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

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STATISTICAL ANALYSIS PLAN

INTERMEDIATE ANALYSES

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
STUDY DRUG:	Rituximab (RO 45-2294)
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PLAN PREPARED BY:	[redacted]
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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 27JAN2017) for Protocol ML28881 (MABRELLA) - Version 4, 05 July 2016

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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1.0	27JAN2017	[redacted]	N/A – First Version

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LIST OF ABBREVIATION

Abbreviation	Definition
AAR	*Administration-Associated Reaction*
AE	*Adverse Event*
ALT (SGPT)	*Alanine Aminotransferase/Serum Glutamic Pyruvic Transaminase*
aPTT	*Activated Partial Thromboplastin Time*
AST (SGOT)	*Aspartate Aminotransferase/ Serum Glutamic Oxalacetic Transaminase*
AUC	*Area Under The Plasma Concentration-Time Curve*
BMI	*Body Mass Index*
BSA	*Body Surface Area*
BUN	*Blood Urea Nitrogen*
CHOP	Cyclophosphamide, Oncovine (Vincristine), Doxorubicin, *Prednisone/Prednisolone*
CHOP-21	*CHOP given Every 21 Days*
CHOP-14	*CHOP given Every 14 Days*
CI	*Confidence Interval*
CTMS	*Clinical Trial Management System*
CL/F	*Apparent Total Clearance of The Drug*
Cmax	*Maximum Plasma Concentration*
CR	*Complete Response*
Cru	*Complete Response Unconfirmed*
CTCAE	*Common Terminology Criteria for Adverse Events*
Ctrough	*Minimal Plasma Concentration*
CVP	*Cyclophosphamide, Vincristine, Prednisone/Prednisolone*
DFS	*Disease-Free Survival*
DLBCL	*Diffuse Large B-Cell Lymphoma*
ECG	*Electrocardiogram*
ECOG	*Eastern Cooperative Oncology Group*

EFS	*Event-Free Survival*
FL	*Follicular Lymphoma*
FLIPI	*Follicular Lymphoma International Prognostic Index*
HBV	*Hepatitis B Virus*
HCV	*Hepatitis C Virus*
HIV	*Human Immunodeficiency Virus*
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*
MedDRA	*Medical Dictionary for Regulatory Activities*
MRI	*Magnetic Resonance Imaging*
NCI	*National Cancer Institute*
NCI CTCAE	*National Cancer Institute Common Terminology Criteria for Adverse Events*
NHL	*Non-Hodgkin's Lymphoma*
OS	*Overall Survival*
PK	*Pharmacokinetic*
PT	*Preferred Term*
PP	*Per Protocol*
PFS	*Progression-Free Survival*
PRO	*Patient-Reported Outcome*
RASQ	*Rituximab Administration Satisfaction Questionnaire*

RBC	*Red Blood Cell Count*
R-CHOP	*Rituximab Plus CHOP Chemotherapy*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SAS	*Statistical Analysis System*
SC	*Subcutaneous(ly)*
SD	*Standard Deviation*
SOC	*System Organ Class*
TEAE	*Treatment-Emergent Adverse Event*
ULN	*Upper Limit Of Normal*
WHO	*World Health Organization*

1. BACKGROUND

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.

The efficacy and safety of rituximab intravenous (IV) is well established. Rituximab IV is administered as an infusion over 3 to 4 hours. Frequently observed Infusion-related reactions (IRR) 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 subcutaneous(ly) (SC) administration has been developed to address these limitations (i.e. infusion/injection-related reactions (IIRR), 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.

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.

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 pharmacokinetic (PK) parameters.

An intermediate analysis will be conducted once all patients completed the Final Staging Visit at the End of Induction period (follicular lymphoma (FL) patients) (or) at end of treatment period (diffuse large B-cell lymphoma (DLBCL) patients).

This document describes the statistical methods and reporting of the data for the study intermediate analyses. The data will comprise all the data collected from the approximate 160 diffuse large DLBCL or FL patients treated with rituximab. This Statistical Analysis Plan (SAP) should be read in conjunction with the protocol and the data transfer specifications.

This SAP includes all details for the analysis and reporting (tables, listings and graphs) of the entire set of core data collected.

2. STUDY DESIGN

This is a phase IIIb, multicentre, single arm Study in approximately 160 patients previously untreated with DLBCL or FL. Diagnosis of DLBCL or follicular Non-Hodgkin's Lymphoma (NHL) before treatment must have included histological diagnosis and initial CD20 expression confirmation.

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 (i.e. 4 additional months of treatment) in addition to standard chemotherapy or patients receiving Maintenance therapy must be able to receive at least 6 cycles of rituximab SC (i.e. 12 months of treatment).

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.

Figure 1 show the study design in DLBCL and FL patients. Appendix 1 shows the Schedule of assessments.

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). 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. 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.

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.

Figure 1– Study Design Scheme for FL patients

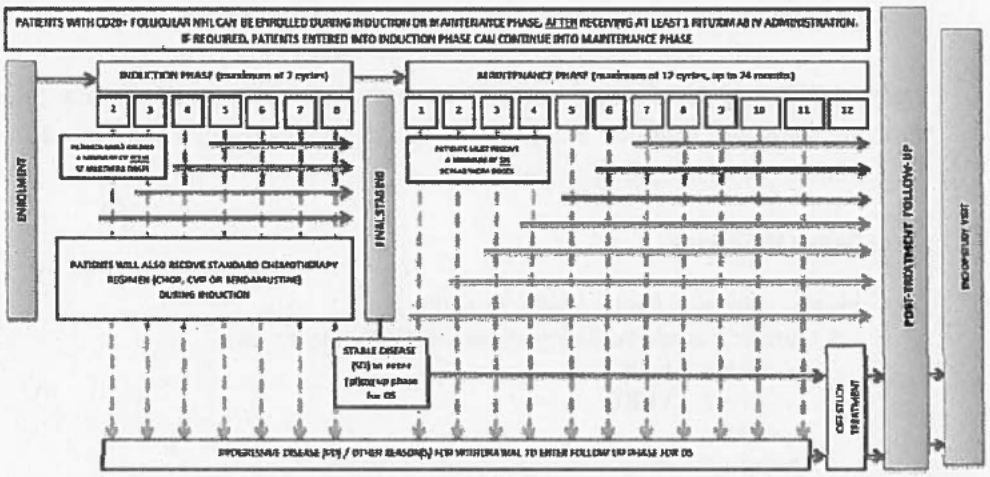
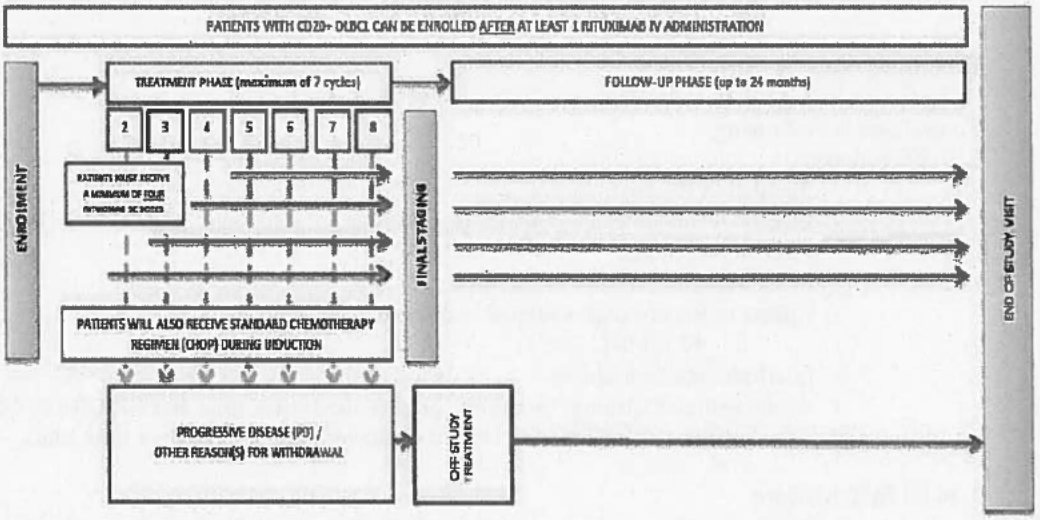


Figure 2– Study Design Scheme for DLBCL patients



2.1 STUDY OBJECTIVES

Primary objective

The primary objective for this Study is as follows:

To evaluate the proportion of administration-associated reaction (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 adverse events (AE) 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 Objectives

The secondary objectives for this Study are as follows:

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

To evaluate the following:

1. In FL patients:
   - Population PK parameter: C_{trough}
   - Effects of subject characteristics (age, gender, weight, body surface area (BSA) on the above mentioned
   - Rituximab population PK parameter
   - Effects of the covariates related to disease at baseline:
     - FLIPI 0-1/ 2/ $\geq$ 3;
   - Interindividual variability
   - 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)

2. In DLBCL patients:
   - Population PK parameters: Ctrough, AUC, Cmax 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 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)
- 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:

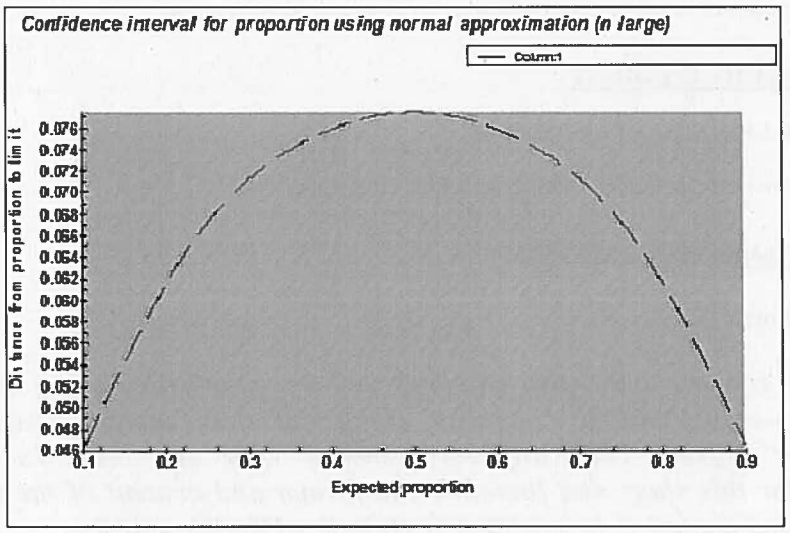
- Patient-assessed satisfaction using Rituximab Administration Satisfaction Questionnaire (RASQ)

2.2 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% confidence interval (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 CI 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).



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)
- Follicular lymphoma international prognostic index (FLIPI) (0-1/ 2 / ≥3)
- International prognostic index (IPI) (0-1/ 2 / 3/ > 3)

In addition it will be relevant to show differences between genders in the systemic exposition (Ctrough).

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.

2.3 ANALYSIS TIMING

An intermediate analysis (safety, PK, efficacy and Patient reported outcomes) will be conducted once all patients completed the Final Staging Visit at the End of Induction and Treatment period. Patients who all are discontinued before final staging assessment also will be included for the intermediate analysis.

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

Power calculations are not based on alpha adjustment for intermediate analysis.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Not Applicable. This is an open label, non-comparative single arm study.

4. STATISTICAL METHODS

General Methodology

In general, all efficacy and safety variables will be summarized using descriptive statistics. All analyses will be conducted using statistical analysis system (SAS) version 9.2 or higher. The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted] Biostatistics.

The following descriptive statistics will be presented in summary tables:

- ***Continuous variables: number (ie. non-missing), mean, 95% 2-sided***

confidence interval (CI), standard deviation (SD), median, minimum and maximum

- *Categorical variables: Summarized by treatment group using frequency tables (frequencies and percentages). Percentages are routinely based on the total category count excluding the missing category if not otherwise mentioned.*

In general, the number of decimal places displayed for each statistic will be determined as follows:

- *Mean and median: 1 more than the number of decimal places allotted in the raw data received from data management.*
- *SD: 2 more than the number of decimal places allotted in the raw data.*
- *Minimum and maximum: equal to the number of decimal places allotted in the raw data.*
- *CIs will be presented using the number of decimal places plus 1 as the parameters (e.g. mean) as appropriate.*
- *Percentages will be reported to 1 decimal place.*

Unless otherwise specified, baseline is defined as the last non-missing measurement taken on or prior to administration of study drug.

Unless otherwise specified, 2-sided CI will be assessed at the 5% significance level using Clopper Person methodology.

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.

4.1 ANALYSIS POPULATIONS

4.1.1 Full Analysis Set Population

All enrolled patients are included in the full analysis set population.

4.1.2 Intent-to-treat Population

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.

This will be the primary analysis population for efficacy parameters.

4.1.3 Per Protocol Population

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.

4.1.4 Pharmacokinetic-Evaluable Population

PK analysis population will include all recruited patients who receive the investigational treatment and have at least one PK sample collected and analyzed.

4.1.5 Safety Population

All enrolled patients who receive at least one dose of study medication will be included in the Safety Population.

This will be the primary analysis population for safety parameters.

5. ANALYSIS OF STUDY CONDUCT

Results, including demographic, patient characteristics, safety and efficacy will be presented overall and for induction (FL) and treatment (DLBCL) phases separately.

5.1 DISPOSITION AND WITHDRAWALS

The following will be summarized for Full Analysis Set Population:

- Number of patients enrolled
- Number and percentage in each analysis population
- Number and percentage completing final staging-induction phase
- Number and percentage completing final staging-treatment phase
- Number and percentage who continued to maintenance phase.
- Number and percentage who prematurely discontinue treatment phase
- Number and percentage who prematurely discontinue induction phase
- Reasons for discontinuation of treatment phase
- Reasons for discontinuation of induction phase

The number and percentage of screen failures overall and by reason for failure will be presented. Study Centre wise enrolled subjects will be summarized.

5.2 PROTOCOL DEVIATIONS

All protocol deviations reported in the study will be reviewed and evaluated by study team with documentation before intermediate analysis data freeze, if any major protocol deviations have an impact on efficacy endpoints. All individual protocol deviations will be presented in a data listing. The number and percentage of subjects with major or minor protocol deviations will be summarized by deviation category on ITT population.

5.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All baseline and demographic characteristics will be summarized for both the safety and ITT populations. Included will be:

- Age
- Age category (>=18 and <=64 , >64 and <=80)
- Sex
- Ethnicity (where applicable)
- Height
- Weight
- Body mass index (BMI)
- Body surface area
- Female reproductive status
- International prognostic index (IPI) (0 bulky-1/ 2 / 3/ 4) and follicular lymphoma International prognostic index (FLIPI Score) (0-1/ 2 / ≥3)
- Cancer history
- ECOG performance status (Grade 0 to Grade 5)
- FL and DLBCL Diagnosis details of lymph node biopsy ,CD20+ expression and Grade of FL

Medical history will be coded using MedDRA version 19.1 and summarized by system organ class and preferred term. Physical Examinations details for each body system will be summarized across each visit.

5.4 SAFETY ANALYSES

All safety variables will be presented for the safety population.

All AEs and laboratory variables will be assessed according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) version 4.0 grading system.

5.4.1 Adverse Events

Incidence of AEs will be presented for the entire induction or treatment period study duration.

Only post study start AEs (AEs occurring on the day of or after the first administration of study drug and up to 28 days after the last dose) will be included in the main summary tables and it is defined as treatment-emergent adverse event (TEAE). Where an AE start date is partially or fully missing, and it is unclear as to whether the AE started after the start of the study, it will be assumed to be on-study.

For summaries for specific periods of time (e.g. Induction therapy only), an AE will be assigned to a specific subgroup if it occurred on or after the first dose of study medication within that subgroup and prior to the first (subsequent) date of a treatment within another subgroup. If there is no subsequent treatment by another route then a 28 day cut off will be applied. Where an AE start date is partially or fully missing, and it is unclear to which subgroup the AE should be assigned, the AE will be assigned to all relevant subgroups.

Proportion of each TEAE will be summarized by the primary system-organ class and by preferred term with 95% confidence interval (using Clopper Person methodology) and will be listed for the following:

- TEAEs
- Treatment-Emergent SAEs
- AARs

- Grade >=3+ TEAEs
- Grade >=3+ Treatment-Emergent SAEs
- Grade >=3+ AARs
- TEAEs leading to rituximab dose modification
- TEAEs leading to rituximab dose discontinuation
- TEAEs leading to chemotherapy dose modification
- TEAEs leading to chemotherapy dose discontinuation
- TEAEs leading to death

The following groups of adverse events will be summarized:

- all TEAEs
- all Treatment-Emergent SAEs
- all AESI
- all AARs
- all IRRs
- grade 3+ TEAEs
- grade 3+ Treatment-Emergent SAEs
- grade 3+ AESI
- grade 3+ AARs
- grade 3+ IIRRs
- TEAEs within the MedDRA SMQ `Anaphylactic reactions' (wide)
- TEAEs leading to dose modification of rituximab
- TEAEs leading to discontinuation of rituximab
- TEAEs leading to dose modification of chemotherapy

- TEAEs leading to discontinuation of chemotherapy
- TEAEs leading to death
- Cutaneous and soft tissue AARs (Localized)
- Cutaneous and soft tissue AARs (Non-Localized)

These groups will be summarized using the following tables by system organ class and preferred term:

- overall
- events related to rituximab
- events related to chemotherapy
- by most extreme intensity
- with an incidence of >5%

A patient with more than one occurrence of the same adverse event in a particular system organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term.

Where AEs are summarized by relationship or by maximum CTC grade, each patient's maximum CTC grade will be used in the summary. If a patient experiences the same adverse event at more than one CTC grade level, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence.

Any missing CTC grade, causality, or outcome will not be imputed but classed as unknown for listing purpose and worst case will be considered for summarization purpose.

'Related' refers to those events where there is a reasonable suspected causal relationship to the study drug, or with an unknown relationship.

Adverse events will be coded using MedDRA version 19.1 and all other information collected will be listed as appropriate.

Deaths

A summary of deaths will be presented, tabulating the number and percentage of patients by primary cause of death and relationship to study drug.

5.4.2 Exposure of Study Medication

Exposure will be summarized as set out in the following sections using the safety population.

Extent of Exposure to rituximab SC

Exposure to rituximab SC will be summarized overall and also within each of the subgroups listed in section 5.

The total number of cycles received will be summarized both by descriptive statistics and frequency counts. Duration of treatment exposure and dose will be summarized by descriptive statistics. These will be presented overall and for induction, and treatment phases separately.

Study drug administration details will be summarized by cycle and overall and will include:

- percentage of full doses
- percentage of non-full doses
- duration of injection
- dose injected
- percentage of injections delayed (by reason).

Extent of Exposure to Chemotherapy

The total number of chemotherapy cycles received will be summarized both by descriptive statistics and frequency counts. These will be presented overall and for induction and treatment phases separately. They will also be separated by type of chemotherapy administered.

Extent of Exposure to New Anti-Lymphoma Treatment

New anti-lymphoma treatment (chemotherapy, radiotherapy, immunotherapy), initiated after the Baseline visit will be presented in summary tables.

The total number of new anti-lymphoma cycles received will be summarized both by descriptive statistics and frequency counts. These will be presented overall and for induction and treatment phases separately. They will also be separated by type of therapy administered.

5.4.3 Previous and Concomitant Treatments

Summaries of prior and concomitant medications will be presented for the safety population and coded using GThes (Global Thesaurus). Prior medications are those that stopped before exposure to study drug; concomitant medications are those taken during the study, including those started before but ongoing at first dose of study drug.

The incidence of prior medications and of concomitant medications will be presented by class system and preferred drug name. All medications other than study drug (rituximab SC) will be summarized in this fashion.

Further summaries of new anti-lymphoma treatment (chemotherapy, radiotherapy, immunotherapy), initiated after the baseline visit are defined in the exposure section.

Where medication start or end dates are partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant. If it is unclear which subgroup to which it should be assigned, the medication will be assigned to both relevant subgroups.

5.4.4 Laboratory Data

Results from the following laboratory parameters will be summarized using descriptive statistics over time for the safety population:

Haematology:

Haemoglobin, red blood cell count (RBC) count, total and differential white blood cell (WBC) count and platelet count.

Biochemistry:

Sodium, potassium, alanine aminotransferase (ALT)/SGPT, aspartate aminotransferase (AST)/SGOT, total bilirubin, and serum creatinine.

Note that the following parameters are measured at the screening visit only and will therefore be listed only: Alkaline phosphatase, albumin, blood urea nitrogen (BUN), C-reactive protein and lactate dehydrogenase (LDH).

Coagulation:

International normalized ratio (INR), activated partial thromboplastin time (aPTT) and prothrombin time (PT).

Changes in haematology, biochemistry and coagulation laboratory values from baseline to each visit will be summarized descriptively.

Shift tables for the haematology and biochemistry laboratory parameters comparing baseline versus worst post-baseline grade during treatment period will be presented.

Notes:

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. All results outside predefined normal ranges will be flagged in the data listings.

Only the most recent set of laboratory results within a cycle (including unscheduled visits) will be used in the summary tables.

5.4.5 Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure, and body temperature) will be summarized over time (including change from baseline) using descriptive statistics for the safety population.

Weight will also be summarized by cycle separately.

Only the latest set of vital sign results within a cycle (including unscheduled visits) will be used in the summary tables.

5.4.6 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (Grade 0 - Grade 5) will be summarized by visit (screening and final staging) by presenting the number and percentage of patients in each category for the safety population. Percentage of patients in different categories will be presented by bar charts at different time points. Only the latest set of results within a cycle (including unscheduled visits) was used for the summary.

5.4.7 Other Safety Measurements

Infection and electrocardiogram (ECG) test results at screening, Pregnancy test results throughout the study, and Physical examination abnormal results at each visit will be listed only.

5.5 EFFICACY ANALYSIS

The Secondary objective also include evaluating efficacy of rituximab SC in terms of EFS, PFS, Cr/CRu and OS and will be analysed for the ITT and for the Per protocol populations. DFS will be analyzed for final analysis.

Event-free Survival (EFS)

EFS is defined as time from first dose to the date of first documented disease progression, or relapse according to the IWG response criteria (see, Protocol Appendix 3) or initiation of non-protocol-specified anti-lymphoma therapy or death from any cause (whichever occurs first). Patients who have neither progressed or relapse, received non-protocol specified anti-lymphoma therapy nor died will be censored on the date of their last visit. Time will be calculated in months as follows:

EFS = (date of event/censor – date of first dose + 1) / 30.4375

Kaplan-Meier (KM) estimates of the median time to event and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

A life-table presenting the number and percentage of patients in each category (progression or relapse, non-protocol -specified anti-lymphoma therapy and death) and the number at risk in 3-monthly time periods will also be presented

Progression-Free Survival (PFS)

PFS is defined as time from first dose to the date of first documented disease progression or relapse, according to the international working group (IWG) response criteria (see, Protocol Appendix 3) or other country standards, or death from any cause (whichever occurs first). Patients who have neither progressed or relapsed nor died will be censored on the date of their last tumour assessment where non progression was documented or last date of follow-up for progression of disease, whichever occurs last. Patients without post baseline tumour assessments who are known to be alive will be censored at the time of first dose. Time will be calculated in months as follows:

PFS = (date of event/censor – date of first dose + 1) / 30.4375

Kaplan-Meier (KM) estimates of the median time to event and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

A life-table presenting the number and percentage of patients in each category (progression or relapse and death) and the number at risk in 3-monthly time periods will also be presented.

CR/CRu

CR/CRu is complete response or complete response unconfirmed and is measured 4 weeks after the end of Induction treatment. It will summarized and presented with the corresponding 95% two-sided Clopper Pearson CI by subgroup of diagnosis and overall.

Overall Survival (OS)

OS is defined as time from first dose to death from any cause. Patients who have not died will be censored on the date they were last known to be alive. Time will be calculated in months as follows:

OS = (date of event/censor – date of first dose + 1) / 30.4375

[where 30.4375 = average number of days per month = 365.25/12]

Kaplan-Meier (KM) estimates of the median time to event and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

A life-table of the number and percentage of patients who died and those at risk in 3-monthly time periods will also be presented.

5.6 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, Geometric mean, standard deviation, Geometric standard deviation, Geometirc CV%, 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.

A repeated measures linear mixed model will be fit to Ctrough on the natural log scale with cycle day as a fixed-repeated effect and subject characteristics (age, weight, body surface area) as fixed effect. From these analyses, LS means, and 90% CI for the LS means on log-scale will be obtained. The results will be transformed back to the original scale by exponentiation to provide treatment geometric LS means and 90% CI.

Interindividual variability results will also be calculated.

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 student's T test or Mann-Whitney U test, based on the normality of data.

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.

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.

A repeated measures linear mixed model will be fit to PK parameters (Ctrough , AUC, Cmax and CL/F) on the natural log scale with cycle day as a fixed-repeated effect and subject characteristics (age, weight, body surface area) as fixed effect. From these analyses, LS means, and 90% CI for the LS means on log-scale will be obtained. The results will be transformed back to the original scale by exponentiation to provide treatment geometric LS means and 90% CI.

Interindividual variability results will also be calculated.

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

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.

5.7 PATIENT-REPORTED OUTCOME ANALYSES

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

PRO data will be summarized by count and percentage and presented by subgroup of diagnosis (DLBCL, Induction) and overall.

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

5.8 MISSING DATA

Missing, unused and spurious data will be dealt with as such. There is no intention to implement any procedure for replacing missing data.

6. CHANGES FROM ANALYSES PLANNED IN THE PROTOCOL

There are no changes in planned statistical analysis from protocol.

7. APPENDIX

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	1-6	6-12	12-18	18-24	End of Study 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) (2)					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

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*	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	
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																									
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
PK samples [j]	X								X													X						
RASQ [l]				(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	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

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*	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	
[k]																												
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

†. 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-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].

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

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	Early Termination/End of Treatment	Post-Treatment Follow-Up				
Timing / Assessments	D -28 to D -1	1*	2	3	4	5	6	7	8			1-6	6-12	12-18	18-24	/End of Study 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)										Post-Treatment Follow-Up				
Timing / Assessments	D -28 to D -1	1*	2	3	4	5	6	7	8	Final Staging	Early Termination/End of Treatment	1-6	6-12	12-18	18-24	/End of Study 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 Protocol 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-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].
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 Protocol **Appendix 4**.
g. ECOG performance status needs to be ≤ 3 for inclusion of the patient into the study. See Protocol **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