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

NCT Number: NCT01987505

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Statistical Analysis Plan: 11-Sep-2017

MABRELLA Study

"A Study to Evaluate the Safety of Switching From Intravenous to Subcutaneous Administration of Mabthera/Rituxan During First-Line Treatment for Lymphoma"

Statistical Analysis Plan for an Interim Analysis
(one year after end of recruitment)
Code ML 28943
22/Jan/2016

Sponsor:	**Roche**
Prepared by:	███████████
Date:	January 2016

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MABRELLA Study

GLOSARY

AE	Adverse Event
SAE	Serious Adverse Event
CRF	Case Report Form
ST	Standard deviation
ECOG	Eastern Cooperative Oncology Group
SD	Stable Disease
PK	Pharmacokinetics
FNA	Fine Needle Aspiration
CI	Confidence Interval
BMI	Body Mass Index
IV	Intravenous
DLBCL	CD20+ diffuse large B-cell lymphoma
FL	CD20+ non-Hodgkin's follicular lymphoma
Max	Maximum
Min	Minimum
N	Sample size
NE	Nonevaluable
DP	Disease progression
Q1	First quartile
Q3	Third quartile
AARs	Administration-Associated Reactions
CR	Complete response
CRu	Unconfirmed complete response
PR	Partial response
IRAE	Infusion/injection-related adverse event
SC	Subcutaneous
OS	Overall survival
DFS	Disease-free survival
EFS	Event-free survival
PFS	Progression-free survival
CT	Computed tomography

1 INTRODUCTION

This open-label, single-arm, phase IIIb study will evaluate the safety of switching from intravenous (IV) to subcutaneous (SC) administration of MabThera/Rituxan during first-line treatment for patients with CD20+ non-Hodgkin's follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL) who have already received at least one full dose of MabThera/Rituxan IV.
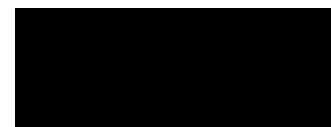
This trial included adult patients with CD20+ DLBCL or CD20+ FL (grades 1, 2 or 3a; LNH), who had already received at least one complete dose of rituximab IV during induction or maintenance.

Given the expected change in the profile of AARs after switching to rituximab SC (Davies et al. 2012), the primary objective of interest will be the incidence of AARs.

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

Modelling and simulation of PK data from stage 1 and the initial results from stage 2 of trial BP22333 (NCT00930514) (Salar et al. 2010; Salar et al. 2012) indicated that the fixed dose of 1400 mg of SC rituximab achieves noninferior trough levels to the IV dose of rituximab 375 mg/m2 in previously treated or untreated patients with FL (grade 1, 2 or 3a). SC rituximab was well tolerated, with an AE profile comparable to IV rituximab. No SAE related to SC rituximab was reported. Therefore, the fixed dose of 1400 mg SC was chosen for all other clinical trials of SC rituximab, both in this trial and in the ongoing registration trials.

The objective of this clinical trial is to evaluate the safety of switching from IV to SC administration of rituximab at any time during standard rituximab-regimens. Since this change may occur in the case of patients undergoing either induction or maintenance treatment, the study population included patients CD20+ FL or CD20+ diffuse large B-cell lymphoma (DLBCL) who had previously received at least 1 dose of IV rituximab as part of an induction or maintenance treatment, and who were candidates for at least 4 more cycles of SC rituximab (for those following an induction treatment) or 6 more admininstrations of SC rituximab (for those following a maintenance treatment).

2 STUDY OBJECTIVES AND DESIGN

2.1 Aim of Statistical Analysis Plan

This document presents the proposed analysis plan for performing the interim statistical analysis of the MABRELLA study.

The analysis plan proposed below describes the aspects that should be known about the study and the methods of statistical analysis that will be applied to the data collected in order to answer the objective of the interim analysis.

2.2 Interim Analysis of Primary Outcome

The aim of this interim analysis is to evaluate patient safety up to one year after the end of recruitment.

2.3 Study Design

Clinical trial, phase III, open-label, non-randomized, single group assignment.

2.4 Study Population

The target population will consist of adults with CD20+ DLBCL or CD20+ FL grade 1, 2 or 3a according to the World Health Organization (WHO) classification system.

It is planned that 139 patients will participate in the study.

2.5 Inclusion Criteria

Study participants must meet ALL of the following criteria in order to be included in the study:

Criteria related to the subject

1. Written informed consent

2. Age >/= 18 and </= 80 years at time of enrolment.

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3

Criteria related to disease

4. Histologically confirmed CD20+ DLBCL or CD20+ follicular NHL (FL) grade 1, 2 or 3a according to the WHO classification system.

5. Induction only:

    a. LBDCG related criteria: An International Prognostic Index (IPI) score of 1-4 or IPI score of 0 with bulky disease, defined as one lesion >/= 7.5 cm (Appendix 4 of protocol).

b. FL treatment-related criteria: Follicular Lymphoma International Prognostic Index (FLIPI) (low, intermediate, high risk). Patients with FL should meet Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria to initiate treatment. (Appendix 4 of protocol).

6. Induction only: At least tumor >/= 1.5 cm as measured by computed tomography (CT) scan

Treatment-related criteria

7. Currently being treated with MabThera/Rituxan IV during first-line therapy and has received at least one full dose of MabThera/Rituxan IV (defined as standard full dose of MabThera/Rituxan IV 375 mg/m2 administered without interruption or early discontinuation (i.e. tolerability issues)

8. Expectation and current ability for the patient to receive at least four additional cycles of treatment during the Induction phase or six additional cycles of treatment during the Maintenance phase (patients with follicular NHL)

2.6 Exclusion criteria

Participants who meet any of these criteria will not be included in the study:
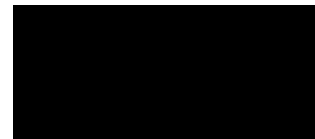
Criteria related to medical history

1. Transformed lymphoma or follicular lymphoma (FL) IIIB

2. Primary central nervous system lymphoma, primary effusion lymphoma, primary mediastinal DLBCL, DLBCL of the testis, primary cutaneous DLBCL or histologic evidence of transformation to a Burkitt lymphoma.

3. History of other malignancy that could affect compliance with the protocol or interpretation of the results; this includes a malignancy that has been treated but not with curative intent, unless the malignancy has been in remission for >/= 5 years prior to treatment administration; 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.

Previous and concomitant treatment

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

Analytical evaluation during screening

5. Impaired renal function defined as creatinine > 1.5 x Upper Limit of Normal, ULN (unless creatinine clearance [CrCl] normal), or calculated CrCl < 40 mL/min (as determined by the Cockcroft–Gault formula)

6.   Inadequate   hematologic   function,   defined   as   follows:

 - Hemoglobin < 9 g/dL

- Absolute neutrophil count < 1.5 x 109/L

- Platelet count < 75 x 109/L (Note: abnormalities outside the above listed are allowed if related to involvement of bone marrow by the underlying disease).

7. Inadequate hepatic function, defined as any of the following abnormal laboratory values:
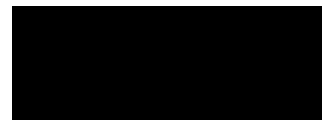
    • Alanine aminotransferase (AST) or aspartate aminotransferase (ALT) > 2.5 x the ULN

    • Total bilirubin ≥ 1.5 x the ULN. (Patients with documented Gilbert disease may be enrolled if total bilirubin is ≤ 3.0 x the ULN.)

Other prior or current medical conditions and 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 anthracycline treatment. For patients with FL: contraindication to standard chemotherapy.

10. Other serious underlying medical conditions (i.e., severe 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 infections (excluding nail fungal infections) or any infection requiring treatment with IV antibiotics or hospitalization within 4 weeks prior to dosing.

13. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Note: Patients testing positive for hepatitis B or C virus antibodies but with an undetectable viral load may be included (i.e., HBV or HCV RNA-negative by PCR).

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

General criteria

15. Any coexisting medical or psychological condition that would preclude participation in the required study procedures

16. Life expectancy < 6 months

17. A positive pregnancy test for women of childbearing potential within 7 days prior to first rituximab administration or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the first administration. 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 subcutaneous rituximab.

3   STATISTICAL METHODS

The methods of analysis to be used to achieve both the objectives of the interim analysis of the study and for description of the study variables are detailed below.

All analyses described will be performed by type of lymphoma (DLBCL / FL) and overall.

Selection criteria will not be checked unless it is expressly requested.

❖ **UNIVARIATE ANALYSIS**

Quantitative variables will be described with measures of central tendency and dispersion: mean, median, SD (standard deviation), Q1 (first quartile) and Q3 (third quartile), minimum and maximum).

Qualitative variables will be described using absolute and relative frequencies. Two columns of percentages will be presented: Total percentage (%) and Percentage valid (% valid).

- Total percentage (%): Percentage over the sum of valid responses plus missing values, that is, over the total study sample.

- Percentage valid (% valid): Percentage over total valid responses, that is, with data in the variable.

Ninety-five percent Clopper-Pearson confidence intervals (CI) were calculated, when necessary, for outcome variables associated with objectives.

In the case of questions with more than one response option, **multiple response** tables will be shown. Two columns of percentages will be shown in these tables:

- Total percentage (%): Percentage over the sum of valid responses plus missing values, that is, over the total study sample. As it is multiple response, the sum of the percentages does not necessarily equal 100 (this percentage may be exceeded).

- Percentage valid (% valid): Percentage over the number of patients with at least one response given from among those possible. As it is multiple response, the sum of the percentages does not necessarily equal 100 (this percentage may be exceeded).

❖ **BIVARIATE ANALYSIS**

In the comparative analysis, parametric tests will be used for those variables that meet the conditions for application (e.g. t-test) and nonparametric tests (e.g. chi-squared, Mann-Whitney U, Wilcoxon, etc.) for ordinal, categorical or other variables that do not meet parametric criteria.

All hypothesis tests will be two-sided and with a significance level of 0.05.

Data will be analyzed using SPSS v22.0.

3.1 Close-out Database Agreement

Following database close-out to perform the analyses, if any anomalous and/or inconsistent values are found in any table of results, the database will not reopened to modify the values, but instead the anomalous data value will be highlighted and it will be indicated how it was handled (e.g., assigning to missing values or eliminating the case depending on the statistical method to be used in the analysis in question). Missing data will not be imputed and will be left as lost.

Any modification to this table will be recorded in writing in the report as well as the procedure followed (e.g. assignment to missing values, interpolation, elimination of the case, etc.).

4 ANALYSIS POPULATIONS

The population that will be included in the analysis is defined below:

- ***The safety population*** will consist of all patients who have received at least one dose of the study medication.

This analysis is planned per protocol one year after the last visit of the last patient enrolled, that is, one year after the end of patient recruitment.

Both descriptive analyses and safety analyses will be based on the safety population.
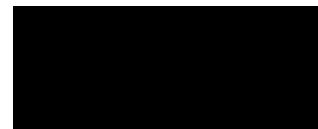
5 DESCRIPTIVE ANALYSIS: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

5.1 Recruitment Period

The dates of inclusion the first and last patient will be provided.

5.2 Lymphoma Diagnosis

- Type of Lymphoma: Diffuse Large B-cell / DLBCL / FL

5.3 Demographic and anthropometric data

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be shown for the following variables:

- Age (years), based on (Date of Visit – Date of Birth).
- Weight
- Height
- BMI

Categorical variables to be described:

- Sex: Male / Female
- Race: Caucasian / Black/ Asian / Other

5.4 Medical History

5.4.1 DLBCL Diagnosis

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following continuous variables:

- Time from diagnosis, defined as the time in months from the date of diagnosis (date of histological diagnosis) to the date of the baseline visit.

Categorical variables to be described:

- Histological diagnosis: FNA / Core needle biopsy /Excisional or Incisional biopsy of peripheral lymph node.

5.4.2 Follicular Lymphoma Diagnosis

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following variables:

- Time from diagnosis, defined as the time in months from the date of diagnosis (date of histological diagnosis) to the date of the baseline visit.

Categorical variables to be described:

- Histological diagnosis: FNA / Core needle biopsy /Excisional or Incisional biopsy of peripheral lymph node.
- Grade of FL: 1 / 2 / 3a

5.5 Physical Examination

Related to baseline visit, the following will be described:

- Was the physical examination performed?: Yes / No

For patients with a physical examination performed, a multiple response table will be shown for those affected systems with the result: Abnormal, clinically significant:

- Head, ears, eyes, nose, throat
- Cardiovascular system
- Dermatological
- Musculoskeletal system
- Respiratory system
- Gastrointestinal system
- Genitourinary system Nervous system
- Other

5.6 ECOG Performance Status

Categorical variable to be described:

- ECOG: 0/ 1 / 2 / 3 / 4 / 5

The ECOG score will be described for each of the visits performed, i.e., at screening and induction and/or maintenance.

5.7 IPI Score

For DLBCL patients: Related to baseline visit, the following will be described: Low risk / Low intermediate risk / High intermediate risk / High risk.

5.8 FLIPI Score

For FL patients: Related to baseline visit, FLIPI score will be described: Low risk / intermediate risk / High risk.
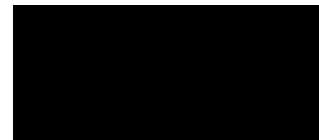
6   EVALUATION OF PATIENT OUTCOME QUESTIONNAIRE

The Rituximab IV Administration Satisfaction Questionnaire (RASQ-IV) will be analyzed on the baseline visit before switching to SC rituximab treatment and the Rituximab IV Administration Satisfaction Questionnaire" (RASQ-SC) at the end of induction or maintenance treatment (when applicable).

The descriptive analysis (N,%) will be shown for each of the items included in the questionnaire.

The protocol does not include a validation or version of these questionnaires, nor is there an algorithm on a possible overall score or by dimensions. If this is provided by the sponsor, the corresponding descriptive analysis can be performed. It will also be taken into account if there are sufficient data to perform the analysis.

7   PREVIOUS TREATMENT

7.1   Chemotherapy

The variable 'type of chemotherapy regimen' that the patient is receiving will be described: CHOP-14 x 6 / CHOP-14 x 8 / CHOP-21 x 6/ CHOP-21 x 8 / CVP-21 x 8 / Other.
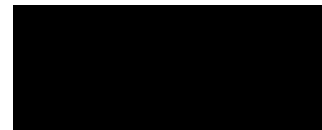
7.2   Previous IV Rituximab Dose: FL

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following continuous variables:

- Time from diagnosis (months), calculated from the date of histological diagnosis to the date of first dose of IV rituximab).
- Dose of most recent IV rituximab cycle

Categorical variables to be described:

- Phase of IV rituximab (most recent IV cycle): Induction Phase / Maintenance Phase
- Cycles of IV rituximab that the subject had received previously: 1/ 2 / 3 / 4 / 5 / 6 / 7 / 8
- Treatment phase in which the patient switched from IV rituximab to the SC formulation: Induction Phase / Maintenance Phase
- First SC treatment cycle on study: Cycle 1 / Cycle 2 / Cycle 3 / Cycle 4 / Cycle 5 / Cycle 6 / Cycle 7

7.3   Previous IV Rituximab Dose: DLBCL

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following continuous variables:

- Time from diagnosis (months), calculated from the date of histological diagnosis to the date of first dose of IV rituximab).

Categorical variables to be described:

- Cycles of IV rituximab that the subject had received previously: 1/ 2 / 3 / 4
- Dose of most recent IV rituximab cycle
- First SC treatment cycle on study: Cycle 2 / Cycle 3 / Cycle 4 / Cycle 5

8   CURRENT TREATMENT

8.1   Study Drug Administration

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following continuous variables:

- For FL patients: Number of induction and/or maintenance cycle administered per patient.
- For DLBCL patients: Number of treatment cycle administered per patient.
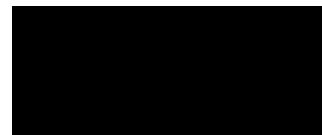
Categorical variables to be described:

- Full dose: Yes / No If No:
    - Reason: Adverse event / Technical problems / Other
        - (If other: specify).
        - If the reason is an AE, specify if it is a grade 3 or 4 IRAE: Yes / No

8.2   Study Drug Discontinuation

Categorical variables to describe are:

- Number of patients who discontinued study treatment.
- Primary reason for patient discontinued treatment: Progression of Disease / Adverse Event / Pregnancy / Patient request - Withdraw consent / Investigator decision / Lack of compliance / Lost to Follow-up / Death / Other

9 FOLLOW-UP PERIOD

The variable 'time in study', defined as the time in months from inclusion to the last available date, will be provided. Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented.

10 DEATHS

Categorical variables to be described:

- The number of patients who died during the study.
- Primary cause of death: Progression of disease / Adverse Event / Unknown / Other.

11 SAFETY

All analyses described will be performed by type of lymphoma (DLBCL / FL) and overall.

11.1 Adverse Events

This analysis will include all adverse events occurring to patients during the study. To obtain the number of adverse events per patient, <u>the maximum of most extreme intensity (maximum intensity grade for each toxicity) will be calculate</u>d for each of the adverse events recorded during the treatment of each patient and the following will be described:
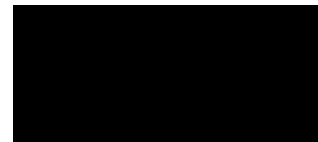
- Number of patients with at least one adverse event (95% CI).
- Number of patients with different adverse events reported by grade (GI, GII, GIII, GIV, GV). A list of the different AEs experienced by patients according to the maximum grade, N and % will be presented.
- Number of patients with at least one adverse event of grade 3 or higher (95% CI).

11.2 Serious Adverse Events

The number of patients with at least one **Serious Adverse Event (95% CI)** will be described, as well as a list of the different events experienced by patients and the main characteristics of the events: causal relationship with chemotherapy or rituximab, duration (start and end date), action taken, treatment required (yes/no), outcome.

11.1 Adverse Event of Special Interest

The number of patients with at least one **Adverse Event of Special Interest (95% CI)** will be described, as well as a list of the different events experienced by patients and the main characteristics of the events: causal relationship with chemotherapy or rituximab, duration (start and end date), action taken, treatment required (yes/no), outcome.

11.2 Adverse Events related to SC Rituximab

In this section, the AEs indicating a relationship to the study treatment (SC rituximab) will be considered.

This analysis will include all adverse events occurring to patients during the study. To obtain the number of adverse events per patient, <u>the maximum of most extreme intensity will be calculated</u> for each of the adverse events recorded during the treatment of each patient and the following will be described:

- Number of patients with at least one AE. The proportion of patients experiencing at least one AE will be provided, and the Clopper-Pearson 95% confidence interval.
- Number of patients with different AEs reported by grade (GI, GII, GIII, GIV, GV). List of the different AEs experienced by patients according to grade, N and %.
- Number of patients with at least one AE ≥ grade 3 (95% CI).
- Number of patients (%) with one fatal AE (leading to death): N, % (CI 95%).

11.3 Administration-Associated Reactions (AARs) for SC Rituximab

AAR: All events where the answer to "If this is an AAR related to the Rituximab SC injection, please specify location" is not "Not applicable"

- Number (%) of patients with at least one AAR (include injection site reactions, administration site conditions and symptoms of these conditions).
- Number of patients with different AARs reported by grade (GI, GII, GIII, GIV, GV). List of the different AARs experienced by patients according to , N and %.
- Number (%) of patients with at least one AAR ≥ grade 3
- Number (%) of patients with at least one serious AARs
- Number (%) of patients with at least one AAR localized at the injection site reaction and generalized and/or remote from the injection site.
- AAR localized at the injection site and generalized and/or remote.

11.4 Action taken related to study treatment Rituximab

The action taken related to the study treatment with rituximab will be described (for all AEs): None / Drug interrupted / Drug delayed / Drug permanently discontinued / Not Applicable.

The number (%) of patients with AEs leading to treatment interruption, dose delay and discontinuation will be described:

- AEs leading to treatment interruption
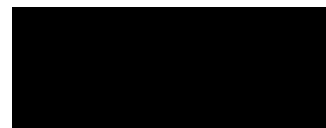
- AEs leading to dose delay

- AEs leading to discontinuation

11.5 Outcome

The outcome (for every AE) will be described: Fatal / Resolved / Resolved – with sequelae / Unresolved - Improving / Unresolved – Persisting / Unresolved – Worsening / Unknown.

The number (%) of AEs leading to patient death will be described:

- AEs leading to death

MABRELLA Study

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

Statistical Analysis Plan for Final Analysis
Code ML 28943
11/September/2017

Prepared by:
Date: 11/09/2017
Signature:

Approved by: Roche
Date:
Signature:

TABLE OF CONTENTS

GLOSSARY

AARs	Administration-Associated Reactions
AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CR	Complete response
CRF	Case Report Form
CRu	Unconfirmed complete response
CT	Computed tomography
DFS	Disease-free survival
DLBCL	CD20+ diffuse large B-cell lymphoma
DP	Disease progression
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
FL	CD20+ non-Hodgkin's follicular lymphoma
FNA	Fine Needle Aspiration
IRAE	Infusion/injection-related adverse event
IV	Intravenous
Max	Maximum
Min	Minimum
N	Sample size
NE	Nonevaluable
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
ST	Standard deviation

1 INTRODUCTION

This open-label, single-arm, phase IIIb study will evaluate the safety of switching from intravenous (IV) to subcutaneous (SC) administration of MabThera/Rituxan during first-line treatment for patients with CD20+ non-Hodgkin's follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL) who have already received at least one full dose of MabThera/Rituxan IV.
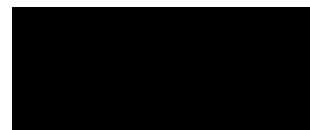
This trial included adult patients with CD20+ DLBCL or CD20+ FL (grades 1, 2 or 3a; LNH), who had already received at least one complete dose of rituximab IV during induction or maintenance.

Given the expected change in the profile of AARs after switching to rituximab SC (Davies et al. 2012), the primary objective of interest will be the incidence of AARs.

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

Modelling and simulation of PK data from stage 1 and the initial results from stage 2 of trial BP22333 (NCT00930514) (Salar et al. 2010; Salar et al. 2012) indicated that the fixed dose of 1400 mg of SC rituximab achieves noninferior trough levels to the IV dose of rituximab 375 mg/m2 in previously treated or untreated patients with FL (grade 1, 2 or 3a). SC rituximab was well tolerated, with an AE profile comparable to IV rituximab. No SAE related to SC rituximab was reported. Therefore, the fixed dose of 1400 mg SC was chosen for all other clinical trials of SC rituximab, both in this trial and in the ongoing registration trials.

The objective of this clinical trial is to evaluate the safety of switching from IV to SC administration of rituximab at any time during standard rituximab-regimens. Since this change may occur in the case of patients undergoing either induction or maintenance treatment, the study population included patients CD20+ FL or CD20+ diffuse large B-cell lymphoma (DLBCL) who had previously received at least 1 dose of IV rituximab as part of an induction or maintenance treatment, and who were candidates for at least 4 more cycles of SC rituximab (for those following an induction treatment) or 6 more admininstrations of SC rituximab (for those following a maintenance treatment).

2 STUDY OBJECTIVES AND DESIGN

2.1 Aim of Statistical Analysis Plan

This document presents the proposed analysis plan for performing the final statistical analysis of the MABRELLA study.

The analysis plan proposed below describes the aspects that should be known about the study and the methods of statistical analysis that will be applied to the data collected in order to answer the objective of the interim analysis.

2.2 Objectives

Primary Objective

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

Secondary Objectives

- To further evaluate the safety of rituximab SC in terms of:
    - Grade ≥ 3 AEs
    - Grade ≥ 3 IIRRs
    - Serious adverse events (SAEs)
- To evaluate the efficacy of rituximab SC in terms of:
    - event-free survival (EFS)
    - progression-free survival (PFS)
    - overall survival (OS)
    - disease-free survival (DFS)
- Treatment response rate 4-6 weeks after the last dose of Induction classified as follows: complete response (CR) (including complete response unconfirmed (CRu), partial response (PR), stable disease (SD) and progression disease (PD).

Exploratory Objectives

██

████████████

Patient reported outcomes

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

2.3 Study Design

Clinical trial, phase IIIb, open-label, non-randomized, single group assignment.

2.4 Study Population

The target population will consist of adults with CD20+ DLBCL or CD20+ FL grade 1, 2 or 3a according to the World Health Organization (WHO) classification system.

It is planned that 140 patients will participate in the study.
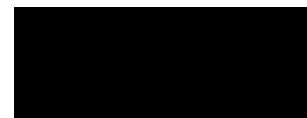
2.5 Inclusion Criteria

Study participants must meet ALL of the following criteria in order to be included in the study:

Criteria related to the subject

1. Written informed consent

2. Age >/= 18 and </= 80 years at time of enrolment.

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3

Criteria related to disease

4. Histologically confirmed CD20+ DLBCL or CD20+ follicular NHL (FL) grade 1, 2 or 3a according to the WHO classification system.

5. Induction only:

    a. DLBCL related criteria: An International Prognostic Index (IPI) score of 1-4 or IPI score of 0 with bulky disease, defined as one lesion >/= 7.5 cm (Appendix 4 of protocol).

    b. FL treatment-related criteria: Follicular Lymphoma International Prognostic Index (FLIPI) (low, intermediate, high risk). Patients with FL should meet Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria to initiate treatment. (Appendix 4 of protocol).

6. Induction only: At least tumor >/= 1.5 cm as measured by computed tomography (CT) scan

Treatment-related criteria

7. Currently being treated with MabThera/Rituxan IV during first-line therapy and has received at least one full dose of MabThera/Rituxan IV (defined as standard full dose of MabThera/Rituxan IV 375 mg/m2 administered without interruption or early discontinuation (i.e. tolerability issues)

8. Expectation and current ability for the patient to receive at least four additional cycles of treatment during the Induction phase or six additional cycles of treatment during the Maintenance phase (patients with follicular NHL)

2.6 Exclusion criteria

Participants who meet any of these criteria will not be included in the study:

Criteria related to medical history

1. Transformed lymphoma or follicular lymphoma (FL) IIIB

2. Primary central nervous system lymphoma, primary effusion lymphoma, primary mediastinal DLBCL, DLBCL of the testis, primary cutaneous DLBCL or histologic evidence of transformation to a Burkitt lymphoma.

3. History of other malignancy that could affect compliance with the protocol or interpretation of the results; this includes a malignancy that has been treated but not with curative intent, unless the malignancy has been in remission for >/= 5 years prior to treatment administration; 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.

Previous and concomitant treatment

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

Analytical evaluation during screening

5. Impaired renal function defined as creatinine > 1.5 x Upper Limit of Normal, ULN (unless creatinine clearance [CrCl] normal), or calculated CrCl < 40 mL/min (as determined by the Cockcroft–Gault formula)

6. Inadequate hematologic function, defined as follows:

 - Hemoglobin < 9 g/dL

- Absolute neutrophil count < 1.5 x 109/L

- Platelet count < 75 x 109/L (Note: abnormalities outside the above listed are allowed if related to involvement of bone marrow by the underlying disease).
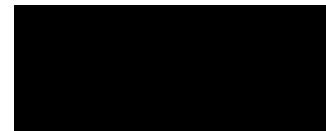
7. Inadequate hepatic function, defined as any of the following abnormal laboratory values:

     • Alanine aminotransferase (AST) or aspartate aminotransferase (ALT) > 2.5 x the ULN

     • Total bilirubin ≥ 1.5 x the ULN. (Patients with documented Gilbert disease may be enrolled if total bilirubin is ≤ 3.0 x the ULN.)

Other prior or current medical conditions and treatments

8. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products.
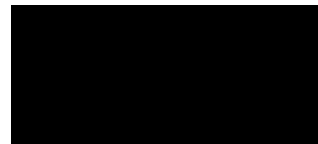
9. For patients with DLBCL: Contraindication to any of the individual components of CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone), including prior anthracycline treatment. For patients with FL: contraindication to standard chemotherapy.

10. Other serious underlying medical conditions (i.e., severe 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 infections (excluding nail fungal infections) or any infection requiring treatment with IV antibiotics or hospitalization within 4 weeks prior to dosing.

13. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Note: Patients testing positive for hepatitis B or C virus antibodies but with an undetectable viral load may be included (i.e., HBV or HCV RNA-negative by PCR).

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

General criteria

15. Any coexisting medical or psychological condition that would preclude participation in the required study procedures

16. Life expectancy < 6 months

17. A positive pregnancy test for women of childbearing potential within 7 days prior to first rituximab administration or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the first administration. 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 subcutaneous rituximab.

3 STATISTICAL METHODS

The methods of analysis to be used to achieve both the objectives of the final analysis of the study and for description of the study variables are detailed below.

All analyses described will be performed by type of lymphoma (DLBCL / FL) and overall.

Analyses of current treatment will be performed by type of treatment (induction therapy / maintenance therapy).

Selection criteria will not be checked unless it is expressly requested.

❖ UNIVARIATE ANALYSIS

Quantitative variables will be described with measures of central tendency and dispersion: mean, median, SD (standard deviation), Q1 (first quartile) and Q3 (third quartile), minimum and maximum).
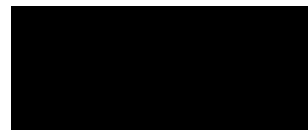
Qualitative variables will be described using absolute and relative frequencies. Two columns of percentages will be presented: Total percentage (%) and Percentage valid (% valid).

- Total percentage (%): Percentage over the sum of valid responses plus missing values, that is, over the total study sample.

- Percentage valid (% valid): Percentage over total valid responses, that is, with data in the variable.

Ninety-five percent Clopper-Pearson confidence intervals (CI) will be calculated, when necessary, for outcome variables associated with objectives.

In the case of questions with more than one response option, **multiple response** tables will be shown. Two columns of percentages will be shown in these tables:

- Total percentage (%): Percentage over the sum of valid responses plus missing values, that is, over the total study sample. As it is multiple response, the sum of the percentages does not necessarily equal 100 (this percentage may be exceeded).

- Percentage valid (% valid): Percentage over the number of patients with at least one response given from among those possible. As it is multiple response, the sum of the percentages does not necessarily equal 100 (this percentage may be exceeded).

❖ **BIVARIATE ANALYSIS**

In the comparative analysis, parametric tests will be used for those variables that meet the conditions for application (e.g. t-test) and nonparametric tests (e.g. chi-squared, Mann-Whitney U, Wilcoxon, etc.) for ordinal, categorical or other variables that do not meet parametric criteria.

All hypothesis tests will be two-sided and with a significance level of 0.05.

The "time to event" variables (i.e. progression-free survival, overall survival, etc.) will be analyzed using the Kaplan-Meier method.

Data will be analyzed using SPSS v22.0.

3.1 Close-out Database Agreement

Following database close-out to perform the analyses, if any anomalous and/or inconsistent values are found in any table of results, the database will not reopened to modify the values, but instead the anomalous data value will be highlighted and it will be indicated how it was handled (e.g., assigning to missing values or eliminating the case depending on the statistical method to be used in the analysis in question). Missing data will not be imputed and will be left as lost.

Any modification to this section will be recorded in writing in the report as well as the procedure followed (e.g. assignment to missing values, interpolation, elimination of the case, etc.).
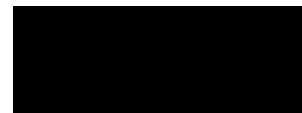
4 ANALYSIS POPULATIONS

The populations that will be included in the analysis are defined below:

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

All enrolled patients will be included in the **Intent-to-Treat (ITT) population**.

Efficacy parameters and patient reported outcome measures will be analyzed using the ITT population.

All analyses described will be performed by type of lymphoma (DLBCL / FL) and overall.
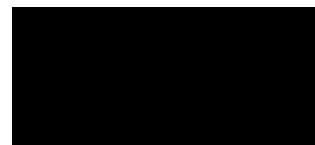
5   DESCRIPTIVE ANALYSIS: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

5.1   Recruitment Period

The dates of inclusion the first and last patient will be provided.

5.2   Lymphoma Diagnosis

- Type of Lymphoma: Diffuse Large B-cell / DLBCL / FL.

5.3   Demographic and anthropometric data

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be shown for the following variables:

- Age (years), based on (Date of Visit – Date of Birth).
- Weight.
- Height.
- BMI.

Categorical variables to be described:

- Sex: Male / Female.
- If female, is patient of childbearing potential: Yes / No.
- Race: Caucasian / Black/ Asian / Other.
- Ethnicity: Hispanic / Not Hispanic / Not applicable as local regulations / Others.

5.4   Medical History

5.4.1   Relevant medical history

Categorical variables to be described:

- Does the patient have any clinical significant relevant medical history other than DLBCL or FL?: Yes / No.

For patients with any clinical significant relevant medical history, a multiple response table will be shown (the table will be shown by System Organ Class and Preferred Term).

5.4.2   Surgery and Procedures history

Categorical variables to be described:

- Has the patient had any cancer or non-cancer surgeries to report?: Yes / No

For patients with any cancer or non-cancer surgeries, a multiple response table will be shown for type of surgery or procedure.
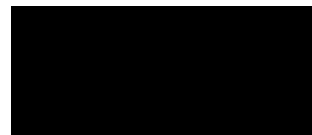
5.4.3 DLBCL Diagnosis

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following continuous variables:

- Time from diagnosis, defined as the time in months from the date of diagnosis (date of histological diagnosis) to the date of the baseline visit.

Categorical variables to be described:

- Histological diagnosis: FNA / Core needle biopsy /Excisional or Incisional biopsy of peripheral lymph node.

5.4.4 Follicular Lymphoma Diagnosis

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following variables:

- Time from diagnosis, defined as the time in months from the date of diagnosis (date of histological diagnosis) to the date of the baseline visit.

Categorical variables to be described:

- Histological diagnosis: FNA / Core needle biopsy /Excisional or Incisional biopsy of peripheral lymph node.
- Grade of FL: 1 / 2 / 3 / 3a.

5.5 Physical Examination

Related to baseline visit, the following will be described:

- Was the physical examination performed?: Yes / No

For patients with a physical examination performed, a multiple response table will be shown for those affected systems with the result: Abnormal, clinically significant:

- Head, ears, eyes, nose, throat.
- Cardiovascular system.
- Dermatological.
- Musculoskeletal system.
- Respiratory system.
- Gastrointestinal system.
- Genitourinary system.
- Nervous system.
- Other.

The physical examination will be described for each of the visits performed.
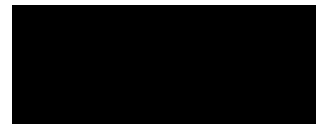
5.6 ECOG Performance Status

Categorical variable to be described:

- ECOG: 0/ 1 / 2 / 3 / 4 / 5.

The ECOG score will be described for each of the visits performed, i.e., at screening and induction and/or maintenance.

5.7 IPI Score

For DLBCL patients: Related to baseline visit, the following will be described: Low risk / Low intermediate risk / High intermediate risk / High risk.

5.8 FLIPI Score

For FL patients: Related to baseline visit, FLIPI score will be described: Low risk / intermediate risk / High risk.
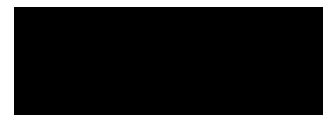
6 EVALUATION OF PATIENT OUTCOME QUESTIONNAIRE

All analyses described will be performed by type of lymphoma (DLBCL / FL) and overall.

The Rituximab IV Administration Satisfaction Questionnaire (**RASQ-IV**) will be analyzed on the baseline visit before switching to SC rituximab treatment and the Rituximab IV Administration Satisfaction Questionnaire" (**RASQ-SC**) at the "end of induction" and/or "maintenance treatment" (when applicable).

The RASQ is a 20-item questionnaire measuring the impact of the mode of treatment administration on five domains: Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. The Physical Impact domain comprises of three items (Pain, swelling, and redness, Pain experience, Side effects as expected), the Psychological Impact domain contains five items (Anxious about injection/IV, Worry condition will get worse, Anxious thinking about disease, Confidence the injection/IV treating disease, Feeling restricted by injection/IV), the Impact on Activities of Daily Living domain contains three items (Interference with usual/daily activities, Limit daily activities, Lost/gained time), the Convenience domain contains three items (Is it convenient to get injection/IV, Length of time to get injection/IV as expected, Bothered by the amount of time to get injection/IV) and the Satisfaction domain includes two items (How satisfied or dissatisfied are you with the injection/IV, Would you recommend the way you received the treatment). All 16 RASQ items included in the above domains have five response options. Reverse-coded response values will be created for eight of the RASQ items (Q2, Q3, Q5, Q6, Q7, Q9, Q14a, and Q14b).

In addition, there are four descriptive questions that are not part of the above domains and scored separately. Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for this domains.

For each domain, if there are no missing responses, the domain will be scored using the formula:

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

However, if there are any missing responses within a domain then the domain will not be scored (i.e. a missing value is assigned to the domain).

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

RASQ domain score = (Mean of completed item responses – 1) x 25.
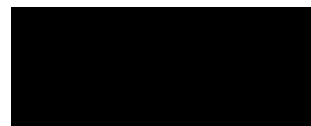
Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for each domain.

7 PREVIOUS TREATMENT

7.1 Chemotherapy

The variable 'type of chemotherapy regimen' that the patient is receiving will be described: CHOP-14 x 6 / CHOP-14 x 8 / CHOP-21 x 6/ CHOP-21 x 8 / CVP-21 x 8 / Other.
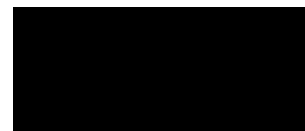
7.2 Previous IV Rituximab Dose: FL

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following continuous variables:

- Time from diagnosis (months), calculated from the date of histological diagnosis to the date of first dose of IV rituximab).
- Dose of most recent IV rituximab cycle.

Categorical variables to be described:

- Phase of IV rituximab (most recent IV cycle): Induction Phase / Maintenance Phase
- Cycles of IV rituximab that the subject had received previously: 1/ 2 / 3 / 4 / 5 / 6 / 7 / 8.
- Treatment phase in which the patient switched from IV rituximab to the SC formulation: Induction Phase / Maintenance Phase.
- First SC treatment cycle on study: Cycle 1 / Cycle 2 / Cycle 3 / Cycle 4 / Cycle 5 / Cycle 6 / Cycle 7.

7.3   Previous IV Rituximab Dose: DLBCL

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following continuous variables:

- Time from diagnosis (months), calculated from the date of histological diagnosis to the date of first dose of IV rituximab).

Categorical variables to be described:

- Cycles of IV rituximab that the subject had received previously: 1/ 2 / 3 / 4.
- Dose of most recent IV rituximab cycle.
- First SC treatment cycle on study: Cycle 2 / Cycle 3 / Cycle 4 / Cycle 5.

8   CURRENT TREATMENT

8.1   Study Drug Administration

Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented for the following continuous variables:

- For FL patients: Number of induction and/or maintenance cycle administered per patient.
- For DLBCL patients: Number of treatment cycle administered per patient.

Categorical variables to be described (this analysis will be presented by cycle):

- Full dose: Yes / No If No:
    - Reason: Adverse event / Technical problems / Other
        - (If other: specify).
        - If the reason is an AE, specify if it is a grade 3 or 4 IRAE: Yes / No.

8.2   Study Drug Discontinuation

Categorical variables to describe are:

- Number of patients who discontinued study treatment.
- Primary reason for patient discontinued treatment: Progression of Disease / Adverse Event / Pregnancy / Patient request - Withdraw consent / Investigator decision / Lack of compliance / Lost to Follow-up / Death / Other.
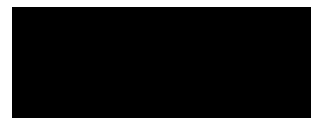
9 RESPONSE

All analyses described will be performed by type of lymphoma (DLBCL/FL) and overall.

The response attained by patients on the <u>End of Treatment visit</u> (4-6 weeks after the last dose of Rituximab SC) will be described, including: Complete Response, Unconfirmed Complete Response, Partial Response, Stable Disease, Disease Progression, as well as the 95% confidence interval.

Depending on the response, the complete response rate (Complete Response + Unconfirmed Complete Response) will be calculated and described, as well as the 95% confidence interval.

All analyses described will be performed by type of lymphoma (DLBCL/FL) and overall.

The response attained by patients on the <u>Final Staging visit</u> will be described, including: Complete Response, Unconfirmed Complete Response, Partial Response, Stable Disease, Disease Progression, as well as the 95% confidence interval.

Depending on the response, the complete response rate (Complete Response + Unconfirmed Complete Response) will be calculated and described, as well as the 95% confidence interval.

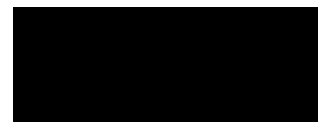All analyses described will be performed by type of lymphoma (DLBCL/FL) and overall.

The variable 'time in study', defined as the time in months from inclusion to the last available date, will be provided. Descriptive statistics (mean, SD, median, Q_1, Q_3, minimum, maximum) will be presented.

10 DEATHS

All analyses described will be performed by type of lymphoma (DLBCL/FL) and overall.

Categorical variables to be described:

- The number of patients who died during the study.
- Primary cause of death: Progression of disease / Adverse Event / Unknown / Other.

11 SURVIVAL

All analyses described will be performed by type of lymphoma (DLBCL/FL) and overall.

11.1 Event free survival (EFS)

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

The median EFS will be described by total and by type of lymphoma (DLBCL/FL), as well as the number of events and censored cases (Kaplan-Meier Analysis).

11.2 Progression free survival (PFS)

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

The median PFS will be described by total and by type of lymphoma (DLBCL/FL), as well as the number of events and censored cases (Kaplan-Meier Analysis).

11.3 Overall survival (OS)

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

The median OS will be described by total and by type of lymphoma (DLBCL/FL), as well as the number of events and censored cases (Kaplan-Meier Analysis).

11.4 Disease free survival (DFS)

It 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.

The median DFS will be described by total and by type of lymphoma (DLBCL/FL), as well as the number of events and censored cases (Kaplan-Meier Analysis)

12 QUALITY OF LIFE

All analyses described will be performed by type of lymphoma (DLBCL/FL) and overall.

Quality of life will be analyzed at any many times as there are recorded in the CRF (at the "end of induction" and/or "maintenance treatment" (when applicable)).

Quality of life will be assessed using the EuroQoL-5D-5L Health Questionnaire. It consists of two parts:

- The first part evaluates 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each dimension, 5 health states are described. The patient then chooses the one that best describes his/her health state.

- The second part consists of a visual analog scale graded from 0 (worst imaginable health state) to 100 (best imaginable health state). The patient has to mark on this scale the point that best describes his/her overall health state on the day of the interview.

In the EQ-5D questionnaire, the individual first self-rates his/her health state on severity levels by dimensions (descriptive system) and then makes a more general assessment of health status on a visual analog scale (VAS). A third element of the EQ-5D is the **index of social values** (or preferences), which is obtained for each health state generated by the instrument (tariffs).

The descriptive system contains 5 health dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each of these dimensions has 5 severity levels (no problems, slight problems, moderate problems, severe problems, cannot perform the activity). The combination of the values of all the dimensions generates 5-digit numbers, with a total of 3125 possible combinations or health states. The second part is a visual analog scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Studies are currently being conducted to obtain index values to facilitate the calculation of the quality-adjusted life years (QALYs) that are necessary in economic evaluations. As the results of these index values values are yet not available, there are cross-tables to calculate the index value of a specific score obtained with the 5D-5L scale, based on the index values of the EQ-5D-3L scale. The **index of preference values** ranges from a value of 1 (best health state) to 0 (death), though there are negative values for the index, corresponding to those health states that are assessed as worse than death.

- The descriptive analysis (N, %) will be shown by severity levels in each dimension and **additionally**
- The descriptive analysis of the VAS will be provided (measures of central tendency and dispersion).
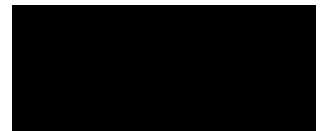
- The descriptive analysis of the index values or tariffs will be provided (measures of central tendency and dispersion).

The index values will be taken from the webpage:

http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html
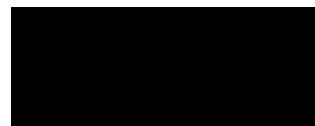
13 SAFETY

All analyses described will be performed by type of lymphoma (DLBCL/FL) and overall.

13.1 Adverse Events

This analysis will include all adverse events occurring to patients during the study. To obtain the number of adverse events per patient, <u>the maximum of most extreme intensity (maximum intensity grade for each toxicity) will be calculate</u>d for each of the adverse events recorded during the treatment of each patient and the following will be described:
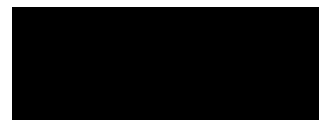
- Number of patients with at least one adverse event (95% CI).
- Number of patients with different adverse events reported by grade (GI, GII, GIII, GIV, GV). A list of the different AEs experienced by patients according to the maximum grade, N and % will be presented. (Events will be run by System Organ Class and Preferred Term).
- Number of patients with at least one adverse event of grade 3 or higher (95% CI).

13.2 Serious Adverse Events

The number of patients with at least one **Serious Adverse Event (95% CI)** will be described, as well as a list of the different events experienced by patients and the main characteristics of the events: system organ class, preferred term, causal relationship with chemotherapy or rituximab, duration (start and end date), action taken, treatment required (yes/no), outcome.

13.1   Adverse Event of Special Interest

The number of patients with at least one **Adverse Event of Special Interest (95% CI)** will be described, as well as a list of the different events experienced by patients and the main characteristics of the events: system organ class, preferred term, causal relationship with chemotherapy or rituximab, duration (start and end date), action taken, treatment required (yes/no), outcome.

13.2 Adverse Events related to SC Rituximab

In this section, the AEs indicating a relationship to the study treatment (SC rituximab) will be considered.

This analysis will include all adverse events occurring to patients during the study. To obtain the number of adverse events per patient, <u>the maximum of most extreme intensity will be calculated</u> for each of the adverse events recorded during the treatment of each patient and the following will be described:

- Number of patients with at least one AE. The proportion of patients experiencing at least one AE will be provided, and the Clopper-Pearson 95% confidence interval.
- Number of patients with different AEs reported by grade (GI, GII, GIII, GIV, GV). List of the different AEs experienced by patients according to grade, N and %. (Events will be run by System Organ Class and Preferred Term).
- Number of patients with at least one AE ≥ grade 3 (95% CI).
- Number of patients (%) with one fatal AE (leading to death): N, % (CI 95%).

13.3 Administration-Associated Reactions (AARs) for SC Rituximab

AAR: All events where the answer to "If this is an AAR related to the Rituximab SC injection, please specify location" is "Localised at the injection site" or "Generalised and/or remote from the injection site"

- Number (%) of patients with at least one AAR
- Number of patients with different AARs reported by grade (GI, GII, GIII, GIV, GV). List of the different AARs experienced by patients according to, N and %. (Events will be run by System Organ Class and Preferred Term).
- Number (%) of patients with at least one AAR ≥ grade 3.
- Number (%) of patients with at least one serious AARs.
- Number (%) of patients with at least one AAR localized at the injection site reaction and generalized and/or remote from the injection site.
- AAR localized at the injection site and generalized and/or remote.

13.4 Action taken related to study treatment Rituximab

The action taken related to the study treatment with rituximab will be described (for all AEs): None / Drug interrupted / Drug delayed / Drug permanently discontinued / Dose modification / Not Applicable.

The number (%) of patients with at least AEs leading to treatment interruption, dose delay, discontinuation and modification will be described:

- AEs leading to treatment interruption.
- AEs leading to dose delay.
- AEs leading to discontinuation.
- AEs leading to modification.

13.5 Outcome

The outcome (for every AE) will be described: Fatal / Resolved / Resolved – with sequelae / Unresolved - Improving / Unresolved – Persisting / Unresolved – Worsening / Unknown.

The number (%) of patients with at least AEs leading to patient death will be described:

- AEs leading to death=Fatal.
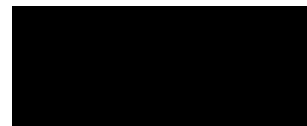
14 ANALYSIS OF OBJECTIVES

14.1 Primary Objective

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

This objective is answered with the descriptive analysis, as detailed in section 13.3 of this document.

14.2 Secondary Objectives

- *To further evaluate the safety of rituximab SC in terms of:*
  - *Grade ≥ 3 AEs*
  - *Grade ≥ 3 IIRRs*
 - *Serious adverse events (SAEs)*

This objective is answered with the descriptive analysis, as detailed in sections 13.1, 13.2 y 13.3 of this document.

- *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)*

This objective is answered with the descriptive analysis, as detailed in section 11 of this document.

- *Treatment response rate 4-6 weeks after the last dose of Induction classified as follows: complete response (CR) (including complete response unconfirmed (CRu), partial response (PR), stable disease (SD) and progression disease (PD).*

This objective is answered with the descriptive analysis, as detailed in section 9 of this document.
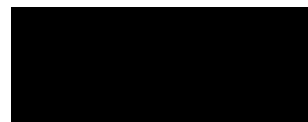
14.3 Exploratory Objectives

[REDACTED]
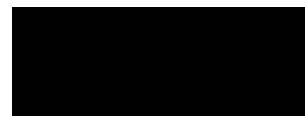
14.4 Patient reported outcomes

To evaluate and compare the methods of rituximab administration (SC vs IV) in terms of patients´ satisfaction using the "Rituximab Administration Satisfaction Questionnaire" (RASQ).

This objective is answered with the descriptive analysis, as detailed in section 6 of this document.

To assess patients' quality of life and utilities by EUROQoL 5D instrument.

This objective is answered with the descriptive analysis, as detailed in section 12 of this document.