Official Title: **A Randomized Study Comparing Maintenance Therapy With Subcutaneous Rituximab Continued Until Progression With Observation Only In Patients With Relapsed or Refractory, Indolent Nonhodgkin's Lymphoma Who Completed and Responded To Rituximab-Based Immunochemotherapy Induction and Initial 2-Year Rituximab Maintenance Therapy Administered Subcutaneously**

NCT Number: **NCT01461928**

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STATISTICAL ANALYSIS PLAN

HOFFMANN-LA ROCHE LTD.

MO25455

A RANDOMIZED STUDY COMPARING MAINTENANCE THERAPY WITH SUBCUTANEOUS RITUXIMAB CONTINUED UNTIL PROGRESSION WITH OBSERVATION ONLY IN PATIENTS WITH RELAPSED OR REFRACTORY, INDOLENT NON-HODGKIN'S LYMPHOMA WHO COMPLETED AND RESPONDED TO RITUXIMAB-BASED IMMUNOCHEMOTHERAPY INDUCTION AND INITIAL 2-YEAR RITUXIMAB MAINTENANCE THERAPY ADMINISTERED SUBCUTANEOUSLY

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V1.1 13JUN2018

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan version 1.1 (Dated 13JUN2018) for Protocol MO25455.

	Name	Signature	Date
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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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1.1	13JUN2018	[redacted]	Not Applicable – No authorized version at this stage

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for the final analysis of Protocol MO25455. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on clinical study protocol (CSP) version 4.0.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of a subcutaneous (SC) formulation of rituximab in terms of Progression-Free Survival after randomization (PFS_{rand}) to either prolonged rituximab maintenance until progression (Maintenance II) or observation in patients with relapsed or refractory, indolent non-Hodgkin's lymphoma (NHL) who responded to Induction and initial 2 years maintenance therapy (Maintenance I).

SECONDARY OBJECTIVES

The secondary objectives are to evaluate the efficacy and safety of SC rituximab during Induction, initial 2-year

maintenance (Maintenance I) and randomized treatment period (Maintenance II). Efficacy will be evaluated in terms of Time to Treatment Failure (TTF), Time to Next Lymphoma Treatment (TNLT), Overall Survival measured from the first Induction dose of Rituximab (OS_{regist}) and from the time of randomization to Maintenance II (OS_{rand}), Overall Response Rate (ORR), Partial Response (PR) to Complete Response (CR) conversion rate at the end of Maintenance I, and PFS measured from the first Induction dose of rituximab (PFS_{regist}). Safety assessments will include frequency of adverse events (AEs), serious adverse events (SAEs), and infusion/injection-related reactions (IRRs) and immunoglobulin (Ig) quantification.

2.2. EXPLORATORY OBJECTIVES

[redacted]

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a multicentre, multinational, open label, randomized study to evaluate maintenance therapy with SC rituximab continued until progression compared to observation only in patients with relapsed or refractory, indolent NHL who completed and responded to Induction and initial 2-year maintenance therapy (see Figure A).

The study flow will include the baseline assessment, Induction phase, Maintenance I phase and the Maintenance II phase

- Baseline assessment: will be performed according to the Schedule of Assessments (CSP Table 5).
- Induction: 8 cycles of rituximab will be administered in combination with 6 - 8 cycles of chemotherapy (selection at the Investigator's discretion). The first administration of rituximab will be by IV infusion on Day 1 of the first Induction cycle, at a dose of 375 mg/m^2 body surface area (BSA). In the absence of infusion-related side effects, rituximab will subsequently be administered SC starting on Day 1 of each Induction cycle at a fixed dose of 1400 mg. Patients who experienced a grade 3 or 4 IRR after the first rituximab infusion (Cycle 1), but were able to receive the full dose of rituximab, can receive the second dose of rituximab SC (Cycle 2, Day 1). Patients who were not able to receive their full dose of rituximab infusion in Cycle 1 as a result of an IRR should receive their second rituximab dose also IV. If this second rituximab infusion is not associated with a grade 3 or 4 IRR, the patient will receive his/her third rituximab dose SC (Cycle 3, Day 1). Patients with a grade 3 or 4 IRR after the second rituximab infusion will be withdrawn from the study. Response assessments will be conducted by the Investigator after 4 cycles (or after 3 cycles if the Induction comprised 6 chemotherapy administrations) and at the end of Induction (i.e. after 8 cycles of rituximab). Patients with progressive disease (PD) at any time during the study will come off study treatment and will start Off-Treatment Follow-Up, being followed for survival until the end of the study. Patients with stable disease at the end of Induction will come off study treatment and will enter Off-Treatment Follow-Up, being followed for PD and survival until the end of the study.
- Maintenance I: SC rituximab maintenance therapy must start within 8-12 weeks after the administration of the last dose of rituximab in the Induction period. Maintenance therapy will consist of 12 cycles of

rituximab, administered as a single SC injection of 1400 mg rituximab every 8 weeks for 2 years. Response assessment will be conducted by the Investigator every 6 months during Maintenance I. Patients with PD at any time during the study will come off study treatment and will start Off-Treatment Follow-Up, being followed for survival until the end of the study.

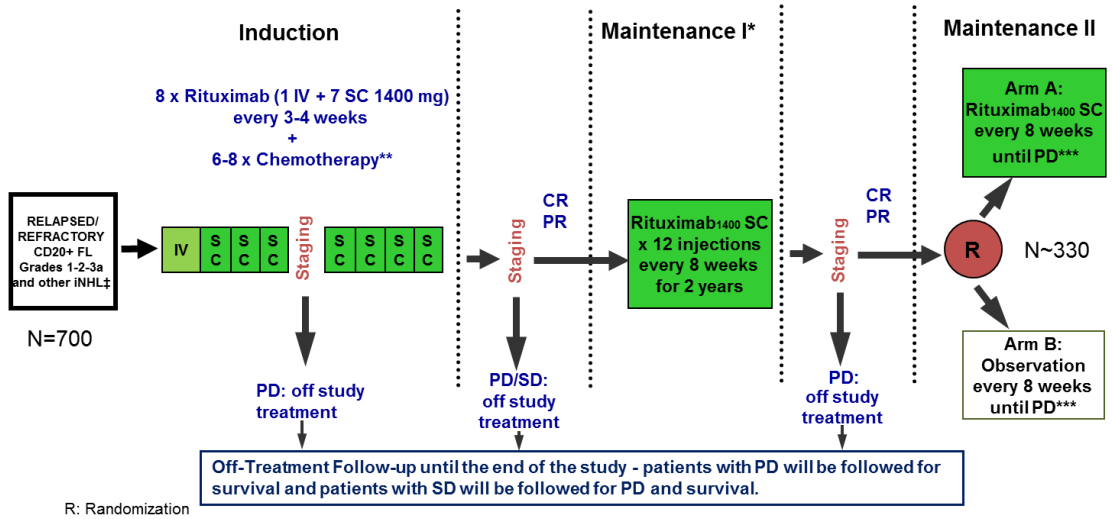
- Maintenance II: at the end of the 2-year Maintenance I, patients with PR or CR will be randomized to maintenance treatment with SC rituximab continued until progression (Arm A) or observation with no further treatment (Arm B). Patients in Arm A will receive one SC rituximab injection at a fixed dose of 1400 mg every 8 weeks until PD, unacceptable toxicity, withdrawal of patient consent or until End of Study. Disease progression will be evaluated by the Investigator every 6 months.

Response assessment will be conducted by the Investigator according to the Cheson response criteria for indolent lymphoma (see Appendix 1 of the CSP) or by the recommendations for Waldenström's macroglobulinemia (see Appendix 2 of the CSP).

Sample size calculation: Assuming a median PFS beyond randomization (Maintenance II) of 38 months in Arm A, and 23 months in arm B (corresponding to a hazard ratio of approximately 0.6), 129 events are required to achieve 80% power for the log-rank test at a two-sided significance level of 5%.
In order to see the required events, approximately 300 patients in Maintenance II were to be followed from randomization (Maintenance II treatment until PD and post-treatment follow-up) for at least 15 months. Therefore, a total of 700 patients were to be enrolled to randomize 330 patients (allowing for a 10% drop-out) after the 2.5-year Induction plus Maintenance I treatment period.

At the conclusion of enrolment and all randomizations 694 patients were enrolled and 276 were randomized to Maintenance II.

Figure A Study Scheme



R: Randomization
* Maintenance must start within 8-12 weeks after completion of Induction treatment
** Chemotherapy options are: Bendamustine, CHOP, CVP, FCM, MCP, CHVP-IFN, Chlorambucil or any fludarabine-containing regimen including oral fludarabine, R-GIFOX
*** Until PD refers to either disease progression or until primary endpoint has been reached.
‡ Other iNHL refers to: Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma, marginal zone lymphoma, according to the WHO classification system

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Table 5 of the CSP.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The analyses planned in the CSP have been expanded upon and the efficacy parameter Event Free Survival has been renamed to TTF throughout this SAP.

In the CSP ORR at end of induction was to be analyzed *by treatment group*. It was clarified during discussions with the study team that 'treatment group' for this specific analysis the induction regime was meant and not (as one may conclude) the randomized arms . This has now been clarified and clearly described in the analysis section.

In the CSP, it was specified that the analysis of the secondary efficacy variables PFSregist, EFS, OSregist, OSrand and TNLT will be performed as described for the primary variable PFSrand. Descriptive statistics and Kaplan-Meier curves will be presented for non-randomized patients and for the two randomized treatment groups.

Within this SAP it now is clearly specified in addition that for time to event analysis from time from registration no statistical testing will be done. The effect of the randomised treatment is not a result of what happened at time of registration which occurred at least 2.6 years prior to randomisation. Therefore, only descriptive statistics will be presented and a disclaimer added to highlight the difficulty of interpretation these results.

In addition, the analysis of non-randomised patients was replaced by the ITT population overall and split by disease type. The rational for this is that non-randomised patients represent all 'early' treatment/study discontinuations and provides little scientific insight. It was felt that analysing the study as a whole would allow an overall measurement of PFS and OS to compare results to current medical expectations in this setting.

4. PLANNED ANALYSES

The following analyses have been performed for this study:

- Analyses for Independent Data Monitoring Committee (IDMC) meetings
- Interim Analysis for safety was performed when 200 patients were enrolled
- [redacted]

This document will focus on the following remaining analysis:

- Final Analysis

4.1. INDEPENDENT DATA MONITORING COMMITTEE

The IDMC were responsible for monitoring, on an ongoing basis, all significant safety events (SSEs).
A SSE is defined as any of the following:

- General toxicity: National Cancer Institute (NCI) Common Terminology Criteria (CTC) grade 3 and grade 4 AEs, SAEs
- Any AE that requires dose interruption, reduction or discontinuation of the study drug
- A patient death
- In addition, progression-free survival data will be reviewed.

The outputs for the first IDMC review were produced by the legacy [redacted] study team. After patients reached randomization and Maintenance II phase, an independent statistician was involved in the outputs production in order that the study team remained blinded to interim primary endpoint information.

4.2. INTERIM ANALYSES

[redacted]

An interim analysis of safety was performed after approximately 200 patients had been enrolled. The following data were summarized:

- Demographics and baseline characteristics
- Summary of AEs (including separate summaries for AEs occurring during the cycles with IV and SC rituximab administration). In addition to the total AE counts, the following events were presented:
    - serious AEs
    - AEs leading to death
    - AEs with CTC AE grade greater than or equal to 3
    - AEs leading to rituximab Interruption
    - AEs leading to rituximab discontinuation
    - Administration Related Reactions (ARR)
- Summary of other safety assessments
- Summary of study drug exposure

Derivations and definitions for the interim analyses were consistent with those required for the final analysis. The interim analyses were described in a separate SAP and are not included in the remainder of this document.

In addition to the analysis outlined above, 8 iDMC data review meetings occurred throughout the conduct of the study. As described above statistical outputs have been provided by the study statistician for all patients treated. For any outputs by randomized treatment (provided for the final 4 meetings) however an independent statistician was used and the data shared only with the iDMC members. This helped ensure that the study team was kept blinded.

4.3. FINAL ANALYSIS

All final, planned analyses will be performed by legacy [redacted] Biostatistics following Sponsor Authorization of this SAP, Database Lock and Sponsor Authorization of Populations. These analyses are the only focus of this document.

5. ANALYSIS POPULATIONS

5.1. ALL SUBJECTS ENROLLED POPULATION [ENR]

The all subjects enrolled (ENR) set will contain all subjects who are registered in the Interactive Voice Recognition System (IVRS).

5.2. INTENT-TO-TREAT POPULATION [ITT]

All patients who have completed a baseline visit and at least one on-treatment assessment will be included in the Intent-To-Treat (ITT) population. The ITT population will be used for the analysis of the secondary efficacy parameters and baseline variables.

There will be an additional Intent-To-Treat (ITT_{rand}) population including only randomized patients for analyzing the primary endpoint of PFS beyond randomization (PFS_{rand}, Maintenance II) and the secondary endpoint of overall survival from randomization (OS_{rand}). All randomized patients will be included in this ITT_{rand} population and analyzed according to the treatment arm they were randomized to.

5.3. PER PROTOCOL POPULATION [PP_{RAND}]

The Per Protocol (PPRand) population will include all patients in the ITT population who were randomized to Maintenance II or Observation and did not have major protocol violations.

During the study, all major protocol deviations were reviewed by the Medical Monitors. These protocol deviations are presented by patient in data listings.

For randomised patients, any major protocol deviations potentially having an potential impact on the primary analysis are defined below will be summarized. The summaries will be based on the predefined Protocol Deviation Management System (PDMS) categories (Inclusion criteria, Exclusion criteria, Medication and Procedural). The following will be considered major protocol deviations potentially having an impact on the analysis:

- Inclusion/Exclusion violations

- Informed consent not available
- Patients randomized without a Tumor assessment done
- Received an induction Chemotherapeutic regimen not included in protocol
- Staging CT scan not done at all based on Medical review as disease specific
- Treatment was not discontinued despite Stable disease (SD)/PD at interim staging prior to maintenance I /II or PD at any time
- Concomitant treatment with other investigational or unlicensed /unapproved agent of any type based on Medical review
- Other concomitant anti-tumor agents not defined in this protocol as study treatment, including lymphoma-therapeutic doses of glucocorticoids based on Medical review

In the PP population all patients will need to have received at least one cycle of maintenance II treatment.

5.4. SAFETY POPULATION [SAF]

All patients who have received at least one dose of rituximab will be included in the Safety population.

Separate SAFs will be derived for each of the three study treatment periods: Induction, Maintenance I and Maintenance II, based on patients receiving at least one dose of rituximab in the study treatment period.

Note that the safety population for Maintenance II includes patients randomized to the observation only arm, who do not receive any dose of rituximab.

5.5. [redacted]

[redacted]

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of rituximab, (Day 1 is the day of the first dose of rituximab), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference start date then:

Study Day = (date of event – reference start date) + 1.

- If the date of the event is prior to the reference start date then:

Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear missing in the listings.

In addition, there will be a reference start date defined for each study treatment period (Induction Period, Maintenance I and Maintenance II), as the day of the first dose of rituximab per study period (where Day 1 for the study period is the day of the first dose of rituximab in that study period), and this will also appear in listings of post-screening data that contains an assessment date or event date:

Study Period Day will be assigned as per Study Day, with reference start date relative to the study period.

Note that for Maintenance II, for patients who do not receive rituximab (the observation arm), reference start date will be the date of randomization.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but AEs and medications commencing on the reference start date will be considered post-baseline.

Baseline will be defined for the study as a whole and also for each study treatment period separately using the last non-missing measurement taken prior to the reference start date for each study treatment period.

Note that for Maintenance II, for patients who do not receive rituximab (observation arm), the reference start date for the purpose of deriving baseline will be the date of randomization.

6.3. RETESTS AND UNSCHEDULED VISITS

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will be presented in the listings.

In the case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries.

For analyses or summaries of data which are not by-visit, unscheduled measurements will be considered and used as appropriate.

6.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.5. STATISTICAL TESTS

The default significant level will be 5%; confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses. The primary efficacy analysis is clearly stated and there will be no adjustments for multiplicity.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The randomization stratification factors

- Follicular Lymphoma International Prognostic Index (FLIPI) risk category (low, intermediate, high)

- indolent NHL subtype (follicular lymphoma, non-follicular lymphoma)

will be included as factors/covariates in the primary efficacy analysis and some secondary efficacy analyses, as detailed in sections 15.1.3 and 15.2.3.

Prior to database lock to examine if there were any potential misstratifications, discrepancies between the FLIPI classification (low risk, intermediate risk or high risk) and current type of NHL (follicular/non-follicular) recorded at screening and that captured on the eCRF (imported from the IVRS system) at the time of randomization will be investigated and a listing of potential misstratifications will be provided.

In addition, the subgroups defined in section 7.5 of this document will also be included as factors/covariates in the primary efficacy analysis and some secondary efficacy analyses, as detailed in sections 15.1.3 and 15.2.3.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to treatment arms is not stratified by country/ center.

7.3. MISSING DATA

When deriving patient age, if components of date of birth are missing, the following rules will be applied:

If day is missing but month and year are not-missing, date of birth will be assumed to be the last possible day of the month

If day and month are missing, but year is not-missing, date of birth will be assumed to be the 31st of December of that year

If day, month and year are all missing, age will be missing.

Missing safety data will not be imputed. However partial dates for AEs and concomitant medications will be handled in accordance with rules described in Appendix 2.

Missing efficacy data will be handled as described in section 15.1.2.

Handling of the missing data for CTSQ and RASQ questionnaires is described in sections 15.4.2.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment for multiplicity will be performed for this study.

7.5. EXAMINATION OF SUBGROUPS

The following subgroups will be used in certain efficacy and safety analyses/summaries:

The randomization stratification factors (based on CRF data):

- Follicular Lymphoma International Prognostic Index (FLIPI) risk category (low, intermediate, high)
- indolent NHL subtype (follicular lymphoma, non-follicular lymphoma)

and also:

- response (CR or PR) at end of Maintenance I, prior to randomization.
- response (CR or PR) at end of Induction, prior to Maintenance I.
- disease type at screening (follicular NHL, Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma (WNLL) or marginal zone lymphoma (MZL)
- age (<60 years, ≥60 years)
- sex (male, female)

Body Surface Area (BSA) at screening:

- Low (BSA ≤1.70m^2)
- Moderate (1.70m^2 < BSA ≤1.90m^2)
- High (BSA > 1.90m^2)

Chemotherapy Regimen during Induction:

- Bendamustine
- CHOP
- CVP
- Other

The use of these subgroups will be mentioned in relevant sections (Sections 9, 10, 14, 15.1.5 and 16.1)

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

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.

9. DISPOSITION AND WITHDRAWALS

All subjects recorded in IVRS system will be accounted for in this study.

Subject disposition and withdrawals will be presented for the Induction period for all patients, and disposition and withdrawal in each of the maintenance periods will be summarized separately, for enrolled patients (Maintenance I) and randomized patients (Maintenance II).

Subject disposition for the Induction period will be summarized by Induction chemotherapy regimen and disease type subgroups defined in section 7.5.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT population by study treatment period (and by randomized treatment and overall for Maintenance II).

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Gender
- Race
- Age (years)
- Height (cm)
- Weight (kg)
- BSA (m^2)

For Induction period, age will be calculated relative to date of consent.

BSA will be calculated according to Dubois formula:

$BSA\ (m^2) = 0.20247 \times Height\ (m)^{0.725} \times Weight\ (kg)^{0.425}$

11. MEDICAL HISTORY

Medical History information will be presented for the ITT.

Medical History will be coded using MedDRA dictionary (version updated every 6 months). Medical History conditions will be presented by System Organ Class (SOC) and Preferred Term (PT).

12. NHL HISTORY AND PREVIOUS ANTI-CANCER THERAPY

NHL History will be presented for the ITT, and for all patients and by randomized treatment for Maintenance II.

- Initial and current type of NHL at screening, current CD20+ status and duration of disease at screening will be summarized
- Ann-Arbor Stage and FLIPI score recorded at screening will be summarized
- Bone marrow assessment at screening will be summarized

Previous Anti-Cancer Therapy will be presented for the ITT.

- Previous Systemic Cancer therapy for NHL (including type of agent and outcome of therapy) and Previous Radiotherapy for NHL will be presented.

Duration of disease in months will be derived as:

(date of first rituximab administration - date of initial diagnosis + 1) * (12/365.25).

13. MEDICATIONS

Concomitant medications will be presented for the SAF, by pre-randomization period (Induction and Maintenance I combined) and by randomized treatment for Maintenance II**.**

Prior medications will be presented for all SAF patients.

Medications will be coded using INN dictionary

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

Table 1 Assignment of concomitant medications to study periods

Medication dates	Medication classification
All SAF patients:	
Medication stopped prior to first dose of rituximab in Induction Period	Prior medication
Medication started more than 28 days after the last dose of rituximab in the study	Post treatment
The above two rules are to be applied first. Any medications which are not classified as a prior medication or as post-treatment will have the period(s) they are concomitant in determined using the below rules.	
For patients who were not randomized	

Medication dates	Medication classification
Medication was neither prior medication or post-treatment	Concomitant in Pre-randomization period
Randomized patients who received rituximab in Maintenance II:	
Medication was neither prior medication or post-treatment and stopped prior to date of first dose in Maintenance II	Concomitant in Pre-randomization period
Medication started prior to first dose of rituximab in Maintenance II and stopped on or after date of first dose of rituximab in Maintenance II	Concomitant in Maintenance II
Medication started after first dose of rituximab in Maintenance II	Concomitant in Maintenance II
Randomized patients who did not receive rituximab in Maintenance II:	
Medication was neither prior medication or post-treatment and stopped prior to date of randomization	Concomitant in Pre-randomization period
Medication started prior to randomization and stopped on or after date of randomization	Concomitant in Maintenance II
Medication started after date of randomization	Concomitant in Maintenance II

A medication can be concomitant in both the pre-randomization period and in Maintenance II.

Subsequent anti-lymphoma treatment (chemotherapy, radiotherapy, immunotherapy) post-discontinuation of rituximab will also be presented separately for the SAF, by pre-randomization period (Induction and Maintenance I combined) and by randomized treatment for Maintenance II**.**

14. STUDY MEDICATION EXPOSURE

Exposure to study medication (rituximab and each chemotherapy drug during Induction, and rituximab for Maintenance I and II) will be presented for the SAF, by study treatment period, and for all patients in the SAF across the entire study.). The following parameters will be summarized:

- Duration of exposure (each of rituximab and chemotherapy) (months)
- Number of rituximab administrations
- Number of chemotherapy cycles
- Dose level (for chemotherapy drugs)
- Intended rituximab dose (per administration)

- o Actual rituximab dose (per administration and overall)
- o % of intended rituximab dose (per administration and overall)
- o Administration of rituximab on-time as per schedule per (per administration)

Interruptions and dose changes, are not taken into account for duration of exposure.

Duration of Induction chemotherapy exposure and number of cycles received will be summarized by the BSA subgroup categories defined in section 7.5.

14.1. DERIVATIONS

Duration of exposure (months) = (date of last study medication administration in study treatment period – date of first study medication administration in study treatment period + 1) *12 / 365.25.

For the entire study period duration of exposure = date of last study medication administration in the study – date of first study medication administration in Induction + 1) *12 / 365.25.

Number of administrations = the number of rituximab administrations where dose is not 0

Number of study drug cycles = the number of cycles where administration was done.

Actual rituximab dose overall = sum of actual total dose given across all cycles.

% of intended rituximab dose per cycle = 100 x actual total dose given / intended total dose. If intended total dose is not provided, the percentage cannot be derived.

% of intended rituximab dose overall = 100 x [sum of actual total dose given across all cycles] / [sum of intended total dose across all cycles]. Only cycles where the intended total dose is not missing are included in the numerator and denominator.

15. EFFICACY OUTCOMES

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is PFS_{rand}. This is defined as the time from date of randomization to the date of first documented disease progression or death, whichever occurs first. Progression will be based on tumor assessment made by the investigator according to the Cheson response criteria for indolent lymphoma or the recommendations for Waldenström's macroglobulinemia or where the documented reason for either end of treatment or end of study is disease progression.

Any patients in the ITT_{rand} population who have not experienced documented disease progression or death at the time of analysis and patients who are are withdrawn from the study without documented progression or lost to follow-up will have PFS_{rand} censored at their last tumor assessment date.

Patients without post baseline tumor assessments but known to be alive will have PFS_{rand} censored at the time of randomization.

15.1.2. Missing Data Methods for Primary Efficacy Variable

Primary efficacy data for patients who are lost to follow-up will be handled as described in Section 15.1.1.

15.1.3. Primary Analysis of Primary Efficacy Variable(s)

The primary objective is to evaluate the efficacy of a SC formulation of rituximab in terms of PFS_{rand} to either prolonged rituximab maintenance until progression (Maintenance II) or observation in patients with relapsed or refractory, indolent non-Hodgkin's lymphoma who responded to Induction and initial 2 years maintenance therapy (Maintenance I).

> PFS_{rand} will be graphically presented using the Kaplan-Meier curves. The median PFS_{rand} with 95% confidence interval will be reported for each treatment arm, along with Kaplan-Meier based estimates (and 95% confidence intervals) of PFS_{rand} at 6, 9, 12, 15 and 18 months post-randomization.

The difference in PFS_{rand} between the two treatment arms (rituximab versus observation) will be tested with a stratified log-rank test using the stratification factors as defined in section 7.1.

Furthermore, for the primary endpoint PFS_{rand} a Cox regression model will be used to estimate the hazard ratio for rituximab vs observation, along with the 95% confidence interval and p-value of the hazard ratio. The stratification factors defined in Section 7.1 will be included as factors in the model.

To supplement the summaries of PFS and PFS_{rand}, the median follow-up time (and associated 95% confidence intervals) will be reported for total patients and for randomized patients by arm. The median follow-up times will be calculated using the reverse Kaplan-Meier method. The reverse Kaplan-Meier plot of progression free survival will also be presented for both PFS and PFS_{rand}.

15.1.4. Sensitivity Analyses of Primary Efficacy Variable

In addition to the stratified log-rank test to compare the randomized treatment arms, an unstratified log-rank test p-value will be calculated.

Furthermore, for the primary endpoint PFS_{rand}, two additional Cox proportional hazards regression models will be used to estimate the hazard ratio for rituximab vs observation, along with the 95% confidence interval and p-value of the hazard ratio. CR/PR at the end of Maintenance I (prior to randomization) will be added along with the stratification factors as covariates in one of the models, while the second model will have no covariates.

The PP_{rand} population will be used for a sensitivity analysis of the primary analysis of the primary efficacy variable and the above mentioned sensitivity analyses.

15.1.5. Subgroup Analyses of Primary Efficacy Variable

Subgroup analyses will be performed on PFS_{rand} for the subgroups (including the stratification factors) defined in Section 7.5. Within each subgroup PFS_{rand} will be graphically presented using the Kaplan-Meier curves for each treatment arm.

Additionally, within each subgroup a Cox proportional hazards regression model on PFS_{rand} will be used to estimate the hazard ratio for rituximab vs observation, along with the 95% confidence interval of the hazard ratio. The model will not contain any covariates. A forest plot of the hazard ratios and 95% confidence intervals within each subgroup will be produced.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed on the ITT population.

Efficacy will be evaluated in terms of TTF, ORR at the end of induction and the end of Maintenance I, OS_{regist} and OS_{rand}, TNLT, Time in Follow-up, PR to CR conversion rate at the end of Maintenance I, and PFS measured from the first Induction dose of rituximab PFS_{regist}. The secondary objectives are to evaluate the efficacy and safety of SC rituximab during either Induction, initial 2-year maintenance (Maintenance I) or randomized treatment period (Maintenance II) whichever is appropriate.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. Progression-Free Survival from date of first Induction treatment

Progression-free survival from date of first Induction treatment (PFS_{regist}) is defined as the time from date of first rituximab dose in the Induction Period to the date of first documented disease progression, or death from any cause.

15.2.1.2. Time to Treatment Failure

Time to treatment failure (TTF) is defined as the time from date of first rituximab dose in the Induction Period to the date of any treatment failure, including disease progression, discontinuation of treatment for any reason, initiation of new anti-lymphoma treatment, or death.

15.2.1.3. Overall Response Rate

Overall response rate (ORR) is defined as the proportion of responders at the end of the Induction Period. A responder is defined as a patient experiencing either CR or PR tumor response according to the Cheson response criteria for indolent lymphoma or the recommendations for Waldenström's macroglobulinemia.

15.2.1.4. Overall Survival

Overall survival from first Induction dose of rituximab (OS_{regist}) is defined as the time from the date of the first dose of rituximab in the Induction Period until the date of death, irrespective of cause.

Overall survival from randomization (OS_{rand}) is defined as the time from randomization until the date of death irrespective of cause.

15.2.1.5. Time to Next Lymphoma Treatment

Time to next lymphoma treatment (TNLT) is defined as the time from the date of first rituximab dose in the Induction Period to the date of first documented intake of any new antilymphoma treatment (chemotherapy, radiotherapy, immunotherapy, etc.).

Intake of new antilymphoma medication will be identified as those entered into the Anti-Cancer treatment for NHL concomitant medication page of the eCRF.

15.2.1.6. PR to CR Conversion Rate

PR to CR Conversion rate is defined as the proportion of patients with PR prior to maintenance therapy (i.e. at the end of the Induction Period) who achieve CR while on rituximab during Maintenance I. Response will be determined by the investigator according to the Cheson response criteria for indolent lymphoma or the recommendations for Waldenströms's macroglobulinemia.

15.2.2. Censoring Rules and Missing Data Methods For Secondary Efficacy Variables

For the time to event secondary efficacy variables, patients who have experienced none of these events at the time of analysis and patients who are lost to follow-up will be censored as follows:

PFS_{regist}: censored at their last clinical assessment date

TTF: censored at their last clinical assessment date

OS_{regist} and OS_{rand}: censored at the last known date they were alive - from the *Follow-up Survival* page of the (e)CRF or latest clinical assessment if later than the date from the *Follow-up Survival* page.

TNLT: patients, who do not have documentation that a new anti-lymphoma treatment has started and patients who are lost to follow-up, will be censored at their last visit where the assessment for start of any new lymphoma medication was made.

For ORR, patients in the ITT population with a missing or unknown response assessment at the end of the Induction Period, for any reason (including death, withdrawal from treatment/study or loss to follow-up), will be considered as non-responders

For PR to CR conversion rate, patients with a missing or unknown response during Maintenance I, for any reason (including death, withdrawal from treatment/study or loss to follow-up), will be considered as not having a complete response during Maintenance I.

For analyses of ORR and PR to CR conversion rate, the response at the end of Induction and end of Maintenance I will be derived based on the investigator's assessment as captured in the (e)CRF.

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

Each of the time to event secondary efficacy endpoints (PFS_{regist}, TTF, OS_{regist}, OS_{rand} and TNLT) will be presented graphically using Kaplan-Meier curves. The median and the corresponding 95% confidence interval will be reported for overall (ITT) and for each randomized treatment group along with Kaplan-Meier based estimates (and 95% confidence intervals) at 6, 9, 12, 15 and 18 months post-randomization for OS_{rand}.and at 6, 9, 12, 18, 24 and 30 months for PFS_{regist}, TTF, OS_{regist}, and TNLT. The difference in each of these time to event secondary efficacy endpoints between the two treatment arms (rituximab versus observation) will not be formally tested and a disclaimer will be added to the descriptive statistics as information prior randomisation is included introducing a bias .

PFS_{regist}, and OS_{regist} will be summarized in tables and also be presented graphically using Kaplan-Meier curves split by diseases type.

The analyses of PFS_{regist}, TTF, OS_{regist}, and TNLT, were specified in the clinical study protocol, as *being performed the same way as the primary variable PFS_{rand}*. Since these endpoints include pre-randomization information, direct statistical comparisons between the two-groups is not possible and comparisons between the two randomized groups is not statistically valid.. Therefore only descriptive statistics will be provided and Kaplan-Meier estimates by randomised arm will be provided.

In addition PFSreg and OS reg will be analysed for all patients (ITT) overall and split by disease type.

Additionally, within each subgroup a Cox proportional hazards regression model on OS_{rand} will be used to estimate the hazard ratio for rituximab vs observation, along with the 95% confidence interval of the hazard ratio. The model will not contain any covariates. A forest plot of the hazard ratios and 95% confidence intervals within each subgroup will be produced.

ORR will be analyzed by frequency tables including a 95% two-sided Pearson-Clopper confidence interval. ORR will be summarized by each of the subgroups defined in section 7.5.

In addition, logistic regression will be performed to assess the influence of baseline covariates on ORR. The baseline covariates are those described in section 7.1. The covariates will be included simultaneously in the logistic regression model.

Odds ratios for ORR, 95% confidence intervals and p-values will be presented for each covariate. For the covariates with more than two categories, the reference categories in the logistic regression models will be as follows: Low risk FLIPI, Low BSA and Induction Chemotherapy = Bendamustine. For these covariates an overall p-value for the covariate will be presented as well as p-values for individual categories of the covariate vs the reference category.

The PR to CR conversion rate will be summarized only (including a 95% two-sided Pearson-Clopper confidence interval). Summaries of the PR to CR conversion rate will be performed for each of the subgroups described in section 7.5.

15.3. ADDITIONAL EFFICACY

The individual components of response at the end of Induction and end of Maintenance I will be summarized for the ITT population. The components will be based on the derived response for analyses described in section 15.2.2. The components are complete response, complete response unconfirmed (CRu) partial response, stable disease, progressive disease. These components will also be summarized by the subgroups defined in section 7.5.

15.4. EXPLORATORY EFFICACY

15.4.1. EXPLORATORY EFFICACY VARIABLES & DEFINITIONS

15.4.1.1. [redacted]

[redacted]

- [redacted]
- [redacted]

15.4.1.2. [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

15.4.2. Missing Data Methods for Exploratory Efficacy Variables

[redacted]

15.4.3. Analysis of Exploratory Efficacy Variables

[redacted]

[redacted]

[redacted]

16. Safety Outcomes

All outputs for safety outcomes will be based on the Safety Population per study treatment period.

Outputs will be provided for each study period (and by treatment received in Maintenance II), and for the entire study.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise

specified within the relevant section.

16.1. ADVERSE EVENTS

Adverse Events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary available at the time of reporting.

The period during which AEs were to be reported are described in Table 14 of the CSP. Since the periods for the majority of AEs (non-serious Grade 1/2 AEs) are dependent on time from last-dose, there is a longer period for AEs to be captured, for patients in the randomized rituximab arm in Maintenance II compared to the observation arm. This means that direct comparison of incidence of AEs between these arms is not possible.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication and up to and including 28 days after the last dose of study medication. TEAEs will be assigned to a study treatment period depending on whether the AE started or worsened in severity on or after the first dose of study medication in that study treatment period. A TEAE can only be assigned to one study treatment period. Adverse Events are defined as AEs that started or worsened in severity on or after the first dose of study medication. In all summaries of AEs no restriction with regards time since last dose of study medication is applied.

Table 2 Assignment of TEAEs and AEs to study periods

Date of AE onset/worsening in severity	Study treatment period assigned
All SAF patients	
Prior to first dose of rituximab in Induction Period	Not treatment emergent
On or after first dose of rituximab in Induction Period and up to and including 28 days after the last dose of study medication and prior to the first dose in Maintenance I For AE summaries this will be on or after first dose of rituximab in Induction Period and up to and including the earliest of the end of study or the first dose in Maintenance I.	Induction
On or after first dose of rituximab in Maintenance I and up to and including 28 days after the last dose of study medication and prior to the first dose (for randomized patients who received rituximab in Maintenance II) or date randomized for randomized patients who did not receive rituximab) in Maintenance II For AE summaries this will be on or after first dose	Maintenance I

Date of AE onset/worsening in severity	Study treatment period assigned
of rituximab in Maintenance I and up to and including the earliest of the end of study or randomization into Maintenance II.	
Randomized patients who received rituximab in Maintenance II	
On or after first dose of rituximab in Maintenance II and up to and including 28 days after the last dose of study medication For AE summaries this will be on or after first dose of rituximab in Maintenance II and up to the end of study.	Maintenance II
Randomized patients who did not receive rituximab in Maintenance II	
On or after randomization date and up to and including 28 days after the last dose of study medication in Maintenance I For AE summaries this will be on or after randomization in Maintenance II and up to the end of study.	Maintenance II

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent.

All treatment emergent AEs will be summarized by study treatment period (and by treatment received for Maintenance II where the actual treatment group is rituximab if the patient received at least one dose of rituximab in Maintenance II, and observation otherwise).

Summaries of number of patients (and number of AEs) within each of the categories described in the sub-section below, will be provided as specified in the templates. Within each study treatment period, a patient with more than one occurrence of the same AE in a particular system organ class/preferred term will be counted only once in the total of those experiencing AEs in that particular system organ class/preferred term. If a patient experiences the same AE 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 be accounted for as "missing" in the tables. If a patient has an event with missing CTC grade and also an event with non-missing CTC grade, for a SOC or for a particular SOC/PT then the maximum non-missing CTC grade will be counted, with the number of such missing CTC grades recorded in the footnotes of relevant tables.

The following AE summary tables will be produced by study treatment period (and by treatment received in Maintenance II) unless otherwise stated below:

o All TEAEs

- All TEAEs (includes those not meeting criteria of TEAEs displayed for Maintenance II and Overall Total only)
- All TEAEs by age and sex subgroups
- All TEAEs during Induction by chemotherapy regimen (all regimens and not just those described in section 7.5)
- All TEAEs during Induction by BSA category
- All TEAEs during Maintenance I by BSA category
- All TEAEs by severity grade
- All TEAEs CTC Grade 3 or higher
- All AEs CTC Grade 3 or higher (includes those not meeting criteria of TEAEs displayed for Maintenance II and Overall Total only)
- All TEAEs CTC Grade 3 or higher by age and sex subgroups
- All AEs CTC Grade 3 or higher by age and sex subgroups (includes those not meeting criteria of TEAEs displayed for Maintenance II and Overall Total only)
- All TEAEs during Induction CTC Grade 3 or higher by BSA category
- Serious TEAEs
- Serious AEs (includes those not meeting criteria of TEAEs displayed for Maintenance II and Overall Total only)
- Serious TEAEs by BSA category, age and sex subgroups
- Serious AEs by BSA category, age and sex subgroups (includes those not meeting criteria of TEAEs displayed for Maintenance II and Overall Total only)
- Serious TEAEs during Induction by chemotherapy regimen
- Serious TEAEs during Induction by BSA category
- Non-Serious TEAEs
- TEAEs leading to rituximab interruption or delay
- TEAEs leading to rituximab discontinuation
- TEAEs related to rituximab
- Serious TEAEs related to rituximab
- IRRs/ARRs
- IRRs/ARRs of CTC Grade 3 or higher by cycle
- Serious IRRs/ARRs by cycle
- AEs of special interest (includes those not meeting criteria of TEAEs displayed for Maintenance II and Overall Total only)
- AEs leading to death (includes those not meeting criteria of TEAEs displayed for Maintenance II and Overall Total only)
- AEs related to rituximab leading to death (includes those not meeting criteria of TEAEs displayed for Maintenance II and Overall Total only)

Listings will include TEAEs and Non-TEAEs.

16.1.1. ALL TEAEs

Incidence of AEs and the Incidence of TEAEs will be presented by SOC and PT and also broken down further by severity and for those related to study medication.

Since all patients in the Induction Period receive IV rituximab at Cycle 1, TEAEs occurring after the first study drug administration and prior to subsequent study drug administration will be summarized separately. For patients with no subsequent study drug administration, TEAEs occurring up to 28 days after the date of the Cycle 1 dose will be included.

16.1.2. TEAEs CTC Grade 3 or Higher

AEs will be graded using the CTC system v 4.0. NCI-CTC grades, as indicated by the Investigator, are graded from 1 to 5. TEAEs with a grade of 3 or higher and a separate summary of grade 3 or higher AEs will be summarized by SOC and PT.

16.1.3. Severity of TEAEs

AEs will be graded using the CTC system v 4.0. NCI-CTC grades, as indicated by the Investigator, are graded from 1 to 5. Incidence of TEAEs will be presented by SOC and PT and severity of event.

16.1.4. Serious Adverse Events

Serious AEs are those events recorded as "Serious" on the Adverse Events page of the (e)CRF. A summary of serious TEAEs and a separate summary of serious AEs will be presented by SOC and PT.

16.1.5. TEAEs Leading to Interruption and Discontinuation of Study Medication

TEAEs leading to permanent interruption, delay or discontinuation of study medication will be identified by using the questions "Action taken regarding study treatment rituximab" on the (e)CRF AE page.

The following categories will be summarized by SOC and PT:

- TEAEs leading to rituximab interruption or delay
- TEAEs leading to rituximab discontinuation

16.1.6. TEAEs Related to Rituximab

Relationship to rituximab, as indicated by the Investigator, is classed as "Related", "Not related" and "Not applicable". Incidence of rituximab related TEAEs will be presented. If within a study treatment period, a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

16.1.7. Infusion-Related Reactions (IRR) and Administration-Related Reactions (ARR)

AEs will be counted as an IRR if the AE occurred within 24 hours after administration of IV rituximab and is

considered related to treatment.

AEs will be counted as an ARR if the AE occurred within 24 hours after administration of SC rituximab and is considered related to treatment.

AEs with onset date = the date of a dose of study drug or the day after a dose of study drug will be considered to have occurred within 24 hours after study drug administration.

IRRs/ARRs will be summarized by SOC and PT.

16.1.8. Adverse Events Of Special Interest

AEs of special interest as assessed by the investigator ("Is this an AE of special interest?" responded "Yes" in the AE page) will be summarized by SOC and PT.

16.1.9. Adverse Events Leading to Death

AEs leading to death are those events which are recorded with outcome 'Died' and/or toxicity grade 5 on the Adverse Events page of the (e)CRF. A summary of AEs leading to death by SOC and PT will be prepared.

16.2. Deaths

If any patients die during the study as recorded on the "deaths" page of the (e)CRF, the number of patients per death reason will be presented in a summary table and a data listing.

16.3. Laboratory Evaluations

Laboratory evaluations will be included in the reporting of this study for hematology, biochemistry and immunoglobulin tests. A list of laboratory assessments to be included in the outputs is included in the CSP, section 5.3.

Presentations will use SI Units. It is anticipated that the data will be provided in SI units with no additional conversions required.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification, or "> X", i.e. above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Baseline values, values by visit and change from Baseline by visit (for quantitative measurements)
- Shift tables of NCI CTCAE grade at Baseline versus worst grade post-baseline (hematology and biochemistry parameters only)

For these summaries laboratory data included all visits up to and including the end of treatment visit will be included.

These summaries will be performed study treatment period baseline. Only visits from the study treatment period of interest will be included as post-baseline visits.

Values outside the laboratory reference range will be flagged in listings.

NCI CTCAE grades for the shift tables will be derived by [redacted] Biostatistics based on the following document:

http://evs.nci.nih.gov/ftp1/CTCAE/Documentation/CTEP_Guidance_Quant-Grade_2010-05-17.doc

16.4. ECG EVALUATIONS

The overall Electrocardiogram (ECG) assessment ('Normal', 'Abnormal, not clinically relevant, 'Abnormal, clinically relevant) at screening/baseline will be summarized for all patients.

16.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Body Temperature (°C)

Baseline value and change from Baseline by visit will be summarized.

These summaries will be performed using study treatment period baseline. Only visits from the study treatment period of interest will be included as post-baseline visits.

16.6. PHYSICAL EXAMINATION

Physical examination abnormalities at screening were to be recorded as medical history.

The limited physical examination during the study is aimed to identify the clinically significant abnormalities which should be reported as AEs. Physical examination data will not be summarized or listed separately.

16.7. ECOG PERFORMANCE STATUS

Shift tables will be produced of Eastern Cooperative Oncology Group (ECOG) score at study period baseline

versus worst score post-baseline.

Additionally, the percentage of patients in each ECOG score category at each time point will be displayed in bar charts.

APPENDIX 1 Programming Conventions for Outputs

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-dd and HH:MM

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, study treatment periods/treatment groups will be represented as follows and in that order:

Treatment Period/Treatment Group	For Tables and Graphs	For Listings
Induction	Induction	N/A
Maintenance I	Maintenance I	N/A
Maintenance II/ Rituximab	Rituximab	Rituximab
Maintenance II/ Observation	Observation	Observation
Maintenance II/ Total	Total (under banner '—Maintenance II--')	N/A
Total	Total (no header spanning text)	N/A
Not Randomized	Not Randomized (for efficacy). These patients will fall into Induction and Maintenance I.	Not Randomized

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- randomized treatment group (or Maintenance II treatment received if it's a safety output), first by rituximab, then observation;
- patient ID,

- date (where applicable).

For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known, Partial or Missing	Follow the rules in Table 2.
Partial, but known components show that it cannot be on or after date of first dose of rituximab in the study	Known, Partial or Missing	Not TEAE
For patients who underwent Observation in Maintenance II: Partial, but known components show that it is definitely more than 28 days post randomization For all other patients: Partial, but known components show that it is definitely more than 28 days post last dose of rituximab	Known, Partial or Missing	Not TEAE
Missing, or partial and known components show that it could be a TEAE	Known	If stop date < date of first dose of rituximab in the study then not TEAE If stop date ≥ date of first dose of rituximab in the study

START DATE	STOP DATE	ACTION
		then TEAE.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then follow the rules in the above row of this table.
	Missing	Assume TEAE

Note: If potential TEAE in more than one study period (having considered the AE stop date) then the event will be assigned to the earliest of the potential periods.

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	Follow the rules in Table 1
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then follow the rules in Table 1.
	Missing	If stop date is missing could never be assumed a prior medication, assign as concomitant or post-treatment based on the rules in Table 1.
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then follow the rules in Table 1.
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then follow the rules in Table 1.
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown). If stop date is missing could never be assumed a prior medication; assign as concomitant or post-treatment based on the rules in Table 1.
Missing	Known	If start date is missing, do not assign as post-treatment. Only use stop date and assign as prior or concomitant based on the rules in Table 1.
	Partial	If start date is missing, do not assign as post-treatment. Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then only use stop date and assign as prior or concomitant based on the rules in Table 1.

START DATE	STOP DATE	ACTION
	Missing	Assign as concomitant

Note: Medications can be concomitant in more than one study period.