not limited to, the following:

- 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 non-compliance, (e.g. dosing instructions, Study visits)
- Patient lost to follow-up
- Major protocol violation
- 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 treatment prematurely will be asked to return to the clinic for a ~~Study~~treatment completion/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 Study drug 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, although date of death should be recorded, where applicable. 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**, **Schedule of Assessments**). As part of physical exams, SC injection sites will be checked at every 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. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved.
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 **Table 5** below.

Table 5 Guidelines for Managing Specific Adverse Events related to R-CHOP treatment

Event	Action to Be Taken
Haematologic toxicity: Grade 4	• 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/m^2 and doxorubicin dose to 35 mg/m^2 for subsequent cycles. • Second episode: If improvement to grade ≤ 2, decrease cyclophosphamide dose to 375 mg/m^2 and doxorubicin dose to 25 mg/m^2 for subsequent cycles. • Third episode: Discontinue CHOP. If improvement to grade ≤ 2, continue rituximab at full dose. • Fourth episode: Discontinue all Study treatment.
Haematologic toxicity: Grade 3	• 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.
Haematologic toxicity: Grade 1 or 2	• No action required.
Neurotoxicity: Grade 4	• 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.
Neurotoxicity: Grade 2 or 3	• 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.
Neurotoxicity: Grade 1	• No action required.

Event	Action to Be Taken
Other non-haematologic toxicities: Grade 3 or 4	• 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/m^2 and doxorubicin dose to 35 mg/m^2 for subsequent cycles. • Second episode: If improvement to grade ≤ 1 or baseline, decrease cyclophosphamide dose to 375 mg/m^2 and doxorubicin dose to 25 mg/m^2 for subsequent cycles. • Third episode: Discontinue CHOP. If improvement to grade ≤ 1 or baseline, continue rituximab at full dose. • Fourth episode: Discontinue all Study treatment.
Other non-haematologic toxicities: Grade 2	• 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.
Other non-haematologic toxicities: Grade 1	• No action required.

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

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)

An 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

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 serious adverse events and non-serious

adverse events of special interest occurring to a subject, the Investigator should report those to the Sponsor (see Section 5.6).
SAEs must be reported to Roche (or designee) within 24 hours of the Investigator becoming aware of the event.
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 some SAEs, 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 6 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 6 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×baseline value) in combination with either an elevated total bilirubin (>2×ULiN) 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×baseline value in combination with total bilirubin >2×ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST >3×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 survival section of 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.

Investigators must also comply with local requirements for reporting SAEs to the local health authority and Ethics Committee (EC).

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 (see *Protocol Administrative and Contact Information & List of Investigators*).

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 notification will be generated by the EDC system: the SAE Responsible will receive the EDC notification then the SAE Responsible will send the report .to Roche Safety Risk Management.

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 (see *Protocol Administrative and Contact Information & List of Investigators*). 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 (see *Protocol Administrative and Contact Information & List of Investigators*).

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. 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 regardless of the relationship 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 (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS AND ETHICS COMMITTEES

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the Mabthera® Rituximab IV Summary of Product Characteristics (SmPC) and the 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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A total of 160 patients will be recruited into this study, with the first enrolled 100 patients evaluated for PK analysis.
The primary safety end-point, the proportion of AARs following multiple doses of rituximab SC during Induction and/or Maintenance therapy will be estimated with a two-sided 95% CI.
From data of the previous study (BP22333) the expected proportion of AARs after rituximab SC was approximately 30%: the sample size of 160 patients will assure that the precision of estimate will be ±7.2%, so the confidence interval will range from 22.8% to 37.2%. In the graph below the relation is shown between the expected proportion and the distance to CI limit of the observed proportion: for expected proportions ranging from 10% to 90%, the precision of the estimate will range from 4.6% to 7.6% respectively (NQuery Advisor 7.0).

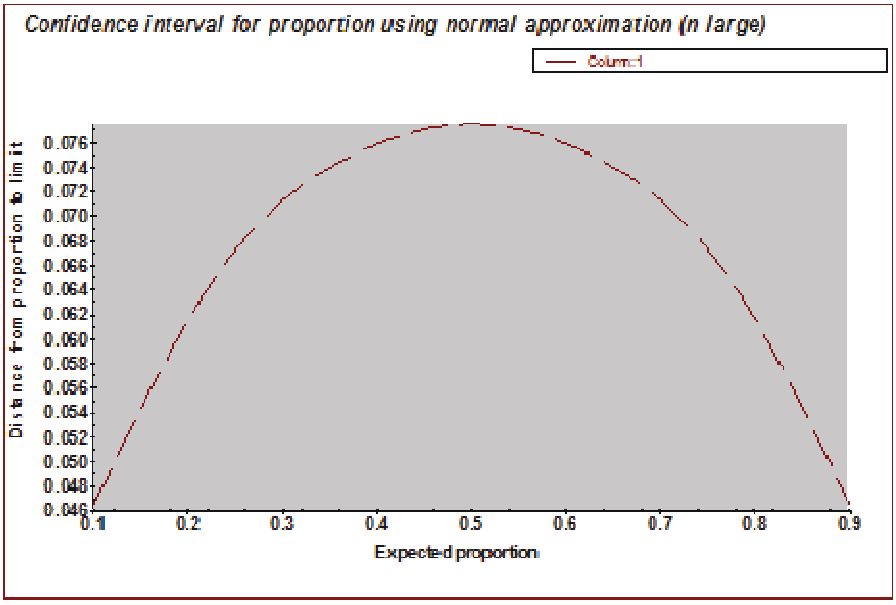


Figure 3 – Confidence interval for proportion using normal approximation

As to PK outcomes evaluation, the sample size of 100 patients will assure the possibility to evaluate the following inter-individual variability's factors:

- gender
- age (≤ 70 years and > 70 years)
- weights and BSA (median, > 25% than median, < 25% than median)
- FLIPI (0-1/ 2 / ≥3)
- IPI (0-1/ 2 / 3/ > 3)

In addition it will be relevant to show differences between gender in the systemic exposition (C_{trough}).
An intermediate PK analysis will be conducted once all patients completed the Final Staging Visit at the End of Induction period.
The final PK analysis will be conducted once all scheduled PK samples are collected.

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 160 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 able to receive at least 4 cycles of rituximab SC in addition to standard chemotherapy. Patients with follicular NHL receiving Maintenance therapy must be able 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 (i.e. 4 additional months of Induction treatment). 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

Screening and baseline characteristics will be summarized, overall and by subgroup of diagnosis of DLBCL and FL, as regards the demographic profile (age, sex, ethnicity), medical history, physical examination, specific cancer history, IPI score (according to Shipp et al. 1993) and/or FLIPI score (see **Appendix 4**), oncological therapy and concomitant medication use, serum pregnancy test and tumour assessment, by means of appropriate descriptive statistics: mean, standard deviation, median and range (minimum and maximum) for the continuous variables, and absolute / relative frequencies for the categorical variables.

Exposure to study treatment (rituximab) and chemotherapy, 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 by subgroup of diagnosis and overall.

The patient disposition will be dispayed by subgroup and overall, presenting the number of recruited patients, the number of patients who prematurely discontinue study treatment and the number of patients who withdraw from the study with reasons for withdrawal.

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

6.3.1 Analysis Populations

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

PK analysis population will consist of all patients who received the investigational treatment (rituximab SC) and have at least one pharmacokinetic sample collected and analysed.

The Intention-to-Treat (ITT) population will include all enrolled patients who receive at least one dose of study medication and who have at least one post-baseline efficacy evaluation, and will be used for the efficacy outcomes analysis.

An additional Per Protocol (PP) set for efficacy analysis is defined as all recruited patients without major protocol violations who have completed at least the fourth cycle of induction therapy or the sixth cycle of maintenance therapy with rituximab SC; the results of the two efficacy analyses will be compared for consistency.

6.4 SAFETY ANALYSES

Safety will be assessed on the following safety parameters: AARs, including IIRRs, AEs, AEs of grade ≥ 3, SAEs, AEs within the MedDRA SMQ `Anaphylactic reactions' (wide), safety routine 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 proportion 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 proportion of each AE will be summarized by the primary system-organ class and by preferred term. The proportion of deaths and cause of deaths will be listed and summarized. The proportion 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.

Safety laboratory parameters (haematology, biochemistry, coagulation tests, as defined in Section 3.4.1), 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 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. 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.
Further details about the planned safety analyses will be presented in the SAP.

6.5 EFFICACY ANALYSES

The efficacy of rituximab SC will be evaluated during Induction and/or Maintenance in terms of EFS, PFS, CR/Cru, DFS and OS and will be analysed for the FAS and for the Per protocol populations defined above.
Response assessments after 4-8 weeks after the completed Induction period 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 SC 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 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.
CR/CRu is complete response or complete response unconfirmed and is measured 4 weeks after the end of Induction treatment. CR/CRu rate at 4 weeks after the last dose of Induction treatment will be summarized and presented with the corresponding 95% two-sided Pearson-Clopper CI by subgroup of diagnosis and overall.
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.
OS is defined as the time from first dose to until death from any cause.
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 by subgroup of diagnosis and overall 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 PHARMACOKINETIC ANALYSES

As defined above the PK analysis population consists of all patients who have received the investigational treatment (rituximab SC) and have at least one pharmacokinetic sample collected and analysed.
FL patients: Descriptive statistics (mean, standard deviation, median and minimum and maximum values), will be computed for the PK parameter: Ctrough
In particular for rituximab concentrations obtained at Ctrough (pre-dose level) descriptive statistics will be presented at Baseline and during Cycle 8 of induction therapy and during Cycles 12 of maintenance therapy.
The effects over time of subject characteristics (age, weight, body surface area) on the above mentioned rituximab population PK parameter will be analyzed descriptively by computing a mixed model for repeated measures.

The effects of gender and of covariates related to disease at baseline in different risk categories (FLIPI 0-1/2/≥3;) on the above mentioned rituximab PK population parameter will be analysed by means of of Student's T test or Mann-Whitney U test, when appropriate.
The relationship of Ctrough (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial) will be summarized by means of descriptive statistics.

In DLBCL patients: Descriptive statistics (mean, standard deviation, median and minimum and maximum values), will be computed for the PK parameters: Ctrough , AUC, Cmax and CL/F (fraction of absorbed drug).
In particular for rituximab concentrations obtained at Baseline and during Cycle 7 and Cycle 8 (if applicable) descriptive statistics will be presented.
The effects over time of subject characteristics (age, weight, BSA) on the above mentioned rituximab population PK parameters will be analysed descriptively by computing a mixed model for repeated measures .
The effects of gender and of covariates related to disease at baseline in different risk categories (IPI 0 bulky/2/3/4) on the above mentioned rituximab PK population parameters will be analysed by means of of Student's T test or Mann-Whitney U test, when appropriate.
Relationship of Ctrough (pre-dose concentration) over time and CR/CRu at 4-8 weeks after the last dose of Induction treatment (concentration defined over time trial) will be described.
The rituximab exposures (concentration over time) will be compared descriptively during the 2 different scheduling of rituximab SC R-CHOP14 or R-CHOP 21.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

Patient-assessed satisfaction will be evaluated using the Rituximab Administration Satisfaction Questionnaire (RASQ).

PRO data will be summarized and presented by subgroup of diagnosis and overall.

Descriptive statistics will be computed for the questions assessing patient responses regarding convenience and satisfaction for rituximab SC.
Details about the RASQ analyses will be presented in the SAP.

6.8 INTERMEDIATE ANALYSES

One intermediate analyses is planned:

- The intermediate analysis will be done once all patients completed the Final Staging Visit at the End of Induction period.

The final analysis will be done at the end of study (i.e. last patient end of study visit).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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.
Roche will supervise the data management of this study. Roche will produce an EDC Study Specification document that describes the quality checking to be performed on the 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

Data for this study will be entered by the site staff from the paper source documents into a fully validated Electronic Data Capture system EDC that conforms to 21 CFR Part 11 requirements. In no case is the eCRF to be considered as source data for this trial.
Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs). Designated investigator site staff will not be given access to the EDC system until they have been trained and the personal username and password will be delivered after ethical and administrative approvals.
On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Roche. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-rom or paper copies of the patient data for archiving at the investigational site.
The Data Manager of the CRO working on behalf of Roche will perform the cleaning session reviewing the warning messages raised by on-line checks and running post-entry checks by means of validation programmes and data listings specific for the study. During this process, if clarifications are needed, the Data Manager will raise queries by means of data query forms through the WEB application.
Designated investigator site staff is required to respond to the query and the CRO data-manager will make the correction to the database.
The Data collection and the Queries flow as well as the on-line and off-line control checks will be detailed in Data Management Plan and Data Validation documents.
At the end of the study, the database has been declared to be complete and accurate and it will be locked.
eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and a 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 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Not applicable.

7.4 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.

7.5 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.

7.6 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).

8.2 INFORMED CONSENT

Roche 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. If applicable, 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 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 patient's legally authorised representative must sign the Consent Form on behalf of the patient, in accordance with ICH/GCP, when the patient shows conditions of legal or real incapacity. 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 ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the EC by the Principal Investigator or, as applicable, the Country Study Manager and reviewed and approved by the EC before the study is initiated. In addition, any patient recruitment materials must be approved by the EC.
The Principal Investigator or, as applicable, the Country Study Manager is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC. 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).
In addition to the requirements for reporting all AEs to the Sponsor, Investigators must comply with requirements for reporting SAEs to the local health authority and EC. Investigators may receive written IND 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, and archived in the site study file.

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.
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 (i.e. LPLV).

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

Please refer to the separate contact list for the contact information of the Sponsor CRO designee study personnel. This information can be found at the local Roche affiliate office, and within the Investigator Site File.

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).

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11. APPENDICES

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

Study Period	Screening / Baseline		Specify assessments required for each time point in the Study. Example, Induction Treatment (including staging), Maintenance Treatment, Post-Treatment Follow-up, Early Treatment Termination / End of Study																								
Visit		Induction (cycles)									Maintenance (cycles)													Post-treatment Follow-Up				
Timing / Assessments	D -28 to D -1	1*	2	3	4	5	6	7	8	Final Staging	1	2	3	4	5	6	7	8	9	10	11	12	Early Termination/End of Treatment (4-8 weeks after last dose)	1-6	6-12	12-18	18-24	End of Study Visit (28 days after last FU visit)
Written informed consent [a]	X																										
Demographic data	X																										
Medical history	X																										
Follicular NHL diagnosis and WHO Classification [b]	X																										
Documentation of/testing for HIV, active hepatitis and other infections [c]	X																										
Tumour evaluation [d]	X									X													(X) (d2)					X
Physical examination, infection assessment, vital signs [e]	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	X
Height and weight	X									X																	
12-lead ECG	X																										
IPI, FLIPI score [f]	X																										
ECOG performance status [g]	X									X																	
Serum pregnancy test [h]	X		If clinically indicated																								

Study Period	Screening / Baseline		Specify assessments required for each time point in the Study. Example, Induction Treatment (including staging), Maintenance Treatment, Post-Treatment Follow-up, Early Treatment Termination / End of Study																										
Visit		Induction (cycles)								Final Staging	Maintenance (cycles)													Early Termination/End of Treatment (4-8 weeks after last dose)	Post-treatment Follow-Up				End of Study Visit (28 days after last FU visit)
Timing / Assessments	D -28 to D -1	1*	2	3	4	5	6	7	8		1	2	3	4	5	6	7	8	9	10	11	12		1-6	6-12	12-18	18-24	
Laboratory: Haematology, Biochemistry, Coagulation tests [i]	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	X
PK samples [j]	X								X													X							
RASQ [l]				(X)†	(X)	(X)	(X)		X			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)			x	X[1]						
Study Treatment (minimum doses)	X					X	X	X	X								X	X	X	X	X	X							
Adverse event recording [k]	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	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	X
Survival										X													X	X	X	X	X	X	X

†. the brackets indicate the possibility of collection at different timepoints since the patients could be enrolled at different points of their previous treatment. See section 4.5.1.8 for further details and administration requirements

* Patients must have previously received at least one cycle of IV rituximab before enrolment. All Screening/Baseline assessments could have been performed at the IV cycle visit.

a. Signed informed consent must be obtained prior to any study-required Screening/Baseline assessments.
b. Diagnosis of follicular NHL before treatment must have included histological diagnosis and initial CD20 expression confirmation.

c. 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 before and during treatment with rituximab. Local guidelines for patient consent to viral testing must be adhered to (See sections 4.1.2 and 4.5.1.6 for further details).

d. 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 45 days the first rituximab IV administration in Induction setting . The end-of-treatment response assessment including radiology/imaging report should be determined on the basis of radiographic and clinical evidence of disease according 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) until PD. Subsequent bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline. 2) Patients who do not complete the study treatment per protocol will undergo end-of-treatment assessment within 4-8 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].

e. As part of physical exam, SC injection sites will be checked at every 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.

f. 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. See **Appendix 4**.

g. ECOG performance status needs to be ≤ 3 for inclusion of the patient into the study. See **Appendix 4**.

h. 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.

i. Haematology parameters at Screening and at any further timepoints during the Study will include haemoglobin, RBC count, total and differential white blood cell (WBC) countand 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.

j. PK sample collection timelines are as follow: *Induction:* a) Baseline = just before the first dose of rituximab s.c.; b) Cycle 8 – Day 1 (before rituximab s.c. administration); *Maintenance:* a) Baseline = just before the first dose of rituximab s.c. (when applicable); b) Cycle 12 – Day 1 (before rituximab s.c. administration).

k. 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 After initiation of study drug, all AEs/SAEs, regardless of relationship to study drug, will be reported until study closure.

l. RASQ will be collected at the following timepoints: patient enrolment (please refer to note †), at the end of induction (Cycle 8) and at the End of Maintenance (Maintenance Visit 12). If the patient prematurely terminates the study the RASQ Questionnaire will be completed at the Early Termination/End of Treatment Visit.

11.1.1 Appendix 2 Schedule of Assessments FOR PATIENTS WITH CD20+ DLBCL

Study Period	Screening / Baseline									Specify assessments required for each time point in the Study. Example, Induction Treatment (including staging), Maintenance Treatment, Post-Treatment Follow-up, Early Treatment Termination / End of Study						
Visit		Treatment (cycles)								Final Staging		Post-Treatment Follow-Up				/End of Study
Timing / Assessments	D -28 to D -1	1*	2	3	4	5	6	7	8		Early Termination/End of Treatment (4-8 weeks after last dose)	1-6	6-12	12-18	18-24	Visit (28 days after last FU visit)
Written informed consent [a]	X															
Demographic data	X															
Medical history	X															
DLBCL diagnosis and WHO Classification [b]	X															
Documentation of/testing for HIV, active hepatitis and other infections [c]	X															
Tumour evaluation [d]	X									X	(X)					X
Physical examination, infection assessment, vital signs [e]	X X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight	X X									X						

Study Period	Screening / Baseline																
		Specify assessments required for each time point in the Study. Example, Induction Treatment (including staging), Maintenance Treatment, Post-Treatment Follow-up, Early Treatment Termination / End of Study															
Visit		Treatment (cycles)								Final Staging		Post-Treatment Follow-Up					
Timing / Assessments	D -28 to D -1	1*	2	3	4	5	6	7	8		Early Termination/End of Treatment (4-8 weeks after last dose)	1-6	6-12	12-18	18-24	/End of Study Visit (28 days after last FU visit)	
12-lead ECG	X																
IPI score [f]	X																
ECOG performance status [g]	X									X							
Serum pregnancy test [h]	X									If clinically indicated							
Laboratory: Haematology, Biochemistry, Coagulation tests [i]	X X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK samples [j]	X							X	X								
RASQ [l]				(X)†	(X)	(X)	(X)		X		X						
Study Treatment						X	X	X	X								
Adverse event recording [k]	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	
Survival										X	X	X	X	X	X	X	

†. the brackets indicate the possibility of collection at different timepoints since the patients could be enrolled at different points of their previous treatment. See section 4.5.1.8 for further details and administration requirements.

* Patients must have previously received at least one cycle of IV rituximab before enrolment. All Screening/Baseline assessments could have been performed at the IV cycle visit.

a. Signed informed consent must be obtained prior to any study-required Screening/Baseline assessments.
b. Diagnosis of diffuse large B-cell lymphoma before treatment must have included histological diagnosis and initial CD20 expression confirmation.
c. 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 before and during treatment with rituximab. Local guidelines for patient consent to viral testing must be adhered to (See sections 4.1.2 and 4.5.1.6 for further details).
d. 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 45 days the first rituximab IV administration in Induction setting . The end-of-treatment response assessment including radiology/imaging report should be determined on the basis of radiographic and clinical evidence of disease according 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) until PD. Subsequent bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline. 2) Patients who do not complete the study treatment per protocol will undergo end-of-treatment assessment within 4-8 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].
e. As part of physical exam, SC injection sites will be checked at every 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.
f. 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**.
g. ECOG performance status needs to be ≤ 3 for inclusion of the patient into the study. See **Appendix 4**.
h. 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.
i. Haematology parameters at Screening and at any further timepoints during the Study will include haemoglobin, RBC count, total and differential white blood cell (WBC) countand 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.
j. PK sample collection timelines are as follow: a) Baseline = just before the first dose of rituximab s.c.; b) Cycle 7 – Day 1 (before rituximab s.c. administration); c) Cycle 7 – Day 7 (± 3 days); d) Cycle 7 – Day 14 (± 3 days); Cycle 8 – Day 1 (before rituximab s.c. administration).

k. 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. After initiation of study drug, all AEs/SAEs, regardless of relationship to study drug, will be reported until study closure.

l. RASQ will be collected at the following timepoints: patient enrolment (please refer to note †), at the end of induction (Cycle 8). If the patient prematurely terminates the study the RASQ Questionnaire will be completed at the Early Termination/End of Treatment Visit.

11.2 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. ≥ 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. ≥ 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 7: Summary of Response Category

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	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver / spleen	≥ 50% decrease	≥ 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.

11.3 APPENDIX 4 GRADING SYSTEMS AND SCALES

11.3.1 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

Table 8: ECOG Status

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.

11.3.2 Follicular Lymphoma International Prognostic Index (FLIPI)

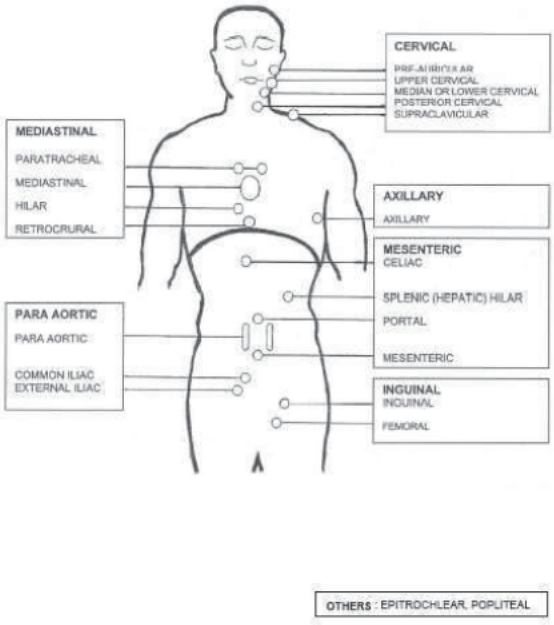

Figure 4 - Localization of the main lymphnodes

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

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. ≤ normal)

Three risk groups were defined:

e. LOW RISK (0-1 adverse factor)

f. INTERMEDIATE RISK (2 adverse factors)

g. POOR RISK (≥ 3 adverse factors)

11.4 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 − 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 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. 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 27 gauge injection needle 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.

11.5 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.

11.6 APPENDIX 7 ELISA ASSAY FOR SERUM DETERMINATION OF RITUXIMAB

This analysis is performed in the [redacted], Italy.
The protocol used (PT) and the operating instructions (IO) are kept in the local document n° 8 of [redacted], Italy.

Validation of ELISA assay for Rituximab quantification

A very sensitive enzyme-linked immunoassay (ELISA) was developed and validated [redacted] and used to measure Rituximab serum levels.

Validation Requirements
Our immunoassay was validated and the results obtained were checked according to the Guidance for Industry guidelines [U.S. Department of Health and Human Services-FDA-Center for Drug Evaluation on Research (CDER) Dec 1998].
The relevant parameters were: linearity of the standard calibration curve within the concentration range; limit of quantification; validation (precision and accuracy); application of the analytical method to the clinical sample (Pharmacokinetic Protocol).
The QCs prepared were evaluated for intra-assay precision and accuracy. Each concentration was assayed in 10 replicates for each plate. The QC samples for evaluation of inter-assay precision and accuracy were tested in six replicates in five assays performed on five different days. Precision is expressed as the coefficient of variation (%CV) for specific added target concentrations, and accuracy as percentage error (%error) of concentration observed compared with target added concentrations.
During analysis of unknown samples, a standard validation curve and one set of quality control samples were assayed during each run. All standards, quality controls, and unknown samples were run in duplicate. The results of the QC samples were the basis for accepting or rejecting the run. At least four of every six QC samples were expected to fall within 20% of their respective nominal value. Two of the six QC samples could acceptably fall outside 15% of their respective nominal value, but not at the same concentration.

ELISA Assay
Microtiter 96-well plates were sensitized by incubating 100 µL of goat anti-2B8 at the concentration of 1 µg/mL in *coating* buffer for 3 hours at 37°C, then overnight at +4°C.
Plates were washed three times with saline solution containing 0.01% Tween 20 and blocked using 200 µL of PBS at +37°C for 1 hour. Then, plates were washed three times with a washing buffer. 100 µL of standard solution, QCs and unknown samples were plated in duplicate. After 2 hours at +37°C followed by three washings, 100 µL of rabbit HRP-anti human IgG diluted 1/15000 in PBS plus 15% calf serum were added to each well.
After 2 hours at +37°C followed by three washings, 100 µL of peroxidase substrate were added to each well and the reaction was allowed to develop in the dark, at room temperature, for 15 minutes. The color reaction was stopped by adding 50 µL 3M H_2SO_4 per well. The plates were shaken for 30 seconds prior to reading at 492 nm. We used a ELISA plate reader (Sunrise-Tecan).

Rituximab concentrations in samples were determined by interpolation from a standard curve prepared diluting known amount of Rituximab into normal human serum. The standard curve ranged from 6.6 μg/mL to 3400 μg/mL and QCs were 100, 500 and 2000 μg/mL. Results were expressed as μg/mL. The method sensitivity was 2 μg/mL. This method is highly sensitive, rapid, accurate and precise, with all validation parameters within the acceptance criteria. During analysis of clinical samples, a standard curve plus at least one set of quality control samples were assayed at each run.

Reagent Preparation

The standard and the quality control sample (QCs) solutions were diluted in phosphate-buffered saline (PBS) containing 2% BSA.

Standard concentrations ranged from 6.6 μg/mL to 3400 μg/mL. Quality control concentrations for assay validation were 50 μg /mL (low), 500 μg /mL (medium) and 1000 μg /mL (high).

RESULTS

ELISA Assay Parameters

Linearity

The standard curve ranged from 6.6 μg/mL to 3400 μg/mL.

Figure 1 shows a mean representative exponential standard curve of Rituximab, with good correlation between the calibration curves and the mean absorbance.

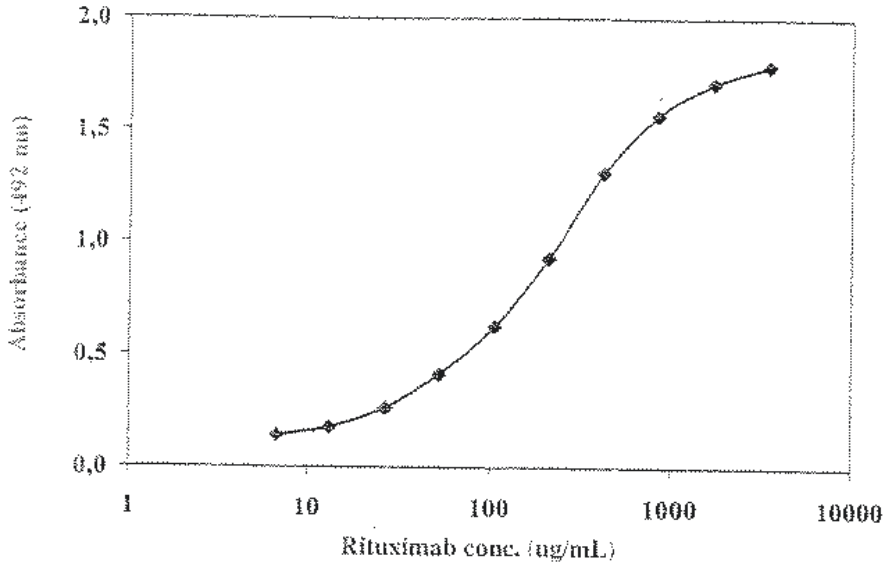

Figure 5 - representative exponential standard curve of Rituximab

Lower limit of quantification

In accordance with the *Guidance for Industry* guidelines, the limit of quantification of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. In our case, this value is 6.6 μg/mL.

Limit of Sensitivity

The limit of sensitivity was 2 µg/mL.

Assay precision and accuracy

The intra-day precision of the method observed on one occasion with 10 replicates per QC was 4.6%, 4.2% e 11.7% for low, medium and high quality control samples, respectively. The corresponding intra-day percentage of inaccuracy was 18.8%, -9.0 % and 0.5%, respectively.
The inter-day precision was 6.3%, 3.7% e 10.2%, for low, medium and high -10.5%, 0.1% for low, medium and high controls, respectively.
Precision and inaccuracy intra- and inter-day were reported in **Table 9**.

Table 9: Precision and Accuracy of QCs

	Mean (µg/mL)	*DS*	*Coefficient of Variation %*	Inaccuracy %
Intra-day				
QCL (50 µg/mL)	54.4	2.8	4.6	18.8
QCM (500 µg/mL)	455.0	19.4	4.2	-9.0
QCH (1000 µg/mL)	10050	117.2	11.7	0.5
Inter-day				
QCL (50 µg/mL)	60.0	3.8	6.3	19.9
QCM (500 µg/mL)	447.5	16.4	3.7	-10.5
QCH (1000 µg/mL)	1000.8	102.0	10.2	0.1

Specificity and Selectivity

We did not observe any false positive results in serum samples from healthy donors and pre-dose samples from patients.

Dilution Linearity

The percent inaccuracy of samples at concentrations of 500 µg/mL and 200 µg/mL ranged from -9.6% to 15.0% and from -18.8% to 20.0% respectively. The results in **Table 10** all fall within the acceptance criteria of ±20% of the nominal value. They show that clinical samples diluted by a high dilution factor could be quantified accurately and precisely.

Table 10: Method linearity test

	DF= 5000		*DF= 10000*		*DF= 15000*		*DF= 20000*	
	500 µg/mL	200 µg/mL	500 µg/mL	200 µg/mL	500 µg/mL	200 µg/mL	500 µg/mL	200 µg/mL
Mean	452.0	192.5	575	188.5	501.5	162.5	533.6	252.3
CV%	12.7	0.4	6.1	1.1	6.1	2.2	4.0	6.6
% inaccuracy	-9.6	-3.7	15.0	-5.7	0.3	-18.8	6.6	20.0

Stability

The Rituximab stock solutions stored at 4°C were stable for at least 26 weeks. Long-term storage stability of the samples has been tested for up to 28 weeks using two quality controls (500 μg/mL and 50 μg/mL). No significant change from the original analysis results was observed (ranged, -4.7% to -1.9%). Six freeze-thaw cycles did not affect the results of Rituximab determination compared to one cycle (range, -0.2% to 0.7%) control.

11.7 APPENDIX 8 RITUXIMAB ADMINISTRATION SATISFACTION QUESTIONNAIRE (RASQ)

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**.

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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

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

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 better than expected	Somewhat better than expected	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

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

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

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

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) Restrict 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 tick only 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

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18. Thinking about the Rituximab treatment, if given the option, which would you prefer (both options treat your disease in the same way)? Please tick 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 usually takes 5 to 7 minutes.
- No preference for treatment option.

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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

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