

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: NCT 01461928

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SPONSOR: F. HOFFMANN-LA ROCHE LTD

Grenzacherstrasse 124
CH-4070 Basel, Switzerland

CLINICAL STUDY PROTOCOL

TITLE: 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

PROTOCOL NUMBER: MO25455

VERSION NUMBER: 4.0

EUDRACT NUMBER: 2010-023407-95

IND NUMBER: Not applicable

TEST PRODUCT: Rituximab (RO 045-2294)

MEDICAL MONITOR: Dr. [REDACTED]

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 19 April 2011

DATES AMENDED: Version 2: 26 July 2012
Version 3: 23 September 2012
Version 4: 06 July 2017

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PROTOCOL AMENDMENT, VERSION 4.0: RATIONALE

The intention of the protocol has been to collect adverse event (AE) and serious adverse event (SAE) information from patients during maintenance II on arms A and B in order to perform a safety comparison as part of the secondary objective. However Table 14 in protocol version 3.0 permits the cessation of AE and SAE data collection from patients on arm B 28 days post-treatment. Protocol version 4.0 was written to balance the AE and SAE reporting requirements.

- Table 14 has been revised to clarify the AE and SAE reporting duration.

Additional minor changes have been made to improve clarity and consistency.

- The end of study section in the synopsis of protocol was revised to clarify that maintenance II arm B patients are expected to follow the same schedule of assessment as patients on arm A
- Protocol cover page, protocol amendment acceptance form, and appendix 7 under the section of medical monitor contact information for all sites have been revised to reflect the new Roche medical contact.
- Protocol cover page has been revised to reflect the new Roche statistician.
- The number of patients section in the synopsis of protocol and Section 3.2 were updated to reflect the final number of patients randomized to maintenance II therapy and the enrolment time line.
- Section 3.1, Table 5 footnotes (i) and (t), section 5.1.3, section 5.1.3.2, section 5.1.5, section 5.2.1 were revised to remove the reference to stable disease at the end of maintenance I.
- Section 3.1.3 has been revised to clarify that the trial can be stopped if the 129th PFS event has been reported.
- In Table 5 for the rituximab treatment administration row the footnote link in the Maintenance II column was corrected.
- In the notes section for Table 5, and section 5.1.6 clarification was added regarding the movement of patients in to off-treatment follow-up following the end of treatment or their participation in maintenance II arm B.
- Section 7.3 has been revised removing the guidance to record and assess the individual symptoms of infusion related reactions and administration related reactions.
- Spelling errors were corrected throughout the protocol

This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 4.0: SUMMARY OF CHANGES

GLOBAL CHANGES

██████████ International Scientific Director has replaced ██████████ International Medical Director as protocol approver and Medical Monitor Contact Information for All Sites.

██████████ Statistician has replaced ██████████ Statistician.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 3.1: OVERVIEW OF STUDY DESIGN

Old Text:

Response assessment will be conducted by the Investigator every 6 months during Maintenance I according to the Cheson response criteria for indolent lymphoma¹ (see Appendix 1) or by the recommendations for Waldenström's macroglobulinemia² (see Appendix 2). 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. ~~Patients with SD at the end of Maintenance I will come off study treatment and will enter Off-Treatment Follow-Up, being followed for PD and survival until the end of the study.~~

SECTION 3.2: NUMBER OF PATIENTS / ASSIGNMENT TO TREATMENT GROUPS

Old text:

Approximately 700 enrolled patients ~~are~~ expected to yield a minimum of 330 randomized patients (Maintenance II).

The ~~estimated~~ recruitment period ~~is~~ approximately 24 months.

New text:

Approximately 700 enrolled patients ~~were~~ expected to yield a minimum of 330 randomized patients (maintenance II). ~~At the conclusion of enrolment and all randomizations 694 patients were enrolled and 276 patients were randomized to maintenance II.~~

The recruitment period ~~was expected to be~~ approximately 24 months. ~~Enrolment of the 694 patients required 31 months~~

TABLE 5: SCHEDULE OF ASSESSMENTS

In Table 5 for the rituximab treatment administration row the footnote in the Maintenance II column was incorrectly associated to footnote (t). The association was corrected to footnote (u).

Footnote (i):

Old text:

Patients with SD at the end of either Induction or Maintenance I will come off study treatment and will enter Off-Treatment Follow-Up, being followed every 6 months for PD and survival until the end of the study.

Note:

New text:

After the end-of-treatment or the end of participation in observation arm B all patients will enter Off-Treatment Follow-up and be followed for resolution of AEs related to SC rituximab induction/maintenance therapy as per Table 14, survival, disease status (which might include bone marrow and tumour assessment if PD not already documented) and whether a new anti-lymphoma treatment has been started.

SECTION 5.1.3: Assessments during the Treatment Period

Old text:

Patients with SD at the end of either Induction or Maintenance I will come off study treatment and will enter Off-Treatment Follow-Up, being followed every 6 months for PD and survival until the end of the study.

SECTION 5.1.3.2: Maintenance I

Old text:

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. ~~Patients with SD at the end of Maintenance I will come off study treatment and will enter Off-Treatment Follow-Up, being followed for PD and survival until the end of the study.~~

SECTION 5.1.5: End of Treatment Assessments

Old text:

Patients with SD at the end of either Induction or Maintenance I will come off study treatment and will enter Off-Treatment Follow-Up, being followed every 6 months for PD and survival until the end of the study.

SECTION 5.1.6: Off-Treatment Follow-up

Old text:

After discontinuation of study treatment patients will enter Off-Treatment Follow-up and will be followed every 6 months until the end of the whole study for resolution of all SAEs, survival, disease status (which might include bone marrow and tumour assessment if PD not already documented) and whether a new anti-lymphoma treatment has been started.

New text:

After discontinuation of study treatment or participation in observation Arm B patients will enter Off-Treatment Follow-up and will be followed every 6 months until the end of the whole study for resolution of all SAEs, survival, disease status (which

might include bone marrow and tumour assessment if PD not already documented) and whether a new anti-lymphoma treatment has been started.

SECTION 5.2.1: Tumour Response Criteria

Old text:

At the end of Maintenance I, patients with PD ~~or SD~~ will come off study treatment. Patients with PD will start Off-Treatment Follow-Up, being followed for survival until the end of the study. ~~Patients with SD will enter Off Treatment Follow Up, being followed for PD and survival until the end of the study.~~ Patients having a CR or PR will be randomized and will continue into Maintenance II.

SECTION 5.2.1: Tumour Response Criteria

Old text:

At the end of Maintenance I, patients with PD ~~or SD~~ will come off study treatment. Patients with PD will start Off-Treatment Follow-Up, being followed for survival until the end of the study. ~~Patients with SD will enter Off Treatment Follow Up, being followed for PD and survival until the end of the study.~~ Patients having a CR or PR will be randomized and will continue into Maintenance II.

Table 14: Duration of Reporting and Follow-up of Adverse Events

Table 14 has been revised to clarify the AE and SAE reporting duration.

AE row was divided in to two rows – one for AEs grade 1 and 2; a second for AEs ≥ grade 3. Each row contains specific guidance for the grade of AE.

SECTION 7.2.3: Reporting of Infusion-Related Reactions (IRRs) or Administration-Related Reactions (ARRs)

Old text:

~~IRRs/ARRs must be recorded on the Adverse Event eCRF. In order to capture potential differences in terms of clinical relevance of IRRs/ARRs, it is important to report and assess the intensity of all individual symptoms of the IRR/ARR.~~



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Grenzacherstrasse 124
CH-4070 Basel, Switzerland

**CLINICAL STUDY PROTOCOL
PROTOCOL NUMBER 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

**RO 045-2294
RITUXIMAB (MABTHERA®)
EUDRACT NUMBER 2010-023407-95
VERSION 4.0**

PROTOCOL APPROVAL

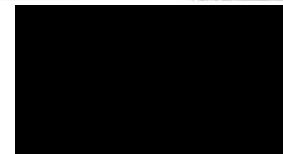
Protocol Number / Version: **MO25455 / Version 4.0**

Protocol approved by:

International Scientific Director



10th July 2017
Date



Signature

Statistician



11th July 2017
Date



Signature

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: 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

PROTOCOL NUMBER: MO25455

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EUDRACT NUMBER: 2010-023407-95

IND NUMBER: Not applicable

TEST PRODUCT: Rituximab (RO 045-2294)

MEDICAL MONITOR: Dr. [REDACTED]

SPONSOR: F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

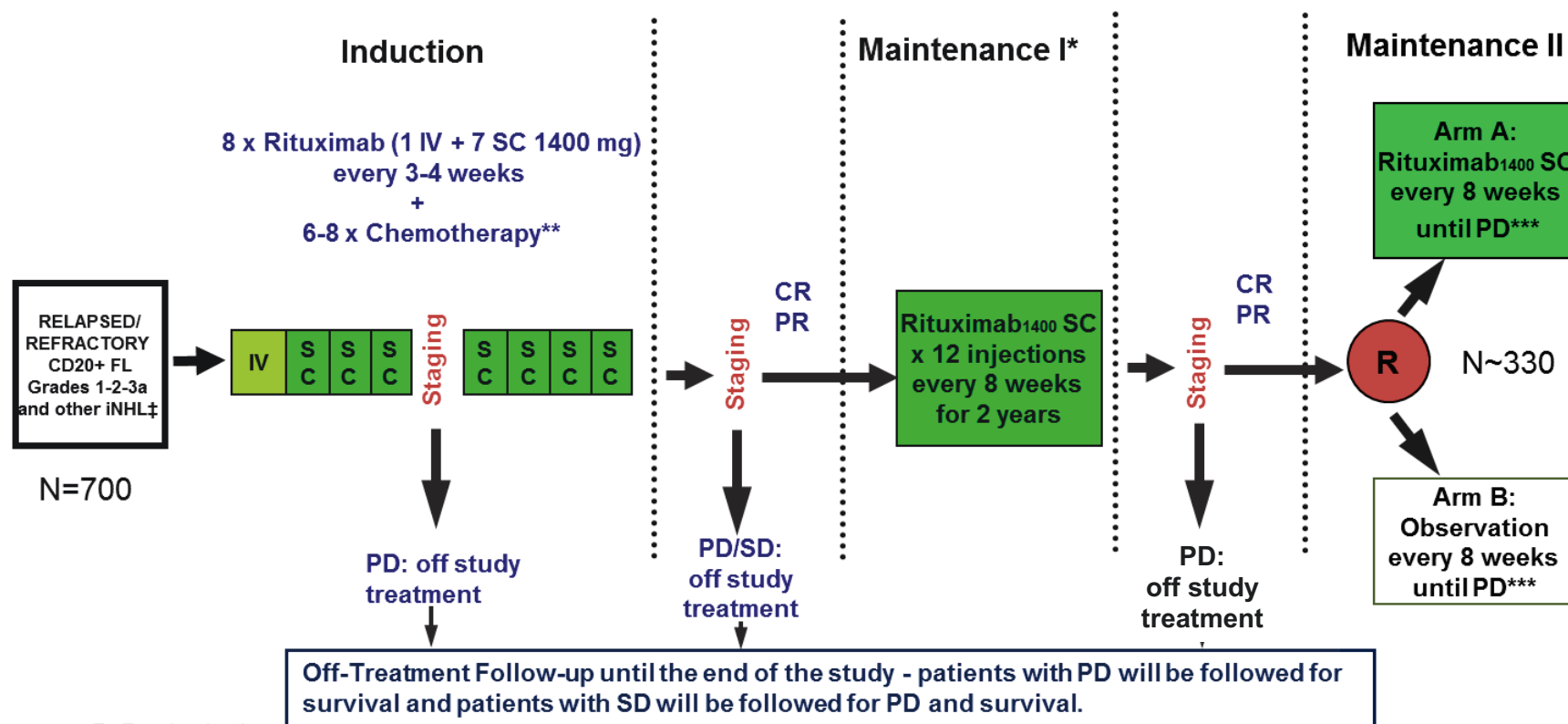
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SYNOPSIS OF PROTOCOL MO25455

TITLE	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.
SPONSOR	F. Hoffmann-La Roche Ltd
CLINICAL PHASE	IIIb
INDICATION	Patients with relapsed or refractory CD20+ follicular non-Hodgkin's lymphoma (NHL) Grade 1, 2 or 3a, or other CD20+ indolent NHL (Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma, marginal zone lymphoma), according to the WHO classification system.
OBJECTIVES	<p><u>Primary objective:</u></p> <p>To evaluate the efficacy of a subcutaneous (SC) formulation of rituximab in term 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 who responded to Induction and initial 2 years maintenance therapy (Maintenance I).</p> <p><u>Secondary objectives:</u> 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 Event-Free Survival (EFS), 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/administration-related reactions (IRRs/ARRs) and immunoglobulin (Ig) quantification.</p> <p><u>Exploratory objectives:</u> [REDACTED]</p> <p>[REDACTED]</p>
TRIAL DESIGN	Multicentre, multinational, open label, randomized study

Figure 1 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

NUMBER OF PATIENTS	<p>Approximately 700 enrolled patients were expected to yield a minimum of 330 patients randomized to maintenance II therapy with SC rituximab continued until progression or to observation after they completed and responded to Induction and initial 2-year maintenance I therapy. The final number of patients randomized to maintenance II therapy was 276.</p>
TARGET POPULATION	<p>The target population will consist of adults with relapsed or refractory CD20+ follicular NHL Grade 1, 2 or 3a, or other CD20+ indolent NHL (Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma, marginal zone lymphoma) according to the WHO classification system.</p> <p>ENROLMENT CRITERIA:</p> <p>Patients must fulfil all of the following criteria at enrolment (i.e. prior to the first dose of Induction Treatment):</p> <p>Inclusion Criteria</p> <ol style="list-style-type: none"> 1. Signed, written informed consent form. 2. Age \geq 18 years. 3. Histologically confirmed, CD20+ follicular NHL Grade 1, 2 or 3a, or other CD20+ indolent NHL (Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma, marginal zone lymphoma) according to the WHO classification system. 4. Patients must have received, and must have relapsed or been refractory to, one or more lines of adequate therapy <i>prior to enrolment</i>, including at least one line consisting of immunotherapy and/or chemotherapy and/or radiotherapy. <p>Note: Rituximab administration in first line is not mandated, but preferred.</p> <ol style="list-style-type: none"> 5. Eastern Cooperative Oncology Group (ECOG) performance status \leq 2. <p>Exclusion Criteria</p> <p>DISEASE-SPECIFIC:</p> <ol style="list-style-type: none"> 1. Transformation to high-grade lymphoma. 2. Patients with aggressive lymphoma (e.g. mantle cell lymphoma). 3. Presence or history of central nervous system (CNS) lymphomatous disease (e.g., CNS lymphoma or lymphomatous meningitis). <p>OTHER MEDICAL CONDITIONS OR TREATMENTS:</p> <ol style="list-style-type: none"> 4. Other malignancy within 5 years prior to enrolment, with the following exceptions (as long as curatively treated): carcinoma

in situ of the cervix, squamous cell carcinoma of the skin, or basal cell skin cancer. Cervical carcinoma stage 1B or less, breast cancer *in situ*, or localized prostate cancer stage T1c or less may be considered, provided that the patient was treated with curative intent and has been relapse- and metastasis-free for at least 2 years prior to enrolment.

5. Inadequate haematological function within 28 days prior to the first rituximab induction dose, defined as any of the following (unless the abnormality is related to involvement of bone marrow by NHL):
 - a. Haemoglobin (Hb) < 9.0 g/dL (5.6 mmol/L)
 - b. Absolute neutrophil count (ANC) < $1.0 \times 10^9/L$ (1,000/ μ L)
 - c. Platelet count < $100 \times 10^9/L$ (100,000/ μ L); lower platelet count (but not below $50 \times 10^9/L$) is acceptable if due to toxicity of previous chemotherapy and not accompanied by bleeding.
6. Patients with severe autoimmune cytopenias as assessed by the physician.

Note: Coombs positive patients without clinical signs of autoimmune haemolytic anemia are eligible for enrolment.
7. Inadequate hepatic function prior to the first rituximab induction dose, defined as any of the following:
 - a. Total bilirubin > 1.5 times the upper limit of normal (ULN). Note: patients with documented Gilbert disease may be enrolled if total bilirubin is $\leq 3.0 \times$ ULN.
 - b. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2.5 times the ULN
 - c. Alkaline phosphatase > 2.5 times ULN
8. Inadequate renal function prior to the first rituximab induction dose, defined as creatinine clearance (CrCl) < 30 mL/minute or serum creatinine > 2 mg/dL (197 μ mol/L).
9. Known human immunodeficiency virus (HIV) infection
10. Active and/or severe infection (e.g. tuberculosis, sepsis and opportunistic infections, active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection).
11. Other serious underlying medical conditions, which, in the Investigator's judgment, could impair the ability of the patient to participate in the study (e.g., uncontrolled diabetes mellitus,

gastric ulcers, active autoimmune disease).

12. Known or suspected hypersensitivity to components of the investigational product, including known hypersensitivity or previous anaphylactic reaction to murine antibodies or proteins.
13. Regular corticosteroid use within 28 days prior to the first rituximab induction dose, unless administered at a dose equivalent to < 20 mg/day prednisone/prednisolone.
Note: inhaled or topical corticosteroids are permitted.
14. Major surgery (excluding lymph node biopsy) within 28 days prior to the first rituximab induction dose.
15. Treatment with an investigational product within 30 days prior to enrolment.

GENERAL:

16. Inability to provide informed consent.
17. Life expectancy of less than 6 months.
18. History of poor compliance during previous lines of therapy.
19. Pregnant or breastfeeding patients. A negative serum pregnancy test is required 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 rituximab 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.
20. Fertile men or women of childbearing potential who do not agree to use a highly effective measure of contraception (such as oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) throughout the study and for at least 12 months after the last dose of rituximab.

CRITERIA FOR PROLONGED MAINTENANCE (Maintenance II):

In addition to the above listed enrolment criteria, patients must fulfil the following criteria in order to be randomized:

1. Completed rituximab-based Induction and initial 2-year maintenance therapy with subcutaneous rituximab (Maintenance I).
2. PR or CR as confirmed by computerized tomography (CT) after Maintenance I. Response assessment is completed according to

	<p>the 1999 International Working Group (Cheson) response criteria for lymphoma¹ or by the recommendations for Waldenström's macroglobulinemia² (see Appendix 2).</p> <p>Randomization will occur using a centralized interactive voice/web response system (IVRS/IWRS) in a 1:1 fashion, stratified according to indolent NHL subtype (follicular lymphoma, non-follicular lymphoma), and Follicular Lymphoma International Prognostic Index (FLIPI) category (low risk, intermediate risk, high risk).</p>
LENGTH OF STUDY	<p>It is expected that approximately 700 patients will be enrolled.</p> <p>The total study duration is approximately 69 months, including:</p> <ul style="list-style-type: none"> • 24 months enrollment period • 6 - 8 months Induction period • 24 months initial rituximab SC maintenance (Maintenance I) • Minimum 15 months randomized period: observation only or maintenance treatment with SC rituximab continued until progression (Maintenance II) or End of Study (EOS), whichever occurs first.
END OF STUDY	<p>End of the study is defined as the last patient's last visit in Maintenance II. The study will end when all patients randomized in Maintenance II have been followed for at least 15 months after randomization, or earlier if one of the following is documented for all patients: disease recurrence, withdrawal from the study, loss to follow-up or death.</p> <p>Patients with progressive disease (PD) at any time during the study will come off study treatment and start Off-Treatment Follow-Up, being followed for survival until the end of the study. Patients with stable disease (SD) at the end of Induction will come off study treatment and will enter Off-Treatment Follow-Up, being followed every 6 months for PD and survival until the end of the study. During Maintenance II, patients in the SC rituximab maintenance arm will be treated until PD, unacceptable toxicity, withdrawal of patient consent or until the primary endpoint has been reached. All patients in Arm A (rituximab 1400 mg, fixed dose 8 weekly) and Arm B (observation, no treatment) will have either treatment or observation visits every 8 weeks until disease progression or EOS, whichever occurs first. Patients on both arms will be actively followed for safety, tumour response/progression, new anti-lymphoma treatments and survival by following the same visit schedule of assessments for at least 15 months after randomization. Enrolled patients who do not complete treatment per protocol for any reason will undergo the end-of-treatment assessment and enter Off-Treatment Follow-up. Arm B: Patients randomized to observation arm</p>

	will undergo the end-of-treatment assessment within 4 weeks of last dose but remain on the same schedule of assessments that Arm A patients are following. Patients on observation who meet one or more of the withdrawal criteria outlined in section 4.6 will enter Off-Treatment Follow-up should they agree to remain in the study.
INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	<p><u>Induction:</u></p> <p><u>Cycle 1:</u> IV rituximab 375 mg/m² body surface area (BSA) as a single infusion, followed by administration of chemotherapy, as applicable (see below).</p> <p><u>Cycles 2 to 8:</u> Each cycle will consist of a single SC injection of rituximab 1400 mg, followed by administration of chemotherapy (see below) and repeated every 3 - 4 weeks, depending on the combination chemotherapy regimen selected.</p> <p>Note:</p> <ul style="list-style-type: none"> Rituximab is always administered prior to chemotherapy (with the exception of the corticosteroid component). Patients who were not able to receive the full dose of rituximab at cycle 1 as a result of IRR should receive also the second rituximab dose intravenously. Patients who do not experience grade 3 or 4 IRR after the second rituximab infusion will receive the 3rd rituximab dose subcutaneously (cycle 3). Patients with grade 3 or 4 IRR after the second rituximab infusion will be withdrawn from receiving study treatment. <p><u>Initial Maintenance (Maintenance I):</u></p> <p>Rituximab 1400 mg (fixed dose), one SC injection every 8 weeks for 24 months (up to 12 injections), administered as described above (without chemotherapy). Maintenance therapy with SC rituximab must start within 8-12 weeks after the administration of the last dose of rituximab in the induction therapy.</p> <p><u>Prolonged Maintenance (Maintenance II):</u></p> <ul style="list-style-type: none"> Arm A: Rituximab 1400 mg (fixed dose), administered as described above (without chemotherapy) one SC injection every 8 weeks until disease progression or EOS, whichever occurs first. Arm B: Observation (no treatment)
CENTRES	This is a multinational, multicentre study.
NON-INVESTIGATIONAL MEDICAL PRODUCT(S)	Approved commercially available combination chemotherapy regimens
COMPARATOR DRUG DOSE/ ROUTE/	No active comparator will be used in the study.

REGIMEN	
ASSESSMENTS OF:	
- EFFICACY	<p>Tumour assessments will be based on CT scans of the neck (if clinically indicated), chest, abdomen and pelvis (if detectable by these techniques) to document nodal disease or organ involvement. Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach). The CT scan used for eligibility or response assessments may be up to 8 weeks old. Response assessments during and after the induction period and after maintenance therapy will be completed according to the International Working Group response (Cheson) criteria for lymphoma (please use version of year 1999 for CT scans)¹ or by the recommendations for Waldenström's macroglobulinemia² (see Appendix 2).</p> <p>The efficacy of SC rituximab will be evaluated during induction, Maintenance I, and Maintenance II in terms of PFS_{rand} and PFS_{regist} (from randomization and from the first rituximab induction dose, respectively), EFS, TNL, OS_{regist} and OS_{rand}, ORR, PR to CR conversion rate (full restaging, at the end of Maintenance I).</p>
- SAFETY	<p>All AEs occurring during the course of the study will be captured, regardless of their intensity / grading. Grading of AEs will be completed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTC-AE), version 4.0.</p> <p>Immunoglobulin (IgG, IgM and IgA) quantification will be completed at baseline, once a year during Maintenance I (maintenance injections #6 and #12), once a year during Maintenance II (Arm A) and in case of suspicious infections.</p>
PHARMACOKINETICS/ PHARMACODYNAMICS	N/A
QUALITY OF LIFE (QOL)	<div></div> <div></div> <div></div> <div></div>
PHARMACOECONOMIC SUB-STUDY	<p>A <i>Time in Motion</i> pharmacoeconomic sub-study will assess Medical Care Utilization (MCU) parameters to enable data collection on time of infusion and resource use based on a site protocol at selected sites. Details of the sub-study will be described in a separate protocol.</p>

STUDY PROCEDURES (summary)

After a patient has consented to participate in this study, the following procedures will be carried out:

- **Baseline assessment:** will be performed according to the Schedule of Assessments ([Table 5](#)).

See Section 6.1.4 for details about dose modifications, interruptions and delays for rituximab and chemotherapy.

- **Induction:** 8 cycles of rituximab will be administered in combination with 6 - 8 cycles of chemotherapy (bendamustine, CHOP, CVP, FCM, MCP, CHVP-IFN, chlorambucil or any fludarabine-containing regimen including oral fludarabine, R-GIFOX; 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 dose of 375 mg/m² BSA. In the absence of infusion-related side effects, rituximab will subsequently be administered SC starting 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, must 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 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 grade 3 or 4 IRR after the second rituximab infusion will be withdrawn from the study.
 - **Study Visit Schedule** for patients during the induction therapy period will occur at the beginning of each 3-week or 4-week treatment cycle, according to the Schedule of Assessments ([Table 5](#)).
 - **Response assessment** will be conducted by the Investigator after 4 cycles (or after 3 cycles should Induction be comprised of 6 chemotherapy administrations) and at the end of Induction (i.e. after 8 cycles of rituximab). Response should be assessed according to the Cheson response criteria for indolent lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)). 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. Patients with SD 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 therapy. Initial 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.
 - **Study Visit Schedule** for patients during Maintenance I will occur according to the Schedule of Assessments ([Table 5](#)).
- **Response assessment** will be conducted by the Investigator every 6 months during Maintenance I according to the Cheson response criteria for indolent lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)). 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 2-year Maintenance I, tumour response will be assessed and compared to the patient's baseline status and patients with PR or CR (as determined by the Investigator using the Cheson response criteria,¹ see [Appendix 1](#), or by the recommendations for Waldenström's macroglobulinemia,² see [Appendix 2](#)) 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 EOS.

- **Study Visit Schedule** for patients during Maintenance II will occur according to the Schedule of Assessments (Table 5) and will include safety, disease progression, new anti-lymphoma treatments and survival. Disease progression will be evaluated by the Investigator every 6 months according to Cheson response criteria for indolent lymphoma¹ (see Appendix 1) or by the recommendations for Waldenström's macroglobulinemia² (see Appendix 2). Patients with PD will come off study treatment and be followed for survival.

STATISTICAL ANALYSES

Analysis Populations

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 set. 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 analysing the primary endpoint of PFS beyond randomization (PFS_{rand}, Maintenance II). All randomized patients will be included in this ITT_{rand} population and analysed according to the treatment arm they were randomized to.

Efficacy

Primary efficacy endpoint PFS_{rand}:

PFS_{rand} will be measured from the day of randomization until the date of first documented disease progression or death by any cause, whichever occurs first.

Patients who have experienced none of these events at the time of analysis (clinical-cut off) and patients who are lost to follow-up will be censored at their last clinical assessment date.

Secondary efficacy endpoints:

- PFS_{regist} (measured from the day of first rituximab induction dose)
- EFS (measured from the day of first rituximab induction dose)
- TNLT (measured from the day of first rituximab induction dose)
- OS_{regist} (measured from the day of first rituximab induction dose)
- OS_{rand} (measured from the day of randomization)
- Overall Response Rate (measured from the day of first rituximab induction dose) at the end of the Induction Phase
- PR to CR conversion rate at the end of Maintenance I

Exploratory efficacy endpoint:

- [REDACTED]

Medical Care Utilization data will be analysed as part of a separate Pharmacoeconomic sub-study.

Safety

All patients who have received at least one dose of SC rituximab will be included in the Safety population. The safety analysis will be based on the Safety population.

Safety assessments will include frequency of AEs, SAEs, and IRRs. Safety data will be analysed and described by study period, i.e. Induction, Maintenance I, Maintenance II, as well as overall.

In addition, IgG, IgM and IgA quantification will be completed once a year during Maintenance I, once a year during Maintenance II (**Arm A**) and in case of suspicious infections.

Sample Size Calculation

The sample size of the proposed study has been estimated based on assumptions derived from the Phase III randomized EORTC 20981 study of 465 patients with previously treated, advanced-staged relapsed FL.³ In this study, median PFS from first randomization was 20.2 months after CHOP vs. 33.1 months after R-CHOP and rituximab maintenance yielded a median PFS from second randomization of 51.5 months vs. 14.9 months with observation.

In the current study, 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 will 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 will be enrolled to randomize 330 patients (allowing for a 10% drop-out) after the 2.5-year Induction plus Maintenance I treatment period.

Interim analysis



There will be no interim analysis for efficacy.

An interim analysis of safety will be performed after approximately 200 patients have been enrolled in the study.

Independent Data Monitoring Committee (IDMC) reports

An IDMC charter is implemented and describes the frequency of data review, as well as which data will be considered. Data outputs prepared for the IDMC may be published.

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
ARR	Administration-related reaction
AST (SGOT)	Aspartate aminotransferase
BSA	Body Surface Area
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone/ prednisolone (chemotherapy regimen)
CHVP	Cyclophosphamide, doxorubicin, etoposide, prednisone/ prednisolone (chemotherapy regimen)
CI	Confidence interval
CLL	Chronic Lymphocytic Leukaemia
Cmax	Maximum plasma concentration
CNS	Central Nervous System
Ctrough	Minimal plasma concentration prior to next drug administration
CR	Complete Response
CrCl	Creatinine clearance
CRu	Complete Response, Unconfirmed
CT	Computer Tomography or Cancer Therapy
CTC-AE	Common Terminology Criteria for Adverse Events
	
CVP	Cyclophosphamide, vincristine, prednisone/prednisolone (chemotherapy regimen)
DLBCL	Diffuse Large B-Cell Lymphoma
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
ET	Expectations of Therapy
EU	European Union
FCM	Fludarabine, cyclophosphamide, mitoxantrone (chemotherapy regimen)

FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FSE	Feelings about Side Effects
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GELA	Groupe d'étude des lymphomes de l'adulte
GIFOX	Gemcitabine, ifosfamide, oxaliplatin (chemotherapy regimen)
GLSG	German Low Grade Lymphoma Study Group
GMP	Good Manufacturing Practices
HACA	Human anti-chimeric antibody
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immuno-deficiency Virus
hpf	High Power Field (microscopy)
HR	Hazard Ratio
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon- α
Ig	Immunoglobulin
IgA, IgG, IgM	Immunoglobulin of type A, G, or M
IQR	Interquartile range
IRR	Infusion/injection-Related Reaction
ITT	Intent to Treat
IV	Intravenous
IVRS/IWRS	Interactive Voice/Web Response System
LDH	Lactate Dehydrogenase
LPL	Lymphoplasmacytic Lymphoma
MCL	Mantle Cell Lymphoma
MCP	Mitoxantrone, chlorambucil, prednisone/prednisolone (chemotherapy regimen)
MCU	Medical Care Utilization
MRI	Magnetic Resonance Image

MZL	Marginal Zone Lymphoma
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
NYHA	New York Heart Association
OBS	Observation
ORR	Overall response rate
OS _{rand}	Overall survival, from randomization
OS _{regist}	Overall survival, from first Induction dose
PD	Progressive disease
PET	Positron Emission Tomography
PFS	Progression-free survival
PFS _{rand}	Progression-free survival, from randomization
PFS _{regist}	Progression-free survival, from first Induction dose
PLL	Prolymphocytic Leukaemia
PML	Progressive Multifocal Leukoencephalopathy
PP	Per Protocol
PR	Partial Response
RM	Rituximab Maintenance
rHuPH20	Recombinant Human Hyaluronidase
R-CHOP	Rituximab plus CHOP chemotherapy
R-CVP	Rituximab plus CVP chemotherapy
R-CHVP	Rituximab plus CHVP chemotherapy
R-FCM	Rituximab plus FCM chemotherapy
R-GIFOX	Rituximab plus GIFOX chemotherapy
R-MCP	Rituximab plus MCP chemotherapy
SAE	Serious Adverse Event
SAKK	Swiss Group for Clinical Cancer Research
SC	Subcutaneous
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results
SLE	Systemic Lupus Erythematosus
SLL	Small Lymphocytic Lymphoma

SUSAR	Suspected Unexpected Serious Adverse Reaction
SWT	Satisfaction with Therapy
TLS	Tumour Lysis Syndrome
TNF	Tumour Necrosis Factor
TNLT	Time to Next Lymphoma Treatment
TTF	Time to Treatment Failure
TTP	Time to Tumour Progression
ULN	Upper Limit of Normal
Vs.	Versus
WHO	World Health Organization
WM	Waldenström's Macroglobulinemia

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 DISEASE BACKGROUND

Non-Hodgkin's lymphoma (NHL), a group of malignancies arising from lymphoid tissue, is one of the leading causes of cancer death in the United States and Europe. As with other lymphoid neoplasms, its etiology remains largely unknown, although risk factors include certain infections as well as treatments and diseases that cause severe immunosuppression. Non-Hodgkin's lymphoma has been classified into two types: aggressive (i.e. fast growing) and indolent (i.e. slow growing).⁴ Indolent NHL comprises a group of incurable, generally slow-growing lymphomas that are highly responsive to initial therapy and are characterized by a relapsing and progressive course.

Follicular lymphoma (FL) is the most common of the indolent NHLs,⁵ accounting for 20-25% of all lymphomas. The disease generally manifests with hypertrophy of peripheral and deep lymph nodes and splenomegaly, together with bone marrow infiltration. Follicular lymphoma is characterized by initial responsiveness to therapy followed by repeated relapses and sometimes with histological progression into high-grade NHL.⁶ In the World Health Organization (WHO) classification the histology is further classified into Grade 1, 2 or 3 FL, depending on the percentage of large cells seen on high power field microscopy (see [Appendix 3](#)).⁷ Grade 3 FL is further subdivided into 3a and 3b, where 3b may represent a distinct biological entity more similar to diffuse large B-cell lymphoma (DLBCL).⁷ Biologically, FL has been associated with the translocation of chromosomes 14 and 18 [t(14;18)], which results in constitutive activation of the *bcl-2* oncogene and the subsequent inhibition of apoptosis of lymphoid cancer cells.⁸

Non-follicular indolent subtypes of NHL include chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and marginal zone lymphomas (MZL). They represent a diverse group of disorders with different presenting features, behaviour patterns and treatment outcomes. Although some subtypes have a prolonged indolent course with a good prognosis (e.g. SLL) others (e.g. nodal and splenic MZLs) can rapidly evolve into more aggressive subtypes. Universally accepted therapeutic guidelines for the treatment of non-follicular indolent NHL do not exist and treatment in asymptomatic patients may be deferred until the disease progresses and the patient becomes symptomatic.⁹

Given that FL is currently incurable with standard treatment options, there is a need to improve the clinical outcomes. The use of known active agents such as rituximab may be optimised to provide as much clinical benefit as possible. Recently, considerable evidence from several randomized phase III studies has reported clinical benefit from rituximab maintenance therapy (see [Section 1.2.3](#)). This study looks to further characterize the efficacy of rituximab maintenance treatment in terms of progression-free survival (PFS) and other relevant clinical outcomes and to expand the safety database for rituximab maintenance therapy following induction therapy.

1.1.1 Epidemiology

NHLs account for almost 5% of all cancers occurring in the United States, with an estimated 56 200 new diagnoses in the year 2001.¹⁰ The incidence and mortality rates for NHL were reported to have risen steadily in the United States (estimated 50%

increase in age-adjusted incidence of NHL from 1970 to 1990) and in other populations over several decades. Although further reports suggested that the steep rise in incidence may have slowed in the late 1990s, this group of closely related diseases is still an important contributor to the overall cancer burden.^{11,12,13,14}

During 2001 to 2003, a total of 71,762 lymphoid neoplasms were diagnosed among residents of the 17 registries of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI). Of these, 87.8% were NHL, 8.5% were Hodgkin's lymphoma, and 3.7% were composite NHL/Hodgkin's lymphoma or unspecified. Among the 62,982 NHLs, B-cell NHL accounted for 90.4%, T-cell NHL accounted for 6.8%, and NHL of unknown cell lineage accounted for 2.8%. The major NHL subtypes of mature B-cell origin consisted of DLBCL (23.1%), followed by CLL/SLL/Prolymphocytic leukaemia (PLL)/Mantle Cell Lymphoma (MCL) (19.4%), lymphoplasmacytic lymphoma (LPL)/Waldenström's macroglobulinemia (2.1%), FL (12.0%), MZL (5.7%), Burkitt lymphoma/leukaemia (1.4%), hairy cell leukaemia (1.0%), and plasma-cell neoplasms (18.3%), whereas the major NHL subtypes of mature T-cell origin consisted of peripheral T-cell lymphoma (3.8%), mycosis fungoides/Sézary syndrome (1.5%), and several other rare subtypes (0.4%).¹⁵

FL is the most common form of indolent lymphoma, accounting for about 70% of indolent lymphomas and 20% to 25% of all cases of NHL.¹⁶ Its incidence is rapidly increasing in Western countries and has nearly doubled within the past three decades. Like many lymphomas, it is increasing in incidence with over 24,000 new cases diagnosed each year. It remains incurable with standard treatment options.

1.1.2 Natural History

Prognosis and selected therapy for indolent lymphoma, which makes up 70% of NHLs, are closely related to the extent of the disease at initial diagnosis. Less than 15% – 20% of patients with indolent lymphoma are diagnosed at an early stage of the disease (Ann Arbor stage I or II), and half of these patients experience long-term disease-free survival after radiotherapy.¹⁷ However, the vast majority of patients with indolent lymphoma is diagnosed with advanced-stage disease (i.e., Ann Arbor stage III or IV) and cannot be cured with conventional therapy.

The clinical course of indolent NHL is characterized by cycles of relapses and remissions, and there are few long-term survivors. Various treatment regimens have been shown to produce a high rate of initial response followed inevitably by relapse. Subsequent remissions can still be obtained with available salvage regimens but these occur at a progressively lower rate and usually with a shorter duration.^{18,19} Prognoses of patients with relapsed disease is poor with a median survival of only 6-10 years.^{6,20,21} Histological transformation to more aggressive NHL with poor prognosis has been documented to occur in 20-80% of patients over time. In addition, the likelihood of progression to resistant lymphoma or occurrence of secondary malignancies such as myelodysplastic syndrome or acute myeloid leukaemia increases with time and in relation to the number, choice and intensity of previous treatments.

Several datasets have demonstrated that the overall survival (OS) of patients with indolent FL has improved over the past 3 decades, probably because of sequential application of different chemotherapy regimens, the use of biologic agents, and improved supportive care.^{6, 22, 23} A recent report indicates considerable increase in relative survival in patients with NHL, from 51% in 1992-1994 to 63% in 2004-2006, along with a 10-year survival of 54%.²⁴

1.1.2.1 Current management

The scale of therapeutic options for FL is wide and ranges from a watch-and-wait policy to aggressive alternatives, such as hematopoietic stem cell transplant. There are several reports of significant improvements in the clinical course of the disease over the past decades.^{23,25} However, the most striking outcome improvement has been achieved with the introduction of anti-CD20 monoclonal antibodies in combination with standard chemotherapy as demonstrated in several phase III studies^{26, 27, 28, 29, 30} and registry data.³¹ The combination of rituximab with chemotherapy as first-line treatment has become the standard induction therapy.

Initial treatment of NHL with chemotherapy such as alkylating agents, prednisone/prednisolone, anthracyclines, vinca alkaloids, purine analogues, combined with interferon or monoclonal antibodies such as rituximab is associated with a high rate of clinical response, although typically followed by relapse. Patients with aggressive B-cell lymphoma are potentially curable when treated with multiagent chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP).³² In 30-70% of the FL cases, the disease eventually transforms to aggressive lymphoma, responding only to combination chemotherapies usually employed for aggressive disease, such as anthracyclines or cytosine arabinoside-containing regimens or high-dose chemotherapy with autologous stem cell transplantation.³³ The standard of care for patients with aggressive lymphoma has changed recently with the implementation of therapy with the chimeric anti-CD20 monoclonal antibody rituximab.³⁴ Combination treatment with rituximab and CHOP (R-CHOP) or similar regimens has resulted in superior treatment outcomes compared with multiagent chemotherapy alone, making combined immunochemotherapy with rituximab the new standard of care for this group of patients.³⁵ The combination of cyclophosphamide, vincristine, and prednisone/prednisolone (CVP) is one of several standard treatment options for advanced FL. Similar to other chemotherapeutic regimens; this combination induces response rates of 60%-80%, with median response duration of under 2 years.²⁶

A recently published large, prospective, longitudinal, observational study to identify current patterns of care of FL in the United States (conducted between 2004 and 2007) found that amongst the 2728 patients enrolled, the most common initial therapeutic

strategy was chemotherapy plus rituximab (51.9%), followed by observation (17.7%), rituximab monotherapy (13.9%), clinical trial-related interventions (6.1%), radiation therapy (5.6%) and chemotherapy alone (3.2%). Chemotherapy plus rituximab regimens were R-CHOP (55.0%), rituximab plus CVP (R-CVP, 23.1%), rituximab plus fludarabine based-chemotherapy (15.5%), and other (6.4%). The choice to initiate therapy rather than observation only was associated with age, Follicular Lymphoma International Prognostic Index (FLIPI), stage, and grade ($p < 0.01$).³⁶

Toxicity of rituximab is mild and occurs most frequently during the first infusion. Importantly, it does not produce treatment-related cytopenias or severe cumulative toxicity.³⁷ Compared to single-agent cytotoxic therapy, single-agent rituximab was better tolerated and had similar efficacy.³⁸ Several Phase II and Phase III multicentre randomized trials demonstrated that the addition of rituximab to various chemotherapy regimens in patients with follicular lymphoma significantly improves outcomes when compared with standard chemotherapy regimens, without adding significant toxicity.³⁷ In clinical trials with rituximab monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During rituximab maintenance treatment for up to 2 years, grade 3/4 leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. In studies with rituximab in combination with chemotherapy, grade 3/4 leucopenia, neutropenia, and pancytopenia were reported higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with rituximab and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone and the neutropenia was not prolonged in the rituximab group. There were no differences reported for the incidence of thrombocytopenia or anaemia.³⁹

Rituximab, an anti-CD20 antibody, has had a large impact on the treatment of indolent NHL. Its effectiveness as a single agent and in conjunction with known chemotherapy regimens has made it a standard of care in the treatment of NHL. Analysis of data obtained from NHL clinical trials, as well as data from the NCI, indicate that the OS of patients with indolent NHL has improved with the use of rituximab and that given its effectiveness and tolerability, rituximab is currently being investigated as a maintenance agent with encouraging results.³⁷

1.2 STUDY DRUG BACKGROUND

Rituximab is a chimeric murine/human monoclonal antibody that specific for the B-cell antigen CD20.⁴⁰ In preclinical studies, rituximab was shown to induce both complement-mediated and antibody-dependent cell mediated lyses of CD20+ cells.⁴¹ Rituximab also induces apoptosis *in vitro* of human B-cell lines and sensitizes drug-resistant human B-cell lymphoma cell lines to the cytotoxic effects of some chemotherapeutic agents.^{42,43}

The efficacy and safety of rituximab is well established. It had demonstrated clinical benefits in combination with chemotherapy and as single agent in the first-line^{26,30,30,44,45} and relapsed setting for induction of remission^{38,46} and more recently, as maintenance therapy for patients after effective induction.³ Since its preclinical development, many studies have been performed to optimize the dose and schedule of rituximab. Rituximab is usually given IV at 375 mg/m², a dose associated with clinical activity and little toxicity. Moreover, given its low toxicity and long half-life, there is accumulating evidence supporting its use as maintenance therapy.⁴⁷

The main results of clinical experience with rituximab in indolent NHL treatment for induction are briefly summarized in Sections 1.2.1 and 1.2.2. The main results for rituximab maintenance therapy are summarized in Section 1.2.3 below. Section 1.2.4 summarizes the safety of rituximab in indolent NHL.

More detailed information concerning rituximab pre-clinical, dose finding, clinical efficacy and safety data can be found in the current version of the Investigator Brochure.

1.2.1 Clinical Studies with Single-Agent Rituximab Induction

Clinical trials evaluating single-agent rituximab as induction treatment in indolent NHL have been conducted in patients with first-line disease and relapsed/refractory disease.

Table 1 MAIN EFFICACY RESULTS FOR RANDOMIZED TRIALS EVALUATING SINGLE-AGENT RITUXIMAB INDUCTION THERAPY

Study / Reference	Population	Interventions	PFS	OS	Other Endpoints	AEs
Phase II Study 102-05, McLaughlin et al 1998³⁸	N=166 Relapsed/refractory low-grade B-cell NHL	Induction: Rituximab 375 mg/m ² , 4 weekly infusions	Median PFS (responders, at median 11.8 mo): 13.0 mo	-	ORR: 48%	Grade 3/4: 12% Most common Grade 1&2: Fever, chills
Phase II Study Colombat et al 2001⁴⁴	N=50 1 st line CD20+ FL	Induction: Rituximab 375 mg/m ² , 4 weekly infusions	Progression-free at 1 year: 31/49 (63%) PD at 1 Year: 15 (1 CR, 9 PR, 5 SD)	-	Day 50 or 78 (Best response): ORR*: 36/49 (73%) CR: 10, CRu: 3, PR: 23, SD: 10, PD: 3	Grade 3/4: 2 (4%) Most common Grade 1&2: headache, fever, pain, laryngitis
Phase II Study 102-06, Piro et al 1999⁴⁶	N=37 (35 evaluable) Relapsed/refractory low-grade B-cell NHL	Induction + Re-treatment: Rituximab 375 mg/m ² , 8 weekly infusions	Median PFS: NR after median 19.4 mo for responders and after median 7.7 mo for the total population.	-	ORR: 60% CR: 5 (14%), PR 16 (46%)	Grade 3/4: 10 (27%); 1 Grade 4 neutropenia Most common Grade 1/2 (IRR _s): fever (38%), chills (35%), asthenia (16%), nausea (11%), headache (8%)

AE: adverse event; CR: Complete Response; CRu: Complete Response, unconfirmed; DFS: Disease-free Survival; FL: Follicular lymphoma; IRR: Infusion-related reaction (within 24 hrs of the infusion); NHL: Non-Hodgkin Lymphoma; NR: not reached; ORR: Overall response Rate; OS: Overall Survival; PFS: Progression-free Survival; R: rituximab

* Primary endpoint in the study

The large multicentre trial by McLaughlin et al (n = 166) served as the basis for approval of rituximab in the United States and Europe.³⁸ In the Phase II clinical study by Colombat et al, a significant correlation (p < 0.0001) was found between molecular and clinical responses: 10 of the 17 patients, who were PCR negative in peripheral blood, were in CR/CRu, whereas none of the 13 patients PCR positive in peripheral blood had CR. In addition, the study showed that early molecular responses can be sustained for up to 12 months and that this response is highly correlated with progression-free survival (PFS).⁴⁴

In the initial dose finding studies and efficacy trials, the adverse events (AEs) associated with single agent rituximab included neutropenia, thrombocytopenia, and asthenia.

Some patients with pre-existing cardiac conditions, including arrhythmia and angina, had recurrences of these cardiac events during rituximab infusion.

1.2.2 Rituximab in Combination with Chemotherapy

Several Phase II and Phase III multicentre randomized trials have demonstrated that the addition of rituximab to first-line therapy for FL significantly improves clinical outcomes when compared with standard chemotherapy regimens of varying intensities, without adding significant toxicity. The combination chemotherapy regimens used in these trials included cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone (CHOP), cyclophosphamide, vincristine, prednisone/prednisolone (CVP), mitoxantrone, chlorambucil and prednisone/prednisolone (MCP), cyclophosphamide, doxorubicin, etoposide, prednisone/prednisolone, interferon- α (CHVP/IFN) and bendamustine; see details in [Table 2](#).

Table 2 MAIN EFFICACY RESULTS FOR RANDOMIZED TRIALS EVALUATING RITUXIMAB IN COMBINATION WITH CHEMOTHERAPY

Study / Reference	Population	Interventions	PFS/TTP/ EFS/DFS	OS	Other Endpoints	AEs
Phase II Study by Czuczman et al 1999⁴⁸ and 2004⁴⁹ OL Single-arm	N=40 (38 treated) Low-grade or follicular B-cell NHL	6 cycles of R-CHOP	<i>At 9 yr Follow-up:</i> <u>Median TTP:</u> 82.3 mo <u>Median DR:</u> 83.5 mo <u>Remission rate (at median 29 mo):</u> 74%	-	<u>ORR:</u> 100% <u>CR/CRu:</u> 33 (87%) <u>PR 5</u> (13%) (2 untreated)	<u>Most frequent AEs:</u> R: fever, chills, pruritus, headache (Grade 1&2 IRRs) CHOP: alopecia, neutropenia, fever
GLSG Study, Hiddemann et al 2005^{28,50} OL RCT	N=630 (428 evaluable) 1 st line FL, immunocytomas, MCL	Induction: 6-8 cycles Q3W: R-CHOP, n=223 CHOP, n=205	<i>At median 28 mo:</i> <u>Treatment failure:</u> R-CHOP: 28 CHOP: 61 <u>TTF:</u> R-CHOP: NR CHOP: 2.6 years P<0.001 <u>DR:</u> P=0.001	<u>3-yr OS:</u> R-CHOP: 95% CHOP: 90% P=0.016	<u>ORR:</u> R-CHOP: 96% CHOP: 90% P=0.011	<u>Grade 3/4 granulocytopenia:</u> R-CHOP: 63% CHOP: 53% P=0.01 <u>Infections:</u> R-CHOP: 5% CHOP: 7% <u>IRRs (R):</u> 7%
Phase II Study by Hainsworth et al 2005⁴⁵ OL Single-arm	N=86 1 st line follicular NHL, grade 1&2	Rituximab 4 weekly doses, followed by 3 cycles of R-CHOP or R-CVP	<u>3-year PFS:</u> 71% <u>4-year PFS:</u> 62%	<u>3-year survival:</u> 95%	<u>ORR:</u> 93% <u>CR:</u> 55%	<u>Grade 3/4 leukopenia:</u> 53%, neutropenia or fever: 7%
Phase III Study M39021 Marcus et al 2005²⁶ & 2008²⁷ OL RCT	N=321 1 st line advanced FL	8 cycles: R-CVP, n=162 CVP, n=159	<i>At median 53 mo:</i> <u>Median TTF*:</u> R-CVP: 27 mo CVP: 7 mo P<0.0001 <u>Median TTP:</u> R-CVP: 34 mo CVP: 15 mo P<0.0001 <u>Median DFS:</u> R-CVP: NR CVP: 21 mo P=0.0001 <u>Median DR:</u> R-CVP: 38 mo CVP: 14 mo P<0.0001	<i>At 48 mo:</i> R-CVP: 83% CVP: 77% P=0.03	<u>ORR:</u> R-CVP: 81% CVP: 57% P<0.0001 <u>CR/CRu:</u> R-CVP: 41% CVP: 10%	<u>Grade 3/4 neutropenia:</u> R-CVP: 24% CVP: 14% <u>Any AEs:</u> R-CVP: 97% CVP: 95% <u>IRRs:</u> R-CVP: 71% CVP: 51% Gr 3/4: 9%

Study / Reference	Population	Interventions	PFS/TTP/ EFS/DFS	OS	Other Endpoints	AEs
EGSG Study, Herold et al 2003⁵¹ and 2007²⁹ OL RCT	N=358 (201 in primary analysis set) Stage III-IV indolent FL (56%) or MCL	8 cycles Q4W: R-MCP, n=181 MCP, n=177 Responders: maintenance with IFN until relapse	<u>At median 47 mo:</u> <u>Median EFS:</u> R-MCP: NR (34 treatment failures) MCP: 26 mo (57 treatment failures) P<0.0001 <u>Median PFS:</u> R-MCP: NR (30 events) MCP: 28.8 mo (50 events) P<0.0001 <u>Median DR:</u> R-MCP: NR MCP: 35 mo P<0.0001 <u>Median TNL:</u> R-MCP: NR MCP: 29.4 mo P=0.0002	<u>4-yr OS:</u> R-MCP: 87% MCP: 74% P=0.01 Median OS NR in either group.	<u>ORR*:</u> R-MCP: 92% MCP: 75% P=0.0009 <u>CR:</u> R-MCP: 50% MCP: 25% P=0.004	<u>Grade 3/4 leukopenia:</u> R-MCP: 72% MCP: 58% <u>Grade 3/4 infections:</u> R-MCP: 7% MCP: 8% <u>Any AEs:</u> R-MCP: 99% MCP: 86%
GELA-GOELAMS Study FL2000, Salles et al 2008³⁰ OL RCT	N=358 1 st line FL with high tumour burden	R-CHVP, 6 courses Q4W, + IFN for 18 mo, n=175 or CHVP+IFN, 6 courses Q4W + 6 courses Q8W, n=183 Over 18 mo	<u>At median 5 yrs:</u> <u>Median EFS*:</u> R-CHVP+IFN: 53% CHVP+IFN: 37% P=0.001 <u>Median DR (4-yr):</u> R-CHVP+IFN: 64% CHVP+IFN: 44% P=0.012	<u>5-yr OS:</u> R-CHVP+IFN: 84% CHVP+IFN: 79% P=0.16	<u>ORR at 6 mo:</u> R-CHVP+IFN: 94% CHVP+IFN: 85% <u>CR/Cru, 6 mo:</u> R-CHVP+IFN: 63% CHVP+IFN: 34% Global P<0.001 <u>ORR at 18 mo:</u> R-CHVP+IFN: 81% CHVP+IFN: 72% <u>CR/Cru, 18 mo:</u> R-CHVP+IFN: 67% CHVP+IFN: 50% Global P=0.035	<u>6-mo Induction:</u> <u>Grade 3/4 leukopenia:</u> R- CHVP+IFN: 59% CHVP+IFN: 62% <u>Grade 3/4 infections:</u> R- CHVP+IFN: 2% CHVP+IFN: 0%
Phase II Study by Rummel et al 2005⁵²	N=63 Relapsed/ refractory low-grade NHL or MCL	R+B, up to 4 cycles Q4W	<u>Median PFS:</u> 24 mo (range 5 to 44+)	<u>Median OS:</u> NR	<u>All patients:</u> <u>ORR*:</u> 90% <u>CR:</u> 60% <u>MCL patients:</u> <u>ORR:</u> 75% <u>CR:</u> 50%	<u>Grade 3/4 leukocytopenia:</u> 16% <u>Grade 3/4 thrombo-cytopenia:</u> 3%
Phase II Study by Robinson et al 2008⁵³	N=67 (66 treated) Relapsed, indolent B-cell NHL or MCL	R+B, 4 - 6 cycles Q4W	<u>Median PFS:</u> 23 mo (95%CI 20-26) <u>Median DR:</u> 21 mo (95%CI 18-24)		<u>All patients:</u> <u>ORR*:</u> 92% <u>CR:</u> 41% <u>CRu:</u> 14% <u>PR:</u> 38%	<u>Grade 3/4 neutropenia:</u> 36% <u>Grade 3/4 thrombo-cytopenia:</u> 9%

AE: adverse event; B: bendamustine; CR: Complete Response; CRu: Complete Response, unconfirmed; CHOP: cyclophosphamide+doxorubicin+vincristine+prednisone/prednisolone; CVP: cyclophosphamide+vincristine+ prednisone/prednisolone; DFS: Disease-free Survival; EGSG: East German Study Group; FL: Follicular lymphoma; GLSG: German Low-Grade Lymphoma Study Group; GOELAMS: Groupe Ouest Est d'Etude des Leucemies et autres Maladies du Sang; IRR: Infusion-related reaction (within 24 hrs of the infusion); MCL: Mantle Cell Lymphoma; MCP: mitoxantrone, chlorambucil and prednisolone/prednisolone; NHL: Non-Hodgkin Lymphoma; NR: not reached; OL: open label; ORR: Overall response Rate; OS: Overall Survival; PFS: Progression-free Survival; R: rituximab; RCT: randomized controlled trial; TNL: Time to next lymphoma treatment; TTF: Time to Treatment Failure; TTP: Time to Progression

* Primary endpoint in the study

Note: rituximab was administered at the 375 mg/m² dose in all trials

1.2.2.1 Rituximab in combination with other chemotherapies and/or other indications

Data for use of rituximab with other chemotherapies and/or in other indications can be found in the current version of the Investigator Brochure.

1.2.3 Rituximab as Maintenance Therapy

Despite the ability of immunochemotherapy to induce high response rates during induction in follicular NHL, the pattern of continuous relapse in responding patients remains problematic. Rituximab is a potentially attractive candidate for maintenance therapy given its lack of cumulative myelotoxicity and evidence that patients previously responding to rituximab may respond to a second course of therapy.

Several randomized studies investigated the benefit of rituximab maintenance therapy compared to observation alone. The efficacy results are summarized in [Table 3](#) below.

Table 3 MAIN EFFICACY RESULTS FOR RANDOMIZED TRIALS COMPARING RITUXIMAB MAINTENANCE THERAPY TO OBSERVATION

Study / Reference	Population	Interventions	PFS	OS	Other Endpoints
Phase II Study by Hainsworth et al 2005 ⁵⁴	N=90 Previously treated FL, SLL	<u>Induction:</u> Rituximab <u>RM:</u> Weekly doses for 4 wks, repeated Q6M for 2 yrs	<u>Median PFS:</u> RM: 31.3. mo OBS: 7.4 mo P=0.007	-	<u>ORR:</u> RM: 73% OBS: 47%
SAKK 35/98 Ghelmini et al. 2004 ⁵⁵	N=151 (73 RM, 78 OBS) 1st line & Relapsed/ Refractory CD20+ FL (Grade I-III)	<u>Induction:</u> Rituximab <u>RM:</u> 4 Single infusions, given Q2M	<u>Median EFS at 35 mo:</u> RM: 23.2 mo OBS: 11.8 mo HR 0.61 P=0.02 <u>Median EFS at 9.5 yrs:</u> RM: 24 mo OBS: 13 mo P<0.001	-	<u>% event-free at 8 yrs:</u> RM: 27% (45% if 1 st -line) OBS: 5% <u>Best Response:</u> RM: 38% OBS: 31% <u>ORR at 24 mo:</u> RM: 45% OBS: 28%
ECOG 1496 Hochster et al 2004 ⁵⁶ Hochster et al 2007 ⁵⁷	N=311 (153 RM, 158 OBS) 1st line FL (n=282), SLL	<u>Induction:</u> CVP <u>RM:</u> Weekly doses for 4 wks, repeated Q6M for 2 yrs	<u>3-yr PFS (all):</u> RM: 68% OBS: 33% HR 0.4 P=4.4x10 ⁻¹⁰ <u>3-yr PFS (FL):</u> RM: 64% OBS: 33% HR 0.4 P=9.2x10 ⁻⁸	<u>OS at 3 yrs:</u> RM: 92% OBS: 86% HR 0.6 (0.4, 1.1) P=0.05	<u>Improvement in Best Response:</u> RM: 22% (CR: 16% → 37%) OBS: 7% (CR: 16% → 22%) P=0.00006
GLSG (R-)FCM Forstpointner et al 2006 ⁵⁸	N=195 162 evaluable (80 RM, 82 OBS) Relapsed/ Refractory FL (n=105), MCL (n=57), Other	<u>Induction:</u> R-FCM, FCM <u>RM:</u> Weekly doses for 4 wks, repeated at 3 mo and 9 mo	-	<u>OS at 3 yrs:</u> RM: 77% OBS: 57% P=0.1 Median survival not reached.	<u>Response duration after med 26 mo):</u> RM: median not reached OBS: 17 mo P=0.0001 <u>Induction phase:</u> <u>ORR:</u> R-FCM: 79-86% FCM: 58%
EORTC 20981 Intergroup study van Oers et al 20063	N=334 (167 RM, 167 OBS) Relapsed/ Refractory FL	<u>Induction:</u> R-CHOP, CHOP <u>RM:</u> Single infusions, given Q3M for 2 yrs	RM: 51.5 mo OBS: 14.9 mo HR 0.40 P<0.0 01	<u>OS at 3 yrs:</u> RM: 85% OBS: 77% HR 0.52 P=0.011 <u>OS at 5 yrs:</u> RM: 74% OBS: 64% P=0.07	<u>Induction phase:</u> <u>ORR:</u> R-CHOP: 85.1% CHOP: 72.3% P<0.001 <u>Median PFS from 1st randomization:</u> R-CHOP: 33.1 mo CHOP: 20.2 mo P<0.001 <u>OS at 3 yrs:</u> R-CHOP: 82.5% CHOP: 71.9% P=0.096

Study / Reference	Population	Interventions	PFS	OS	Other Endpoints
PRIMA Salles et al 2011 ⁵⁹	N=1018 (ITT) (505 RM, 513 OBS) 1 st line FL (Grade I-IIa; n=994)	<u>Induction:</u> R-CHOP, R-CVP, or R-FCM <u>RM:</u> 12 infusions, given Q8W for 2 yrs	<u>3-yr PFS:</u> RM: 74.9% OBS: 57.6% HR 0.55 (0.44, 0.68) P<0.0001	<u>Deaths, 3 yrs:</u> RM: 26/505 OBS: 30/513 HR 0.87 (0.51, 1.47)	<u>CR/CRu at 2 yrs:</u> RM: 71.5% OBS: 52% P=0.0001
NHL 2-2003 StiL Group Rummel et al. 2010 ⁶⁰	N=219 random. (208 analysed, 109 R-B, 99 R-F) RM: N=40 (23 R-B, 17 R-F) Relapsed FL, indolent or MCL	<u>Induction:</u> R+bendamustine R+fludarabine <u>RM:</u> up to 8 infusions, given Q3M for 2 yrs (n=40, 23 R-B, 17 R-F)	R-B: 30 mo R-F: 11 mo HR 0.51 (0.34, 0.67) P<0.0001 <u>PFS (RM vs. no mainten.):</u> HR 0.27 (0.27, 0.59) P<0.0001	<u>Deaths after 33 month median follow-up:</u> R-B: 42 R-F: 46 NSD <u>OS (RM vs. no maintenance):</u> HR 0.21 (0.22, 0.67) P=0.0008	<u>ORR:</u> R-B: 83.5% R-F: 52.5% P<0.0001 <u>CR:</u> R-B: 38.5% R-F: 16.2% P=0.0004

Abbreviations: CR, complete response; CRu, Complete response, unconfirmed; FL, follicular lymphoma; HR, hazard ratio (expressed with 95% confidence interval limits); ITT, intent to treat; MCL, Mantle Cell Lymphoma; mo, months; NSD, no significant difference; OBS, observation; ORR, Overall response Rate; Q6M, every 6 months; Q2M, every 2 months; RM, rituximab maintenance; wks, weeks;

1.2.3.1 Rituximab maintenance therapy following chemotherapy induction

In a large Phase III prospective randomized trial (**ECOG1496**) by Hochster and colleagues,^{56,57} patients with low-grade NHL achieving a response or stable disease after induction treatment with CVP were randomized to receive rituximab maintenance therapy (RM, 4 weekly infusions every 6 months, n = 153) over 2 years or no further therapy (observation group, OBS, n = 158). The study was terminated early after an interim analysis significant superiority of the maintenance arm. After a median follow-up of 14 months, the Kaplan-Meier estimate for PFS at 2 years was 74% of patients in the RM arm compared with 42% of patients in the OBS arm (p = 0.0008). The median PFS for the whole study population was 4.2 years compared to 1.5 years in the OBS arm; median follow-up was 18 months.^{56,57} Best response improved in 22% of RM patients vs. 7% of OBS patients (p = 0.00006). Toxicity was minimal in both study arms. Three-year PFS after randomization was 68% RM vs. 33% OBS (hazard ratio [HR] 0.4; p = 4.4 x10⁻¹⁰) in the total population and 64% RM v 33% OBS (HR 0.4; p = 9.2x10⁻⁸) in patients with FL. There was an advantage for RM regardless of FLIPI score, tumour burden, residual disease, or histology. OS at 3 years was 92% RM vs. 86% OBS (HR 0.6; log-rank one-sided p = 0.05) and, among patients with FL, OS was 91% RM vs. 86% (HR 0.6; log-rank one-sided p = 0.08).⁶¹

There were differences in neutropenia between the two arms, but overall there were no unexpected grade 3/4 toxicities (see [Table 4](#)).

1.2.3.2 Rituximab as maintenance therapy following rituximab monotherapy induction

Extended rituximab monotherapy (rituximab maintenance therapy) following rituximab monotherapy induction was shown to significantly prolong EFS or PFS in previously untreated patients with follicular NHL.

The benefit of maintenance rituximab therapy was evaluated in 114 patients with relapsed/refractory indolent NHL enrolled in a **Phase II study by Hainsworth et al.** Of the 114 enrolled patients receiving 4 doses of rituximab for induction therapy over 1 month, 90 (79%) with objective response or stable disease were randomly assigned to receive either maintenance rituximab therapy (3 standard 4-week courses administered at 6-month intervals) or rituximab re-treatment at the time of lymphoma progression. Patients receiving maintenance rituximab had a significantly prolonged PFS (31.3 vs. 7.4 months; $p = 0.007$) and higher ORR (73% vs. 47%, respectively) compared to re-treatment. Duration of rituximab benefit was similar in the maintenance and re-treatment groups (31.3 vs. 27.4 months, respectively).⁵⁴ Both treatment approaches were well tolerated; see [Table 4](#).

The Swiss Group for Clinical Cancer Research (**SAKK 35/98 trial**) evaluated the potential benefits of extended rituximab treatment in a randomized trial comparing the standard schedule with prolonged treatment in 202 patients with newly diagnosed or refractory/relapsed FL. After all patients received standard treatment consisting of 4 doses of 375 mg/m² rituximab weekly, the overall RR was 67% in chemotherapy-naïve patients and 46% in pre-treated cases ($p < 0.01$) within in a subset of 185 evaluable patients. Responders and patients with stable disease at week 12 ($n = 151$) were then randomized to no further treatment (OBS) or prolonged rituximab administration (four 375 mg/m² doses every 2 months). At a median follow-up of 35 months, the median EFS was 12 months in the OBS group vs. 23 months in the prolonged treatment arm ($p = 0.02$), the difference being particularly notable in chemotherapy-naïve (first-line) patients (19 vs. 36 months; $p = 0.009$) and in patients responding to induction treatment (16 vs. 36 months; $p = 0.004$).⁵⁵ A summary of toxicities is provided in [Table 4](#).

According to a recent update on the SAKK 35/98 study, at a median follow-up of 9.5 years and with all living patients having been observed for at least 5 years, the median EFS was 13 months for the OBS arm and 24 months for the prolonged exposure arm ($p < 0.001$). In the OBS arm, 5% of patients were event-free at 8 years compared to 27% in the prolonged exposure arm. The percentage of event-free patients at 8 years was highest (45%) amongst previously untreated patients. The only favourable prognostic factor for EFS in a multivariate Cox regression analysis was the prolonged rituximab schedule (HR 0.59, 95% CI 0.39 to 0.88; $p = 0.009$), whereas being chemotherapy naïve, presenting with disease stage lower than IV, and showing a VV phenotype at position 158 of the Fc-gamma RIIIA receptor were not of independent prognostic value. No long-term toxicity potentially due to rituximab was observed.⁶²

1.2.3.3 Rituximab maintenance therapy following rituximab plus chemotherapy induction

In a phase III **EORTC 20981 study** ($n = 465$) evaluating the role of rituximab maintenance treatment in relapsed/resistant FL, 334 of the 366 patients achieving PR or CR after 6 cycles of induction therapy with CHOP without or with 375 mg/m² IV rituximab underwent a second randomization to maintenance with 375 mg/m² IV rituximab once every 3 months for a maximum of 2 years or to observation alone. Induction with R-CHOP compared to CHOP yielded a significantly higher overall response rate (85.1% vs. 72.3%, respectively; $p < 0.001$) and CR rate (29.5% vs. 15.6%; $p < 0.001$). Median PFS from first randomization was 33.1 months vs. 20.2 months, respectively (HR 0.65; $p < 0.001$). Importantly, this was the first trial demonstrating that rituximab maintenance significantly prolonged PFS from second randomization (median 51.5 months vs. 14.9 months with observation alone, HR 0.40; $p < 0.001$), regardless of whether the induction included CHOP (HR 0.30; $p < 0.001$) or R-CHOP (HR 0.54; $p = 0.004$). A further

important finding of this study is the significant prolongation in 3-year OS from second randomization to rituximab maintenance compared to observation alone (85% vs. 77%, HR 0.52; $p = 0.011$).³ The toxicity profile is shown in [Table 4](#).

A subsequent follow-up indicated that the 5-year OS was 74% in the rituximab maintenance arm and 64% in the observation arm ($p = 0.07$). Of note, after progression, a rituximab-containing salvage therapy was given to 59% of patients treated with CHOP followed by observation, compared with 26% after R-CHOP followed by rituximab maintenance. During rituximab maintenance treatment, neutropenia was the only significant toxicity; 11.5% experienced grades 3 to 4 neutropenia in the rituximab maintenance arm versus 6.0% in the observation arm. This probably contributed to the increased grades 3 to 4 infection rates of 9.7% in the maintenance group and 2.4% during observation ($p = 0.01$). The majority of these infections were in the ear-nose-throat area and no opportunistic or viral infections were observed. No patient had to be withdrawn because of persisting IgG levels less than 3 g/L. Only seven of the 167 patients withdrew from maintenance treatment because of toxicity.⁶³

The data from the pivotal **EORTC 20981** Intergroup study has formed the basis for a label extension for rituximab to be administered as rituximab maintenance therapy.

In addition, the **GLSG** performed a randomized study comparing induction with 4 courses of FCM or R-FCM in patients with advanced stage relapsed or refractory FL or MCL. Responding patients underwent a second randomization to observation alone or to rituximab maintenance (RM) comprising 2 further rituximab courses of weekly doses for 4 weeks, repeated at 3 months and 9 months. The initial randomization was stopped after 147 patients due to demonstrated clinical superiority in the R-FCM arm. All subsequent patients received R-FCM induction therapy prior to the second randomization. Of the 176 evaluable patients at the time of the latest published report, 138 received R-FCM for remission induction. A total of 184 patients underwent randomization to RM or observation alone. After a median observation time of 26 months (range, 1 - 64 months), a significantly longer response duration was observed for the total group of patients on the R-maintenance arm, with the median not being reached in this evaluation, compared with an estimated median of 17 months for patients receiving no further treatment. In the subgroup of patients receiving R-FCM induction, prolonged RM produced a significantly longer response duration, with the median not reached vs. an estimated median of 16 months in the observation group ($p = 0.001$). This beneficial effect (RM vs. observation) was also observed when analysing the subgroups of patients with FL ($p = 0.035$) and MCL ($p = 0.049$) separately.⁵⁸

In a randomized phase III study conducted by the German Study Group Indolent Lymphomas (Stil) 219 pts with relapsed FL, indolent or MCL were randomized to rituximab 375 mg/m² (day 1) plus either bendamustine 90 mg/m² (R-B, days 1 and 2) or fludarabine 25 mg/m² (R-F, days 1 to 3) Q4W for a maximum of 6 cycles. The primary endpoint was PFS. The protocol was amended in 2006 to allow rituximab maintenance therapy (rituximab 375 mg/m² every 3 months for up to 2 years) in both arms, following regulatory approvals in this setting. After a median observation time of 33 months, the group receiving R-B, compared to R-F had a significantly prolonged PFS (30 vs. 11 months, respectively; HR 0.51, 95% CI 0.34 to 0.67; $p < 0.0001$), ORR (83.5 vs. 52.5%, respectively; $p < 0.0001$), whereas overall survival did not differ significantly between arms, with 42 and 46 deaths documented in the two groups, respectively. An exploratory analysis showed significantly prolonged overall survival (HR 0.21, 95% CI 0.22 to 0.67; $p = 0.0008$) and PFS (HR 0.27, 95% CI 0.27 to 0.59; $p < 0.0001$) in the small group of 40

patients who received rituximab maintenance treatment (23 B-R, 17 F-R), compared with those who did not.⁶⁰

The latest data confirming the benefit of rituximab maintenance therapy following rituximab plus chemotherapy in first line advanced FL is available from the phase III, open-label, randomized **PRIMA** (Primary Rituximab and Maintenance) **study**. After induction of response with one of 3 rituximab-containing chemotherapy regimens (R-CHOP, R-CVP, or R-FCM, at the discretion of the treating physician), 1019 of the 1217 patients with a partial or complete response were randomized to observation alone (n = 513) or maintenance with 375 mg/m² rituximab, once every 8 weeks for 2 years (n = 505). The primary endpoint was PFS. At a median follow-up of 36 months (interquartile range or IQR 30-42), PFS was 74.9% (95% CI 70.9 to 78.9) in the RM group (130 patients progressed) and 57.6% (95% CI 53.2 to 62.0) in the observation only group (218 progressed; HR 0.55, 95% CI 0.44 to 0.68; p < 0.0001). Two years after randomization, 361 patients (71.5%) in the RM group were in CR or CRu vs. 268 (52.2%) in the observation alone group (p = 0.0001). Overall survival did not differ significantly between groups (HR 0.87, 95% CI 0.51 to 1.47).⁵⁹

Of the 1009 patients assessed for safety, adverse events were reported in 281 of 501 (56%) patients in the rituximab maintenance group and 189 of 508 (37%) in the observation group (risk ratio 1.51, 95% CI 1.32 to 1.73; p < 0.0001). Grade 3 and 4 AEs were recorded in 121 patients (24%) in the rituximab maintenance group and 84 (17%) in the observation only group (risk ratio 1.46, 95% CI 1.14 to 1.87; p = 0.0026); see [Table 4](#). Infections (grades 2-4) were the most common AE, occurring in 197 (39%) and 123 (24%) patients respectively (risk ratio 1.62, 95% CI 1.35 to 1.96; p < 0.0001). Nineteen (4%) and eight (2%) events, respectively, resulted in treatment discontinuation (risk ratio 2.41, 1.06 to 5.45; p = 0.029). This study provided first evidence of a significant PFS benefit associated with long-term (2-year) maintenance treatment with rituximab.⁵⁹

Lastly, a systematic review and meta-analysis of randomized controlled trials that compared rituximab maintenance therapy with observation or no treatment at relapse identified 5 trials comprising 985 adult patients with FL overall and each with adequate OS data. Induction therapy used in these trials included three options: chemotherapy alone, chemotherapy with or without rituximab, and rituximab alone. In all trials, a dose of rituximab consisted of 375 mg/m²/day. The maintenance treatment schedule differed among the trials: in three trials, rituximab was administered weekly for 4 consecutive weeks (four doses) every 6 months, and in two trials, a single infusion of rituximab was administered every 2 – 3 months. The duration of treatment also varied, from 8 – 9 months to 2 years. Patients treated with RM had statistically significantly better OS than patients in the observation only arm or patients treated at relapse (HR 0.60, 95% CI 0.45 to 0.79). Of note, the survival benefit was significant in the subgroup of patients with refractory or relapsed (i.e. previously treated) FL (HR 0.58, 95% CI 0.42 to 0.79), but not in previously untreated patients (HR 0.68, 95% CI 0.37 to 1.25). The rate of infection-related AEs was higher with RM (HR 1.99, 95% CI 1.21 to 3.27). The study results led the authors to conclude that maintenance therapy with rituximab, either as 4 weekly infusions every 6 months or as a single infusion every 2 - 3 months, should be added to standard therapy for patients with relapsed or refractory FL after successful induction therapy.⁶⁴

1.2.4 Clinical Safety of Rituximab

Comprehensive rituximab safety information is available in the current Investigator Brochure. Safety considerations relevant to this study are summarized here.

Safety data from randomized clinical trials comparing rituximab maintenance therapy with observation (no treatment) are summarized in [Table 4](#) below, with focus on Grade 3/4 toxicities.

Table 4 SAFETY SUMMARY OF RANDOMIZED TRIALS COMPARING RITUXIMAB MAINTENANCE THERAPY TO OBSERVATION

Study / Reference	Population, Intervention	Grade 3/4 AEs				Other AEs	
Phase II Study Hainsworth et al 2005 ⁵⁴	N=90 <u>Induction:</u> Rituximab <u>Maintenance:</u> RM: Weekly doses for 4 wks, repeated Q6M for 2 yrs or R re-treatment at PD	Grade 3 AEs, n	RM	R Re-treatment	No withdrawals due to toxicity.		
		Grade 3 IRRs	2	0			
		Neutropenia	1	0			
		Fatigue	1	0			
		Anemia	0	1			
		Dyspnea	0	1			
SAKK 35/98 Ghielmini et al. 2004 ⁵⁵	N=151 <u>Induction:</u> Rituximab RM: 4 Single infusions, given Q2M			IND, N=202		SAEs: RM: 9 cases (incl. 2 infections) OBS: 4 cases (incl. 1 infection) <u>Late toxicities (1-yr):</u> RM: 7% OBS: 7% Causes: infection (5), leucocytopenia (2), teeth loss (1), asymptomatic neutropenia (1), cachexia (1).	
		Non-haematologic, n (%)					
		Overall		19 (10)			
		Hypotension		5 (3)			
		Asthenia		8 (4)			
		Other		13 (6)			
		Haematologic, n (%)					
		Anemia		4 (2)			
		Leukocytopenia		6 (3)			
		Neutropenia		19 (9)			
		Thrombocytopenia		8 (4)			
				MAINT, N=151			
				RM N=73	OBS N=78		
		Non-haematologic, n (%)		7 (10)	2 (3)		
		Haematologic, n (%)		13 (18)	13 (17)		
ECOG 1496 Hochster et al 2004 ⁶¹	N=311 <u>Induction:</u> CVP RM: Weekly doses for 4 wks, repeated Q6M for 2 yrs		CVP IND N=394	RM N=178	OBS N=177	<u>Toxic deaths:</u> CF: 8 RM: 4 OBS: 1 Causes: infection (9) liver failure (2) CNS gliosis (1)	
		Neutropenia	30%	3%	1%		
		Infection	7%	1%	1%		
		Pulmonary	2%	1%	1%		
		Other	N/A	7%	4%		
GLSG (R)-FCM Forstpointner et al 2006 ⁵⁸	N=195 <u>Induction:</u> R-FCM, FCM RM: Weekly doses for 4 wks, repeated at 3 mo and 9 mo			RM	OBS	<u>Withdrawal due to AE</u> RM: 1 pt (severe allergic reaction) OBS: 0	
		Lymphocytopenia		22%	16%		
		Granulocytopenia		13%	6%		
		Leukocytopenia		10%	5%		
		Infection		4%	3%		
		Fever		4%	0		
		Thrombocytopenia		4%	3%		
		Anemia		3%	3%		
		Cardiac dysfunction		1%	0		
		Pulmonary toxicity		1%	0		
		ALT abnormal		1%	0		
EORTC 20981 Intergroup study van Oers et al 20063	N=334 <u>Induction:</u> R-CHOP, CHOP RM: Single infusions, given Q3M for 2 yrs		OBS		RM		Overall incidence of neutropenia: RM: 11% OBS: 5% <u>Withdrawals due AE</u> RM: 6/167 (6/7 due to infections)
			Gr3	Gr4	Gr3	Gr4	
		Leucopenia	4 (2)	3 (2)	10 (6)	1 (1)	
		Granulo-cytopenia	6 (4)	3 (2)	11 (7)	7 (4)	
		Infection	3 (2)	1 (1)	12 (7)	3 (2)	
		Cardiac	7 (4)	--	7 (4)	3 (2)	

Study / Reference	Population, Intervention	Grade 3/4 AEs				Other AEs	
PRIMA Salles et al 2011 ⁵⁹	N=1018 (ITT) <u>Induction:</u> R-CHOP, R-CVP, or R-FCM <u>RM:</u> 12 infusions, given Q8W for 2 yrs		OBS		RM		<u>Incidence of AEs:</u> RM: 281 (56%) OBS: 189 (37%) P<0.0001 <u>Most common AEs:</u> Gr2-4 infections RM: 197 (39%) OBS: 123 (24%) P<0.0001 <u>Grade 3/4 AEs</u> (RM vs OBS): Risk ratio 1.41, P=0.003 <u>Withdrawal due to AE</u> RM: 19 (4%) OBS: 8 (2%)
			Gr3/4	WD	Gr3/4	WD	
		All AEs	84 (17)	8 (2)	121 (24)	19 (4)	
		Neoplasia	17 (3)	6 (1)	20 (4)	5 (1)	
		Neutropenia	5 (1)	0	18 (4)	0	
		Febrile neutropenia	2 (<1)	0	1 (<1)	1 (<1)	
		Infections	5 (1)	0	22 (4)	4 (1)	
		CNS disorders	13 (3)	0	10 (2)	0	
		Cardiac disorders	5 (1)	0	11 (2)	1 (<1)	
NHL 2-2003 StiL Group Rummel et al. 2010 ⁶⁰	N=219 random. RM: N=40 <u>Induction:</u> R+bendamustine R+fludarabine <u>RM:</u> up to 8 infusions, Q3M for 2 yrs	Grade 3/4 neutropenia: R-B: 9% R-F: 9% Grade 3/4 leukocytopenia: R-B: 12% R-F: 12%				SAEs: R-B: 17% R-F: 22%	
Abbreviations: AE, adverse event; FL, follicular lymphoma; mo, months; OBS, observation; Q6M, every 6 months; Q2M, every 2 months; RM, rituximab maintenance; wks, weeks; WD, (Leading to) Withdrawal							

Infusion-related symptoms

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

In the pivotal rituximab monotherapy trials (IDEC 102-01,⁶⁵ 102-02,^{66,67} 102-05,³⁸ 102-06,⁴⁶ 102-08B,⁶⁸ and 102-08R⁶⁹) in relapsed/refractory patients with follicular NHL, the incidence of IRRs was 77% (7% grade 3/4) with the first infusion, which decreased to approximately 30% (2% grade 3/4) with the fourth infusion and to 14% (no grade 3/4 events) with the eighth infusion. In pivotal trial (M39021) of first-line treatment of follicular NHL, where rituximab was combined with CVP chemotherapy, the incidence of grade 3/4 acute IRRs was 9%.²⁶ An incidence of 9% for grade 3/4 infusion-related events was also reported in patients with diffuse large B-cell lymphoma, when they received their first rituximab infusion combined with CHOP chemotherapy in DLBCL (GELA/BO16386).⁷⁰

In the U0824n⁷¹ non-randomized trial of patients who had not previously been treated with systemic therapy for indolent NHL, participants received rituximab weekly for 4

weeks. Those who responded then received RM. IRRs (chills/rigors, fever, nausea/vomiting and flushing) were observed with the first course of rituximab, consistent with the known safety profile of rituximab. It was reported that toxicity observed during RM was less than with the first course, but data on the number and type of AEs were not provided.

Thus, patients treated with RM who have previously been exposed to rituximab during induction, may have fewer and less severe reactions than patients treated with rituximab for the first time. It is unlikely that infusion reactions in the rituximab maintenance setting will be any different from those seen during later infusions of induction therapy. During this study, rituximab maintenance infusions will be administered in a hospital or outpatient clinic by oncologists and their staff, who are familiar with such adverse effects.

Infection

Patients with NHL are at risk of infection because of disturbances in immune functions as a result of their underlying malignant disease. Treatment with chemotherapeutic agents leads to immunosuppression and therefore also may increase the incidence of infections.

Because rituximab depletes B cells, which play an important role in the normal immune response, treatment with rituximab may further increase the risk of infection in these immunocompromised patients. In two cohorts of patients treated with rituximab monotherapy in relapsed/refractory follicular NHL, median immunoglobulin (Ig) G and IgA levels remained stable during treatment and during follow-up, but IgM dropped below the normal range at 3 months post-treatment with a median time to recovery of 2 months.^{72,73} Infections occurred in 30.3% of 356 patients reviewed. Since there was no comparator arm in these studies, the contributory role of rituximab in the development of these infectious events relative to the underlying NHL and its treatment with other drugs could not be determined.

In Phase III randomized controlled trials comparing the combination of rituximab and various chemotherapy regimens (R-CHOP, R-MCP, R-CHVP+IFN) with chemotherapy alone (CHOP, MCP, and CHVP+IFN, respectively) in patients with NHL, the incidence of grade 3 and 4 infections ranged between 2% and 7% in the combination arms compared to 0% to 8% in the chemotherapy arms.^{28,29,30} In the pivotal study comparing R-CVP vs. CVP alone for first line induction treatment of follicular NHL (M39021²⁶) the overall proportion of patients with infections was comparable between treatment groups (33% R-CVP, 32% CVP), despite more patients in the R-CVP arm experiencing grade 3/4 neutropenia (R-CVP 24%, CVP 14%). In the R-CHOP vs. CHOP alone pivotal trial in elderly patients with DLBCL (GELA/BO16386⁷⁰) grade 3 and 4 leucopenia and neutropenia occurred more frequently in the R-CHOP arm than in the CHOP arm (88% vs. 79% and 97% vs. 88% respectively), but the incidence of grade 2 to 4 infections was only slightly higher (46% in the R-CHOP arm compared to 42% in the CHOP arm). More cases of herpes zoster and localized fungal infections were recorded when rituximab was added to CHOP chemotherapy in a separate study investigating rituximab in aggressive NHL.⁷⁰ In the U0824n trial,⁷¹ no opportunistic infections were observed during rituximab maintenance therapy over 18 months and no patient discontinued from the study due to toxicity.

In two large Phase III randomized controlled trials (EORTC 20981 and PRIMA) up to two years of maintenance therapy with rituximab administered every two months was associated with higher rates of grade 3 and 4 infections compared to observation (4% to

9% compared to 1% to 3%, respectively).^{3,59} In the SAKK 35/98 trial,⁵⁵ the rate of serious infections was 3% in the RM group compared to 1% in the observation group. In the RM group, reduction in IgM levels to 86% and 72% of baseline level were observed at 3 and 12 months respectively, these changes, however were not associated with an increase in the incidence of AEs. The grade 3 and 4 infection rates were comparable between the RM and observation arms in other Phase III trials (1% to 4% and 1% to 3%, respectively); refer to [Table 4](#) for further details.^{58,61}

Other toxicities

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

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

In studies evaluating rituximab in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9 %) as compared to the CHOP group (3 patients, 1.5 %). During maintenance treatment, the incidence of grade 3 and 4 cardiac disorders was comparable between patients treated with rituximab and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3 % of patients treated with rituximab compared to < 1 % on observation.³⁹

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

Two spontaneous cases of progressive multifocal leukoencephalopathy (PML) resulting in death, have been reported in patients with Systemic Lupus Erythematosus (SLE) receiving off-label rituximab. Rituximab is not approved for the treatment of SLE. PML has also been reported in SLE patients not treated with rituximab. A causal relationship between rituximab and PML has not been established.

Some other patients who were treated with rituximab and chemotherapy have developed gastro-intestinal perforation.

The safety of immunization with any vaccine following rituximab therapy has not been extensively studied. It is recommended that any course of immunization for patients should be completed at least 4 weeks before starting rituximab maintenance therapy and patients should not receive any vaccinations that contain live or attenuated organisms during the study.

Further information concerning rituximab safety can be found in the current version of the Investigator Brochure.⁷⁴

1.3 REGULATORY STATUS

Rituximab is a chimeric murine/human monoclonal antibody that binds to CD20, a hydrophobic transmembrane protein present on B lymphocytes. Rituximab is marketed

under the brand names MabThera® in Europe and other countries and Rituxan® in the US.

Rituximab has been approved for treatment of relapsed or chemo-resistant, low-grade or follicular, CD20+, B-cell NHL in over 100 countries including the EU and US, and for treatment of rheumatoid arthritis in the US and EU.

In oncology, Rituxan (rituximab) is indicated in the US as follows:

- Relapsed or refractory, low-grade or follicular, CD20+, B-cell NHL as a single agent;
- Previously untreated follicular, CD20+, B-cell NHL in combination with first-line chemotherapy and as a single-agent maintenance therapy after achieving a response to Rituxan in combination with chemotherapy;
- Non-progressing (including stable disease), low-grade, CD20+, B-cell NHL as a single agent, after first-line CVP chemotherapy;
- Previously untreated diffuse large B-cell, CD20+ NHL in combination with CHOP or other anthracycline-based chemotherapy regimens;
- Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide.

In oncology, MabThera (rituximab) is indicated in the EU as follows:

- Previously untreated or relapsed/refractory CLL in combination with chemotherapy;
- Previously untreated patients with stage III-IV FL in combination with chemotherapy;
- As maintenance treatment for FL responding to induction therapy;
- CD20+ DLBCL in combination with CHOP chemotherapy;
- As monotherapy stage III-IV FL chemo-resistant or has is in second or greater relapse after chemotherapy.

In Rheumatology, rituximab is indicated as follows:

In the US: Rituximab (Rituxan®) received Food and Drug Administration approval for rheumatoid arthritis in February 2006 and is currently indicated in combination with methotrexate to reduce signs and symptoms of disease and to slow the progression of structural damage in adult patients with moderate-to-severe active rheumatoid arthritis who have had inadequate response to one or more tumour necrosis factor (TNF) antagonist therapies.

In April 2011, the Food and Drug Administration (FDA) approved rituximab in combination with flucocorticoids for the treatment of patients with active, severe Wegerner's Granulomatosis or Microscopic Polyangiitis.

In the EU: Rituximab (MabThera®) in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response to initial anti-TNF therapy. For regulatory status and approved indications in other countries, please refer to the Investigators' Brochure⁷⁴ and the local Product Information respectively.

1.4 RATIONALE FOR THE STUDY

The efficacy and safety of rituximab is well established. Several phase III trials demonstrated that the addition of rituximab to standard induction chemotherapy compared to chemotherapy alone significantly improved clinical outcomes in terms of OS, PFS, EFS, response duration, particularly in patients with FL.^{26,28,29,30,45,48,51,52,53} Consequently, rituximab-containing regimens have become the standard of care for patients suffering from various CD20+ B-cell malignancies, including indolent NHLs.

More recently, based on two large randomized phase III trials showing significant clinical benefits with rituximab maintenance compared to observation in relapsed FL (EORTC 20981 Study)³ and first-line FL (PRIMA Study),⁵⁹ rituximab maintenance has also become standard of care in these settings. The EORTC 20981 study (n = 465) was the first trial demonstrating that rituximab maintenance significantly prolonged PFS from second randomization (median 51.5 months vs. 14.9 months with observation alone, HR 0.40; p < 0.001) in patients with relapsed/resistant FL, regardless of whether the induction included CHOP (HR 0.30; p < 0.001) or R-CHOP (HR 0.54; p = 0.004).³ The PRIMA trial (n = 1018) reported a PFS benefit for rituximab induction plus maintenance in previously untreated FL patients, along with increased conversion rates from PR to CR following rituximab maintenance. After a median follow-up of 25 months from randomization (31 months from study entry), 2-year PFS was 82% with rituximab maintenance compared to 66% for the observation only group (HR 0.50, 95% CI 0.39 to 0.64; stratified log-rank, p < 0.0001).⁵⁹

A systematic review and meta-analysis of randomized controlled trials by Vidal *et al*⁶⁴ that compared RM therapy with observation or no treatment at relapse identified five trials including 985 adult patients with FL and adequate OS data. The maintenance treatment schedule differed among the trials: in three trials, rituximab was administered weekly for 4 consecutive weeks (four doses) every 6 months, and in two trials, a single infusion of rituximab was administered every 2 – 3 months. Patients treated with RM had statistically significantly better overall survival than patients in the observation arm or patients treated at relapse (HR 0.60, 95% CI 0.45 to 0.79). Of note, the survival benefit was significant in the subgroup of patients with refractory or relapsed (i.e., previously treated) FL (HR 0.58, 95% CI 0.42 to 0.79).⁶⁴

Since its preclinical development, many studies have been performed to optimize the *dose* and *schedule* of rituximab. In randomized controlled trials completed to date, maintenance therapy with rituximab 375 mg/m² was administered every 2 months for 8 months,⁵⁵ weekly for 4 weeks, repeated every 6 months for 2 years,^{54,56} every 3 months for 2 years,^{3,60} and more recently, every 2 months for 2 years.⁵⁹ Current clinical investigations aim to determine the optimal *duration* of rituximab maintenance therapy. One currently ongoing study (n = 165 randomized) will compare short maintenance consisting of four doses of rituximab (375 mg/m²) every two months with prolonged maintenance consisting of rituximab every two months for a maximum of five years or until disease progression or unacceptable toxicity, following 4 weekly doses (375 mg/m²) of induction therapy. Primary endpoint is event-free survival and preliminary safety data indicate that rituximab maintenance beyond two years is feasible without evidence for increased toxicity.⁷⁵ In the StiL NHL 7-2008 (MAINTAIN) study, patients with FL will receive induction therapy with bendamustine plus rituximab, followed by maintenance therapy with rituximab every 2 months for 4 years (experimental arm) or rituximab every 2 months for 2 years (standard arm).⁷⁶

Currently, rituximab is administered as an IV infusion over several hours. These long infusion times and the side effects related to the infusion were cited by some patients as

uncomfortable consequences of the current therapeutic treatment. Furthermore, the required procedure to establish IV access is considered invasive and can be painful, particularly in patients with malignant diseases who are treated repeatedly. Subcutaneous administration could significantly simplify treatment, shorten the administration to less than 10 minutes and improve patient satisfaction with the treatment.

Currently, rituximab is administered as an intravenous (IV) infusion over several hours. Frequently observed infusion-related reaction may require prolonging the infusion time further. For other monoclonal antibodies in other clinical settings the switch from IV administration to subcutaneous (SC) administration has resulted in an improved tolerability with less infusion-related reactions, an increased patient-convenience and an improved cost-effectiveness.^{77, 78} These advantages are anticipated for the subcutaneous administration of rituximab as well. However, so far the relatively large volume of the established rituximab dose (375 mg/m²) has hindered the subcutaneous administration of rituximab. Hence, the development of a rituximab SC formulation addresses an unmet medical need.

The results of a recently presented IV/SC pharmacokinetic/pharmacodynamic (PK/PD) cynomolgus monkey study (B cell depletion model) suggest that the SC versus IV dosing routes do not influence the pre-clinical efficacy of rituximab. Cynomolgus monkeys were treated twice, one week apart, with the rituximab SC formulation or with IV rituximab. The SC formulation contained recombinant human hyaluronidase (rHuPH20), which transiently degrades the local interstitial matrix component, hyaluronan, at the SC injection site, acting as a permeation enhancer and allowing SC administration of high volumes. The results indicate similar rituximab trough concentrations in serum as well as similar B-cell depletion efficacy in both peripheral blood and distal secondary lymphoid tissue after IV and SC dosing.⁷⁹

Results from Stage 1 of a two-stage, randomized, open-label, multicentre phase Ib study (BP22333) investigating the PK, safety and tolerability of SC rituximab maintenance treatment in patients with previously treated or untreated FL (grade 1, 2 or 3a) have recently been reported. Eligible patients, who had responded to a rituximab-containing induction regimen and had received at least 1 dose of rituximab IV (375 mg/m²) in the maintenance setting, were randomized to 1 of 4 rituximab maintenance treatment groups. Patients received a single dose of rituximab: 375 mg/m² IV, 375 mg/m² SC, 625 mg/m² SC, or 800 mg/m² SC, followed by maintenance rituximab IV every 2 or 3 months for a further year. After one year of maintenance therapy and determination of the final fixed SC dose (based upon C_{trough} levels after a single SC dose compared with IV), patients in the SC cohorts could choose to either switch to rituximab SC or continue rituximab IV until completion of the 2-year maintenance period. Data from 124 randomized patients indicate comparable rituximab concentrations at C_{trough} and extent of serum exposure (AUC₀₋₅₇) in patients administered rituximab SC between 625 mg/m² and 800 mg/m² and those administered rituximab 375 mg/m² IV. Simulations of mean C_{trough} values based on body surface area data from 54 patients predicted that a fixed dose of rituximab SC 1400 mg would be non-inferior to the rituximab IV dose of 375 mg/m². Treatment with SC doses of rituximab was well tolerated with an AE profile comparable to that of rituximab IV; of the 4 SAEs reported, none were treatment-related. A total of 157 AEs occurred in 65 patients (52%). The most commonly reported AE was local administration-associated reactions (n = 30), including rash, erythema and mild discomfort; general reactions were very rare. There were no AEs leading to death, withdrawal or treatment discontinuation.⁸⁰

It is generally accepted that for monoclonal antibodies undergoing target-mediated drug disposition linear pharmacokinetics are observed, once target sites are saturated.⁸¹ The PK of the currently approved IV dose (375 mg/m²) indicates that target sites are saturated in patients with NHL, even at trough concentrations.⁸² Therefore, achieving the same trough concentrations should lead to a comparable saturation of target sites and comparable therapeutic effect. A fixed SC dose of 1400 mg has therefore been selected for formal C_{trough} non-inferiority testing in Stage 2 of the above described trial as well as for further clinical testing of maintenance therapy with rituximab SC. Registration studies are currently ongoing.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

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 who responded to Induction and initial 2 years maintenance therapy (Maintenance I) at the end of study (EOS).

2.2 SECONDARY OBJECTIVES

Secondary objectives of the study 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 EFS, Time to Next Lymphoma Treatment (TNLT), OS measured from first induction dose of rituximab (OS_{regist}) and from the time of randomization to Maintenance II (OS_{rand}), ORR, PR to 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 AEs, SAEs, IRRs/ARRs and immunoglobulin quantification.

2.3 EXPLORATORY OBJECTIVES

[REDACTED]

3. STUDY DESIGN

3.1 OVERVIEW OF STUDY DESIGN

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 1).

The total study duration and active patient participation in the study is approximately 69 months, including:

- 24 months enrollment period
- 6 - 8 months Induction period
- 24 months initial rituximab SC maintenance (Maintenance I)

Minimum 15 months randomized period: observation only or maintenance treatment with SC rituximab continued until progression (Maintenance II).

After a patient has consented to participate in this study, the following procedures will be carried out:

- Baseline assessment: will be performed according to the Schedule of Assessments (Table 5). Refer to Section 5.1.1 for details.

See Section 6.1.4 for details about dose modifications, interruptions and delays for rituximab and chemotherapy.

- **Induction:** 8 cycles of rituximab will be administered in combination with 6 - 8 cycles of chemotherapy (bendamustine, CHOP, CVP, FCM, MCP, CHVP-IFN, chlorambucil or any fludarabine-containing regimen including oral fludarabine, R-GIFOX; selection at the Investigator's discretion). The switch between different chemotherapy regimens is not permitted. The first administration of rituximab will be by IV infusion on Day 1 of the first Induction cycle, at dose of 375 mg/m² body surface area (BSA). In the absence of infusion-related side effects, rituximab will subsequently be administered SC starting 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 grade 3 or 4 IRR after the second rituximab infusion will be withdrawn from the study.
 - **Study Visit Schedule** for patients during Induction will occur at the beginning of each 3-week or 4-week treatment cycle, according to the Schedule of Assessments (Table 5). Refer to Section 5.1.3.1 for details.
 - **Response assessments** will be conducted by the Investigator after 4 cycles (or after 3 cycles in case the Induction comprised of 6 chemotherapy administrations) and at the end of Induction (i.e. after 8 cycles of rituximab). Response should be assessed according to the Cheson response criteria for indolent lymphoma¹ (see Appendix 1) or by the recommendations for Waldenström's macroglobulinemia² (see Appendix 2). 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. Patients with SD 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 therapy. 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. See Section 6.1.4 for details about dose modifications, interruptions and delays.

- - **Study Visit Schedule** for patients during Maintenance I will occur according to the Schedule of Assessments (Table 5). Refer to Section 5.1.3.2 for details.
- **Response assessment** will be conducted by the Investigator every 6 months during Maintenance I according to the Cheson response criteria for indolent lymphoma¹

(see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)). 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, tumour response will be assessed and compared to the patient's baseline status and patients with PR or CR (as determined by the Investigator using the Cheson response criteria,¹ see [Appendix 1](#), or by the recommendations for Waldenström's macroglobulinemia,² see [Appendix 2](#)) will be randomized to maintenance treatment with SC rituximab continued until progression or until EOS (**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 EOS.

- **Study Visit Schedule** for patients during Maintenance II will occur according to the Schedule of Assessments ([Table 5](#)) and will include safety, disease progression, new anti-lymphoma treatments and survival; refers to Section [5.1.3.3](#) for details. Disease progression will be evaluated by the Investigator every 6 months according to Cheson response criteria for indolent lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)). Patients with PD will come off study treatment and be followed for survival.

3.1.1 Rationale for Study Design

Although the effectiveness of rituximab as a single agent and in conjunction with known chemotherapy regimens has made it a standard of care in the treatment of NHL, there is a clear medical need for an optimized route of administration and maintenance schedule.^{9,38} Results of several prospective trials and a recently published systematic review of randomized controlled trials suggest that maintenance therapy with rituximab, either as 4 weekly infusions every 6 months or as a single infusion every 2-3 months, should be added to standard therapy for patients with relapsed or refractory (i.e. previously treated) FL after successful induction therapy.⁶⁴ However, the optimum rituximab maintenance regimen, including duration of treatment has not yet been determined.

The current open label multinational randomized controlled trial will evaluate whether continuous maintenance therapy with SC rituximab compared to observation (no treatment) will provide additional clinical benefits and be safe in patients with relapsed, Grade 1, 2 or 3a CD20+ indolent NHL who responded to induction plus 2-year maintenance therapy with rituximab. The randomized controlled design will allow for an unbiased treatment allocation. Considering that the continuous maintenance treatment with rituximab will be compared with no treatment (observation only), allocation concealment is not feasible. PFS is a standard efficacy outcome and commonly selected as primary endpoint in clinical trials evaluating maintenance treatment in NHL.^{3,59}

Rituximab maintenance therapy after effective induction has been shown to prolong progression-free survival, compared with no further treatment until relapse, in randomized, prospective phase III clinical trials in FL. In addition, the use of RM therapy is likely to have an important psychological and emotional impact for many patients. Currently, all patients are expected to relapse eventually following induction treatment: the knowledge that they are being actively treated to delay relapse for as long as possible may provide significant reassurance and emotional support. Overall, therefore,

rituximab maintenance therapy might be expected to improve quality of life for patients with FL over and above the observed clinical benefits in PFS.⁸³

The economic burden of follicular NHL is significant, but available data are generally limited to retrospective considerations of hospital-based direct treatment costs, with little information available regarding societal cost of illness, and with most direct cost information originating from the US. Rituximab is considered cost effective when added to induction chemotherapy, and when used as maintenance therapy.^{84,85,86,87} However, no studies of per-patient or national indirect costs of illness were identified. In most studies the focus was on the direct costs of rituximab.⁸⁴ Therefore there is a need for more real-life cost data, particularly related to the extended maintenance dosing. These aspects will be addressed in the *Time in Motion* pharmacoeconomic sub-study (detailed in a separate protocol).

3.1.2 Rationale for Treatment

Induction Treatment

Given the options available for induction regimens, and varying benefits for each according to patient group and line of treatment, no single standard chemotherapy regimen has been universally adopted for the treatment of patients with NHL. Therefore the chemotherapy to be combined with SC rituximab will not be stipulated in the current study, although it will include only approved commercially available products. In keeping with current recommendations for induction therapy in the relapsed setting, the first IV infusion and 7 SC rituximab administrations will be required during induction in the current study before a patient demonstrating initial response (PR or CR) at the end of induction can proceed to maintenance treatment with single agent rituximab. 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, as such they will receive 6 SC administrations (see Section 5.1.3.1). Prior exposure to rituximab induction (and maintenance in countries where prescribed) in the first-line setting is preferred as it will provide valuable information on the potential benefit and safety profile of rituximab re-treatment.

Considering that rituximab is currently not indicated for the treatment of indolent NHL other than low-grade malignant lymphoma or follicular lymphoma, the study will not mandate that patients with relapsed indolent NHL (other than FL) be previously treated with rituximab as first-line treatment.

Maintenance Treatment

The pivotal **EORTC 20981 Intergroup study**,³ the results of which formed the basis for submitting an application to the European Medicines Agency (EMA) for a new indication of rituximab maintenance therapy in FL used a once every 3-month dosing schedule. However, data from several phase II and pharmacokinetic studies reported after the start of the EORTC 20981 study suggested that a shorter interval between infusions may be more suitable to reach an adequate serum rituximab concentration level for all patients.^{88, 89} Data from a phase II study investigating individualised rituximab maintenance therapy found that to maintain the level of rituximab above 25 µg/mL after two prior rituximab infusions, patients required a repeat bolus at a median of 3 months after the second infusion. The range for this estimate was 2 - 4 months, suggesting that for some patients, a 3-month dosing interval may be inadequate to maintain rituximab serum concentration above 25 µg/mL.⁸⁸ The scheme of rituximab maintenance therapy as one infusion every 8 weeks was further tested in two Phase II clinical trials, enrolling

patients with indolent (low-grade or follicular) NHL or patients with MCL. In both studies four additional doses of rituximab at 8-week intervals resulted in significantly prolonged EFS.^{55, 90} Consequently, the recently reported phase III randomized PRIMA study,⁵⁹ compared rituximab maintenance therapy administered once every 2 months for 2 years to observation alone following a defined rituximab-containing induction therapy (R-CVP, R-CHOP or R-FCM) in 1217 patients with previously untreated FL. Maintenance rituximab, compared to observation alone, was associated with significantly higher PFS (74.9% vs. 57.6% respectively; HR 0.55, 95% CI 0.44 to 0.68; $p < 0.0001$) after a median follow-up of 36 months, and significantly higher CR/Cru rate (71.5% vs. 52.2%; $p = 0.0001$) 2 years after randomization. OS did not significantly differ between the groups. Importantly, rituximab maintenance was well tolerated in these studies, with a limited number of AEs leading to treatment discontinuation and no unexpected safety findings.^{59, 75}

Currently there is one phase Ib randomized, open-label clinical study (BP22333) ongoing with rituximab SC in patients with FL. Study BP22333 comprises two stages: dose-finding stage 1 and dose confirmation stage 2. In stage 2, the final fixed SC dose of 1400 mg identified in stage 1 is administered to patients randomized to the SC arm until the end of maintenance therapy. Results from Stage 1 ($n = 124$) indicate that SC rituximab can be delivered quickly, comfortably and safely while achieving serum exposure comparable to the approved IV formulation of rituximab in FL patients during maintenance treatment. The study compared a maintenance regimen comprised of a single administration of one of four rituximab doses (375 mg/m² IV, 375 mg/m² SC, 625 mg/m² SC, or 800 mg/m² SC), followed by rituximab IV every 2 or 3 months for a further year. Comparable rituximab concentrations at C_{trough} and extent of serum exposure (AUC_{0-57}) were achieved in patients administered rituximab SC between 625 mg/m² and 800 mg/m² and those administered rituximab 375 mg/m² IV. Simulations of mean C_{trough} values based on body surface area data from 54 patients predicted that a fixed dose of rituximab SC 1400 mg would be non-inferior to the rituximab IV dose of 375 mg/m². Importantly, treatment with SC rituximab was well tolerated with an AE profile comparable to that of rituximab IV; while general reactions were very rare. There were no treatment-related SAEs, AEs leading to death, withdrawal or treatment discontinuation.⁸⁰

The above detailed Stage 1 PK data formed the basis for selecting the 1400 mg fixed SC dose testing as maintenance therapy in the current trial.

3.1.3 End of Study

The end of study is defined as the last patient's last visit in Maintenance II. The study will end when all patients randomized in Maintenance II have been followed for at least 15 months after randomization, or earlier if the 129th PFS event has been reported or one of the following is documented for all patients: disease recurrence, withdrawal from the study, loss to follow-up, or death.

3.2 NUMBER OF PATIENTS / ASSIGNMENT TO TREATMENT GROUPS

Approximately 700 enrolled patients were expected to yield a minimum of 330 randomized patients (maintenance II). At the conclusion of enrolment and all randomizations 694 patients were enrolled and 276 patients were randomized to maintenance II.

The recruitment period was expected to be approximately 24 months. Enrolment of the 694 patients required 31 months

3.3 CENTRES

This is a multinational, multicentre study, with approximately 190 centres worldwide.

4. STUDY POPULATION

4.1 OVERVIEW

The target population will consist of adults with relapsed or refractory CD20+ indolent follicular NHL Grade 1, 2 or 3a, or other CD20+ indolent NHL (Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma, marginal zone lymphoma) according to the WHO classification system.

4.1.1 Recruitment Procedures

Patients will be identified for potential recruitment using pre-screening enrolment logs; Independent Ethics Committee (IEC) approved newspaper/radio advertisements and/or mailing lists.

4.2 INCLUSION CRITERIA

Patients must fulfil all of the following criteria at enrolment (i.e. prior to the first dose of Induction Treatment):

1. Signed, written informed consent form.
2. Age \geq 18 years.
3. Histologically confirmed, CD20+ follicular NHL Grade 1, 2 or 3a, or other CD20+ indolent NHL (Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma, marginal zone lymphoma,) according to the WHO classification system.
4. Patients must have received, and must have relapsed or been refractory to, one or more lines of adequate therapy *prior to enrolment*, including at least one line consisting of immunotherapy and/or chemotherapy and/or radiotherapy.

Note: Rituximab administration in first line is not mandated, but preferred.

5. Eastern Cooperative Oncology Group (ECOG) performance status \leq 2.

4.3 EXCLUSION CRITERIA

A patient will be excluded if they meet any of the following criteria:

DISEASE-SPECIFIC:

1. Transformation to high-grade lymphoma.
2. Patients with aggressive lymphoma (e.g. MCL).
3. Presence or history of central nervous system (CNS) lymphomatous disease (e.g., CNS lymphoma or lymphomatous meningitis).

OTHER MEDICAL CONDITIONS OR TREATMENTS:

4. Other malignancy within 5 years prior to enrolment, with the following exceptions (as long as curatively treated): carcinoma *in situ* of the cervix, squamous cell carcinoma of the skin, or basal cell skin cancer. Cervical carcinoma stage 1B or less, breast cancer *in situ*, or localized prostate cancer stage T1c or less may be considered, provided that the patient was treated with curative intent and has been relapse- and metastasis-free for at least 2 years prior to enrolment.
5. Inadequate haematological function within 28 days prior to the first rituximab induction dose, defined as any of the following (unless the abnormality is related to bone marrow involvement by NHL):
 - a. Haemoglobin (Hb) < 9.0 g/dL (5.6 mmol/L)
 - b. Absolute neutrophil count (ANC) < $1.0 \times 10^9/L$ (1,000/ μ L)
 - c. Platelet count < $100 \times 10^9/L$ (100,000/ μ L); lower platelet count (but not below $50 \times 10^9/L$) is acceptable if due to toxicity of previous chemotherapy and not accompanied by bleeding.
6. Patients with severe autoimmune cytopenias as assessed by the physician.

Note: Coombs positive patients without clinical signs of autoimmune haemolytic anemia are eligible for enrolment.
7. Inadequate hepatic function prior to the first rituximab induction dose, defined as any of the following:
 - a. Total bilirubin > 1.5 times the upper limit of normal (ULN). Note: patients with documented Gilbert disease may be enrolled if total bilirubin is ≤ 3.0 x ULN.
 - b. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2.5 times the ULN
 - c. Alkaline phosphatase > 2.5 times ULN
8. Inadequate renal function prior to the first rituximab induction dose, defined as creatinine clearance (CrCl) < 30 mL/minute or serum creatinine > 2 mg/dL (197 μ mol/L).
9. Known human immunodeficiency virus (HIV) infection.
10. Active and/or severe infection (e.g. tuberculosis, sepsis and opportunistic infections, active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection).
11. Other serious underlying medical conditions, which, in the Investigator's judgment, could impair the ability of the patient to participate in the study (e.g., uncontrolled diabetes mellitus, gastric ulcers, active autoimmune disease).
12. Known or suspected hypersensitivity to components of the investigational product, including known hypersensitivity or previous anaphylactic reaction to murine antibodies or proteins.

13. Regular corticosteroid use within 28 days prior to the first rituximab induction dose, unless administered at a dose equivalent to < 20 mg/day prednisone/prednisolone.

Note: inhaled or topical corticosteroids are permitted.

14. Major surgery (excluding lymph node biopsy) within 28 days prior to the first rituximab induction dose.
15. Treatment with an investigational product within 30 days prior to enrolment.

GENERAL:

16. Inability to provide informed consent.
17. Life expectancy of less than 6 months.
18. History of poor compliance during previous lines of therapy.
19. Pregnant or breastfeeding patients. A negative serum pregnancy test is required 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 rituximab 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.
20. Fertile men or women of childbearing potential who do not agree to use a highly effective measure of contraception (such as oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) throughout the study and for at least 12 months after the last dose of rituximab.

4.4 CRITERIA FOR PROLONGED MAINTENANCE (MAINTENANCE II)

In addition to the above listed enrolment criteria, patients must fulfil the following criteria in order to be randomized:

1. Completed rituximab-based Induction and initial 2-year maintenance therapy with subcutaneous rituximab (Maintenance I).
2. PR or CR as confirmed by computerized tomography (CT) after Maintenance I. Response assessment is completed according to the International Working Group response criteria for lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)).

Note: Patients enrolled at sites using PET scan as part of their routine response assessment must have achieved CR or PR in CT scan according to the International Working Group (Cheson) response criteria for lymphoma.¹

Randomization will occur using a centralized interactive voice/web response system (IVRS/IWRS) in a 1:1 fashion, stratified according to indolent NHL subtype (FL, non-follicular lymphoma), and FLIPI category (low risk, intermediate risk, high risk).

Under no circumstances are patients who enrol in this study permitted to be re-entered onto the study for a second course of treatment.

4.5 CONCOMITANT MEDICATION AND TREATMENT

All medications (prescription and over-the-counter drugs) taken within 28 days prior to study screening must be recorded on the electronic case report form (eCRF). In addition, any diagnostic, therapeutic or surgical procedure performed during the study period, should be recorded including the date, indication, description of the procedure(s) and any clinical findings. Patients should receive full supportive care (such as G-CSF support, transfusions of blood and blood products, antibiotics, anti-emetics etc., where applicable.) The reason(s) for treatment, dosage and dates of treatment must be recorded in the eCRF.

4.5.1 Permissible Concomitant Medication and Treatment

4.5.1.1 Prophylaxis of infusion/injection-related reactions

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

- paracetamol (acetaminophen)
- diphenhydramine hydrochloride or alternative antihistamine.
- steroids (prednisone/prednisolone).

Premedication with glucocorticoids should be considered if rituximab is not given in combination with glucocorticoid-containing chemotherapy. If given, these medications must be documented on the Concomitant Medications eCRF.

Rituximab should be administered on Day 1 of each cycle, after intravenous administration of the glucocorticoid component of the chemotherapy, if applicable.

4.5.1.2 Prophylaxis of nausea and vomiting

Premedication to prevent nausea and vomiting is allowed as per institutional practice. They should be administered prior to the chemotherapy administration and should be documented on the Concomitant Medications eCRF accordingly.

4.5.1.3 Antimicrobial and antiviral prophylaxis

Antimicrobial and antiviral prophylaxis may be used as per institutional practice. If given, they must be documented on the Concomitant Medications eCRF.

4.5.1.4 Prophylaxis for haemorrhagic cystitis

Mesna (2-Mercapto Ethane Sulfonate sodium) may be used as prophylaxis according to institutional practice and should be documented on the Concomitant Medications eCRF.

4.5.1.5 Tumour-lysis syndrome prophylaxis

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

4.5.1.6 Hydration, alkalization of urine and urostatics

The mainstays of TLS prevention include hydration and prophylactic rasburicase (recombinant urate oxidase) in high-risk patients, hydration plus allopurinol or

rasburicase for intermediate-risk patients, and close monitoring of electrolyte abnormalities for low-risk patients. Primary management of established TLS involves similar recommendations, with the addition of aggressive hydration and diuresis, plus allopurinol or rasburicase for hyperuricemia, whereas alkalinization is not recommended.^{91,92}

Recently four cases of Stevens-Johnson-Syndrome/Toxic epidermal necrolysis (SJS/TEN) have been reported in patients who were treated with allopurinol and bendamustine with or without rituximab. There may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly. Allopurinol should be used with caution and only if deemed necessary by the treating physician but not as a standard preventive measure for possible tumour lysis syndrome. Preventive measures include maintaining adequate volume status, and close monitoring of serum chemistry, particularly potassium and uric acid levels. If patients experience any skin reactions during treatment, they should be monitored closely and in case of any suspicion of evolving to a serious muco-cutaneous reaction, treatment with any suspected drugs including but not limited to bendamustine, rituximab, allopurinol and amoxicillin should be discontinued until complete resolution of event.

4.5.1.7 Other Premedication

Institutions should follow their standard premedication procedures regarding other supportive care, including transfusions of blood and blood products, or haematopoietic colony-stimulating factors (G-CSF). Regular application of G-CSF is not generally recommended. However, it should be applied according to the ASCO guidelines especially in case of infections and prolonged neutropenia in previous cycles.⁹³

4.5.2 Prohibited Concomitant Medication and Treatment

The following treatments are prohibited during study treatment:

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

Patients receiving any of the prohibited therapies will be discontinued and followed for survival. Patients whose study treatment is discontinued due to reasons other than progressive disease will continue to be followed until progression or death.

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

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

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

4.6 CRITERIA FOR PREMATURE WITHDRAWAL

Patients have the right to withdraw from the study at any time for any reason. Should a patient decide to withdraw, he/she will be encouraged to return to the study centre within 4 weeks for an end-of-treatment evaluation (see Section 5.1.5); all efforts will be made to

complete and report the observations prior to withdrawal as thoroughly as possible. The primary reason for discontinuation must be recorded on the appropriate eCRF page.

Discontinuing patients should also be asked if they can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF. If lost to follow-up, the Investigator should contact the patient or a responsible relative to establish as completely as possible the reason for the withdrawal.

Besides due to disease progression, the Investigator may discontinue study treatment and/or withdraw patients from the study for the following reasons:

- Intercurrent illness
- Occurrence of life-threatening or severe reactions
- Occurrence of TLS
- Any significant AE that compromises the patient's ability to participate in the study
- Pregnancy
- Need for prohibited treatment (see Section 4.5.2)
- Lack of compliance with the study and/or study procedures (e.g. dosing instructions, study visits)
- Any reason where the investigator considers that withdrawal is in the best interest of the patient

All end-of-treatment procedures should be performed at the time of discontinuation.

Patients should be informed of circumstances under which their participation may be terminated by the Investigator without their consent.

The reason(s) for treatment discontinuation and/or withdrawal must be documented in the eCRF. In case of death or disease progression the Death eCRF or Progression/relapse eCRF pages must be completed respectively. If the reason for treatment discontinuation and/or withdrawal is an AE, the principal specific event will be recorded on the eCRF. The patient should be followed until the AE has resolved or reached a stable/chronic condition.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. To the extent feasible, discontinuations should be limited to the study treatment only, with further follow-up continuing until the end of the study.

4.7 REPLACEMENT POLICY

4.7.1 For Patients

Patients randomized into the study will not be replaced.

4.7.2 For Centres

A centre may be replaced for the following administrative reasons:

- Excessively slow recruitment.

- Poor adherence to the protocol or Good Clinical Practices.
- Inaccurate/inappropriate clinical data entry into the eCRFs
- Excessively slow submission of study data to the Sponsor

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

A summary of visits and clinical procedures is found in [Table 5](#) Schedule of assessments and procedures.

Table 5 SCHEDULE OF ASSESSMENTS

Study Period	Screening / Baseline Visit	Induction Rituximab IV/SC +/- Chemotherapy [a]				Maintenance I Rituximab SC		Maintenance II A: Rituximab SC B: Observation	End of Treatment	Off-Treatment Follow-up
Visit		V1-V4	Staging [b]	V5-V8	Staging [c]	V9-V20	Staging [d]	V21+		
Timing / Assessments	D-28 to D-1	D1 every 21-28 days [± 2 days] 4 cycles	End Cycle 3 or 4	D1 every 21-28 days [± 2 days] 4 cycles	End Cycle 8 (End of induction therapy)	D1 every 8 wks [56 ± 7 days] 12 cycles [2 yrs]	End mainten. therapy	D1 every 8 wks [56 ± 7 days] until PD or EOS	Within 4 weeks of last dose	Every 6 months until EOS [± 14 days]
Written informed consent [e]	X									
Demographic data	X									
NHL diagnosis and Ann Arbor staging [f]	X									
Bone marrow assessment [g]	X		If CR and baseline involvement		If CR and baseline involvement	If CR and baseline involvement	If CR and baseline involvement	If CR and baseline involvement		If CR and baseline involvement
Medical history	X									
Documentation of/testing for HIV, hepatitis and other infections [h]	X									
12-lead ECG	X									
Tumour evaluation using CT scan [i]	X		X		X	Every 6 months (V11, V14, V17, V20)	X	Every 6 months (V23, V26, V29, etc.)		X
Physical examination, infection assessment, vital signs [j]	X	X		X	X	X		X	X	
Height, weight and BSA	X									
FLIPI score [k]	X									
ECOG performance status [l]	X		X		X	X	X	X	X	
Serum pregnancy test [m]	X									
Safety laboratory: haematology and biochemistry [n]	X	X	X	X	X	X	X	X	X	
IgG, IgM and IgA quantification [o]	X				X	Every 12 months (V14, V20)		Every 12 months (V26, V32, etc.)		
Review of inclusion / exclusion criteria	X									

Study Period	Screening / Baseline Visit	Induction Rituximab IV/SC +/- Chemotherapy [a]				Maintenance I Rituximab SC		Maintenance II A: Rituximab SC B: Observation	End of Treatment	Off-Treatment Follow-up
Visit		V1-V4	Staging [b]	V5-V8	Staging [c]	V9-V20	Staging [d]	V21+		
Timing / Assessments	D-28 to D-1	D1 every 21-28 days [± 2 days] 4 cycles	End Cycle 3 or 4	D1 every 21-28 days [± 2 days] 4 cycles	End Cycle 8 (End of induction therapy)	D1 every 8 wks [56 ± 7 days] 12 cycles [2 yrs]	End mainten. therapy	D1 every 8 wks [56 ± 7 days] until PD or EOS	Within 4 weeks of last dose	Every 6 months until EOS [± 14 days]
Enrolment via eCRF										
Review of criteria for prolonged maintenance Randomization by IVRS\IWRS								V21		
Rituximab treatment administration [p]		X		X		X		X [u]		
Adverse event recording [q]	X	X	X	X	X	X	X	X	X	X
Concomitant treatments & therapies [r]	X	X	X	X	X	X	X	X	X	X
Assessment of disease status, including progression [t]		X	X	X	X	X	X	X		X
Survival										X

- Approved commercially available chemotherapy can include bendamustine, CHOP, CVP, FCM, MCP, CHVP-IFN, chlorambucil or any fludarabine-containing regimen including oral fludarabine, GIFOX; selection at the Investigator's discretion
- Staging assessment performed within 14–28 days after D1 of Visit when the Induction treatment includes 8 cycles of chemotherapy (or within 14–28 days after D1 of Visit 3 when the Induction treatment includes 6 cycles of chemotherapy. Refer to Section 6.1.1 for chemotherapy options.
- Staging assessment performed within 14–28 days after day 1 of the last cycle of rituximab-based Induction. The second tumour staging will occur after the 8th cycle of rituximab-based Induction treatment.
- Staging: Post-maintenance assessment performed within 28 days of the last rituximab maintenance dose, with results compared to the patient's baseline status. The required procedures can be performed either at the previous visit or at staging.
- Signed informed consent must be obtained prior to any baseline assessments or activities.
- Diagnosis of non-Hodgkin's Lymphoma must have included histological diagnosis and initial CD20 expression confirmation.
- For patients who have had a previous bone marrow assessment within 6 months prior to enrollment: 1) if bone marrow involvement was documented, these patients are considered positive and do not require another bone marrow assessment prior to entering the study; 2) if bone marrow involvement was **not** documented, another bone marrow assessment is only required prior to entering the study if the patient now exhibits signs/symptoms suggesting bone marrow involvement (e.g. anemia without haemolysis, thrombocytopenia, etc.). For patients who had a bone marrow assessment ≥ 6 months prior to enrolment, or who have not had a previous bone marrow assessment, a baseline

bone marrow assessment must be done within 28 days prior to the first rituximab induction dose. In addition, bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline. Once the CR is confirmed bone marrow assessment is not needed unless clinically indicated.

- h. Patients known to have HIV, Hepatitis C, active Hepatitis B or signs or symptoms of other active and/or severe infection must not be included in the study. Serology should be performed according to clinical judgment before and during treatment with rituximab. Patients found to have HIV, Hepatitis C or active Hepatitis B must either not start, or stop rituximab induction/maintenance therapy and enter active follow-up. Local guidelines for patient consent to viral testing must be adhered to.
- i. Tumour assessments will be based on CT scans with contrast: neck (if clinically indicated), chest, abdomen and pelvis (if detectable by these techniques) to document nodal disease or organ involvement. Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach). The CT scan used for eligibility assessment may be up to 8 weeks old prior to study entry. The on-treatment CT scan used for response assessment may be up to 8 weeks old and should be compared to pre-induction CT. The end-of-Induction response assessment including radiology/imaging report must be provided within 8 weeks of the last Induction cycle. At the end of the 2-year rituximab maintenance period, tumour response will be assessed and compared to the patient's baseline status. Patients with CR or PR will be randomized. Patients with PD at any time during the study will come off study treatment and will start Off-Treatment Follow-Up, being followed every 6 months for survival until the end of the study. Patients with SD at the end of Induction will come off study treatment and will enter Off-Treatment Follow-Up, being followed every 6 months for PD and survival until the end of the study. Achievement of CR after initial PR on rituximab maintenance therapy should be recorded. Patients maintaining response may continue receiving treatment. Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline. In patients not progressing at EOS treatment, tumour assessments should be done every 6 months until PD.
- j. Patients should be assessed for presence of active infections throughout the treatment periods. Vital signs assessment includes resting heart rate, body temperature and blood pressure.
- k. FLIPI score determined at baseline (prior to the first Induction dose). Where possible, the baseline FLIPI score should be calculated from the patient notes. Missing FLIPI scores will not preclude enrolment or randomization.
- l. ECOG performance status needs to be ≤ 2 for inclusion of the patient into the study.
- m. Women of childbearing potential (defined as pre-menopausal women or women who are < 2 years after the onset of menopause and not surgically sterile) must undergo serum pregnancy test within 7 days prior to first rituximab administration or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the first rituximab administration.
- n. Haematology parameters will include haemoglobin, haematocrit, red blood cell count, white blood cell count with differentials, and platelet count. Biochemistry parameters will include sodium, potassium, calcium, phosphate, alanine aminotransferase (ALT/SGPT), total bilirubin, serum creatinine, alkaline phosphatase, albumin, BUN, C-reactive protein and Lactate Dehydrogenase (LDH), and if possible aspartate aminotransferase (AST/SGOT). The results from the safety laboratory assessments must be available on the day of rituximab administrations.
- o. After baseline, IgG, IgM and IgA quantification will be completed once a year during the 2-year rituximab maintenance period (maintenance injections #6 and #12), once a year during randomized rituximab maintenance (**Arm A**) and in case of suspicious infections. The results from these assessments must be available on the day of the next rituximab injection. Samples can be taken up to two weeks before the date of injection. In case the results of the Ig measurements could not be obtained before the planned treatment administration, the treatment does not have to be postponed until the Ig results become available. However, the Ig results must be reviewed as soon as possible and a new sample for Ig measurement must be drawn before the next injection visit in order to have the new Ig results available for the next injection visit.
- p. The first rituximab dose during Induction will be administered as IV infusion on Day 1 of Cycle 1, at a dose of 375 mg/m^2 BSA. In the absence of an IRR, subsequent rituximab doses will be administered SC, 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 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 grade 3 or 4 IRR after the second rituximab infusion will be withdrawn from the study. Induction chemotherapy selected by the study Investigator will be administered in accordance with schedules outlined in Section 6.1.1 of the protocol. The first rituximab maintenance dose must be administered within 8 -12 weeks after the administration of the last dose of rituximab in the induction therapy (see Section 6.1.2). The first visit in maintenance II must occur 8 weeks (± 7 days) after the administration of the last dose of rituximab in maintenance I (see Section 6.1.2).
- q. After ICF signing, but prior to initiation of any study drugs, only SAEs caused by a protocol-mandated intervention (e.g. an invasive procedure such as biopsy or medication washout) will be collected. All AEs reported during the study will be documented and graded using the NCI CTC-AE criteria, version 4.0. Serious adverse events (SAEs) will be reported according to the ICH E2 Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting; refer to Section 7.1.2. Once a patient has permanently discontinued study treatment, all SAEs will continue to be followed until resolution.

- r. Recording of concomitant treatments & therapies will include any new anti-lymphoma treatment initiated after the baseline visit. In patients who have permanently discontinued study treatment, only new anti-lymphoma treatments will be recorded.

- t. For requirements regarding tumour evaluations, refer to item "h" above. Clinical assessment of disease status should be made at all visits by Investigators according to local practice. Progression of disease (physical examination) is to be assessed from Visit 1 onwards. During the randomized treatment period, patients in the rituximab SC maintenance arm will be treated until PD, unacceptable toxicity, withdrawal of patient consent or until EOS. All patients in **Arm A** and **Arm B** will be actively followed for safety, tumour response/progression, new anti-lymphoma treatments and survival for at least 15 months after randomization. Enrolled patients who do not complete treatment per protocol for any reason will undergo the end-of-treatment assessment and enter Off-Treatment Follow-up. 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. Patients with SD 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.
- u. Not applicable for patients in **Arm B** (observation, no treatment).

Note:

- After the end-of-treatment or the end of participation in observation arm B all patients will enter Off-Treatment Follow-up and be followed for resolution of AEs related to SC rituximab induction/maintenance therapy as per Table 14, survival, disease status (which might include bone marrow and tumour assessment if PD not already documented) and whether a new anti-lymphoma treatment has been started.
- For details on the assessments or Medical Care Utilization parameters, please refer to the *Time in Motion* pharmacoeconomic Sub-study protocol.

5.1 SCHEDULE OF ASSESSMENTS

5.1.1 Screening and baseline Examination and Eligibility Screening Form

All patients must sign and date the most current IEC-approved written informed consent before any study specific assessments or procedures are performed. An original signed consent form will be retained by the Investigator and the patient will receive a copy to take home. Potential risks will be explained to all candidates.

All the following assessments must be performed within 28 days prior to the first planned dose of study medication:

- Written informed consent
- Demographic data (date of birth, gender, race/ethnicity)
- Preliminary review of Inclusion/Exclusion criteria
- Confirmation/documentation of adequate NHL diagnosis, staging and CD20 expression, as per medical history and medical files
- Ann Arbor staging (see [Appendix 4](#))
- Bone marrow assessment:

Patients who have had a previous bone marrow assessment within 6 months prior to enrolment:

- If bone marrow involvement was documented, these patients are considered positive and do not require another bone marrow assessment prior to entering the study
- If bone marrow involvement was **not** documented, another bone marrow assessment is only required prior to entering the study if the patient now exhibits signs/symptoms suggesting bone marrow involvement (e.g. anemia without haemolysis, thrombocytopenia, etc.).

For patients who had a bone marrow assessment \geq 6 months prior to enrolment or who have not had a previous bone marrow assessment

- a baseline bone marrow assessment must be done within 28 days prior to initiation of study treatment.
- Complete medical history, including confirmation/documentation of adequate prior therapy:
 - Patients must have received and must have relapsed or been refractory to one or more lines of adequate induction therapy prior to enrolment, including at least one line consisting of immunotherapy and/or chemotherapy.
- Confirmation of negative history for HIV, Hepatitis B or C infection. Hepatitis B, C and HIV serology should be performed according to clinical judgment
- 12-lead ECG
- Tumour assessment / Current disease staging:

- CT scan with contrast: neck (if clinically indicated), chest, abdomen and pelvis (if detectable by these techniques) to document nodal disease or organ involvement.
- Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach)

Note:

- The baseline CT scan, or appropriate measurements replacing radiographic images for lymphomas that cannot be measured by radiographic techniques, may be performed up to 8 weeks prior to first rituximab administration.
- During this study, bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline.
- Physical examination, infection assessment and vital signs (resting heart rate, blood pressure and body temperature)
- Height, weight, and BSA
- FLIPI index assessed before Induction therapy (see [Appendix 4](#)). Where possible, the baseline FLIPI score should be calculated from the patient notes. **Note:** missing FLIPI scores do not preclude enrolment (or randomization).
- ECOG performance status (see [Appendix 4](#))
- Laboratory assessments (see Sections [5.3](#) and [7.1.4](#) for details about individual laboratory assays and reporting or abnormalities)
 - Serum pregnancy test (women of childbearing potential only) must be performed within 7 days of the first rituximab administration (or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the first rituximab dose) to rule out pregnancy.
 - Routine safety laboratory: haematology and biochemistry, including LDH.
 - IgG, IgM and IgA quantification
- Final review of Inclusion / Exclusion criteria and enrolment via eCRF
- AE recording (starting from Informed Consent signature). **Note:** SAEs occurring after informed consent, but prior to initiation of any study medications are only collected if caused by a protocol-mandated intervention (e.g. invasive procedures such as biopsies, or medication washout).
- Concomitant treatments and therapies

5.1.2 Procedures for Enrolment of Eligible Patients

Once a patient has been determined to meet the study entry criteria, he/she will be assigned a study Patient Enrolment and Identification Code. A Patient Enrolment and Identification Code List (PEICL) must be maintained by the Investigator.

5.1.3 Assessments during the Treatment Period

Eligible patients will receive treatment in three phases:

- Induction (6 to 8 months, depending on the combination chemotherapy regimen)
- Maintenance I (24 months)
- Maintenance II (SC rituximab continued until progression or until EOS [**Arm A**] or observation [**Arm B**]; minimum 15 months).

During Maintenance II, patients in the rituximab SC maintenance arm will be treated until PD, unacceptable toxicity, withdrawal of patient consent or until EOS. All patients in **Arm A** and **Arm B** will be actively followed (every 8 weeks, with tumour assessments every 6 months), for safety, tumour response/progression, new anti-lymphoma treatments and survival for at least 15 months after randomization. Enrolled patients who do not complete treatment per protocol for any reason will undergo the end-of-treatment assessment and enter Off-Treatment Follow-up. Patients with PD at any time during the study will come off study treatment and will start Off-Treatment Follow-Up, being followed every 6 months for survival until the end of the study. Patients with SD at the end of Induction will come off study treatment and will enter Off-Treatment Follow-Up, being followed every 6 months for PD and survival until the end of the study.

5.1.3.1 Induction


A total of 8 treatment visits and two staging visits are planned during Induction. Eight cycles of rituximab will be administered in combination with 6 - 8 cycles of chemotherapy (bendamustine, CHOP, CVP, FCM, MCP, CHVP-IFN, chlorambucil or any fludarabine-containing regimen including oral fludarabine, R-GIFOX; selection at the Investigator's discretion). The switch between different chemotherapy regimens is not permitted. The first administration of rituximab will be by IV infusion on Day 1 of the first Induction cycle, at dose of 375 mg/m² BSA. In the absence of infusion-related side effects, rituximab will subsequently be administered SC starting Day 1 of each Induction cycle at a fixed dose of 1400 mg, every 3-4 weeks, followed by administration of chemotherapy. 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 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), as such she/he will receive 6 SC administrations in total. Patients with grade 3 or 4 IRR after the second rituximab infusion will be withdrawn from the study.

See Section 6.1.4 for details about dose modifications, interruptions and delays for rituximab and chemotherapy.

Study visits scheduled for patients during the Induction therapy period will occur at the beginning of each 3-week or 4-week treatment cycle, according to the Schedule of Assessments ([Table 5](#)) and will include the following assessments:

Induction Cycles 1 – 4 (Visits 1 to 4) and 5 – 8 (Visits 5 to 8)

- Physical examination, infection assessment and vital signs (resting heart rate, blood pressure and body temperature)

- Laboratory assessments (see Sections 5.3 and 7.1.4 for details about individual laboratory assays and reporting of abnormalities)
 - Routine safety laboratory: haematology and biochemistry, including LDH
- Study treatment administration
- AE recording
- Concomitant treatments and therapies
- 
- Clinical evidence of disease status

Staging (Middle of Induction Cycles 3 or 4 and End of Induction Therapy)

- Physical examination, infection assessment and vital signs (resting heart rate, blood pressure and body temperature) - (End of Induction Therapy only)
- Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline
- Tumour assessment / Current disease staging:
 - CT scan with contrast: neck (if clinically indicated), chest, abdomen and pelvis (if detectable by these techniques) to document nodal disease or organ involvement.
 - Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach).

The on-treatment CT scan used for response assessment may be up to 8 weeks old and should be compared to pre-Induction CT. The end-of-Induction response assessment including radiology/imaging report must be provided within 8 weeks of the last Induction cycle. All imaging performed should be documented in the eCRF, and any changes from baseline should be documented.

Response assessment (staging) will be conducted by the Investigator after 4 cycles (or after 3 cycles should Induction be comprised of 6 chemotherapy administrations) and at the end of Induction (i.e. after 8 cycles of rituximab) according to the Cheson response criteria for indolent lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)). Patients with PD at any time during the study will come off study treatment and will start Off-Treatment Follow-Up, being followed every 6 months for survival until the end of the study. Patients with SD at the end of Induction will come off study treatment and will enter Off-Treatment Follow-Up, being followed every 6 months for PD and survival until the end of the study.

Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline.

- ECOG performance status (see [Appendix 4](#)),
- Laboratory assessments (see Sections [5.3](#) and [7.1.4](#) for details about individual laboratory assays and reporting or abnormalities)
 - Routine safety laboratory: haematology and biochemistry, LDH
 - IgG, IgM and IgA quantification (End of Induction Therapy only)
- AE recording
- Concomitant treatments and therapies, including new anti-lymphoma treatment (if applicable)
- Clinical evidence of disease status.

5.1.3.2 Maintenance I

A total of 12 treatment visits, followed by one staging visit are planned during Maintenance I. Maintenance therapy with SC rituximab must start within 8-12 weeks after the administration of the last dose of rituximab in the induction therapy. 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.


See Section 6.1.4 for details about dose modifications, interruptions and delays.

Study visits for patients during Maintenance I will occur at the beginning of each 8-week treatment cycle, according to the Schedule of Assessments ([Table 5](#)) and will include the following assessments:

Maintenance I Cycles 9 – 20 (Visits 9 to 20)

- Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline
- Tumour assessment (conducted every 6 months, at Visits 11, 14, 17 and 20):
 - CT scan with contrast: neck (if clinically indicated), chest, abdomen and pelvis (if detectable by these techniques) to document nodal disease or organ involvement.
 - Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach).

The CT scan may be up to 8 weeks old. All imaging performed should be documented in the eCRF, and any changes from baseline should be documented. Response assessment (staging) will be conducted by the Investigator according to the Cheson response criteria for indolent lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)). 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.

- Physical examination, infection assessment and vital signs (resting heart rate, blood pressure and body temperature)
- ECOG performance status (see [Appendix 4](#))
- Laboratory assessments (see Sections [5.3](#) and [7.1.4](#) for details about individual laboratory assays and reporting or abnormalities):
 - Routine safety laboratory: haematology and biochemistry, including LDH
 - IgG, IgM and IgA quantification (every 12 months, at Visits 14 and 20)
- Study treatment administration
- AE recording
- Concomitant treatments and therapies, including new anti-lymphoma treatment (if applicable)
- 
- Clinical evidence of disease status

Staging (End of 2-year Maintenance Therapy)

At the end of the 2-year rituximab maintenance period, tumour status will be assessed and compared to the patient's baseline status.

- Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline
- Tumour assessment / Current disease staging:
 - CT scan with contrast: neck (if clinically indicated), chest, abdomen and pelvis (if detectable by these techniques) to document nodal disease or organ involvement.
 - Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach)

The CT scan used for response assessment may be up to 8 weeks old. All imaging performed should be documented in the eCRF, and any changes from the patient's baseline assessment should be documented. Response assessment (staging) will be conducted by the Investigator according to the Cheson response criteria for indolent lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)). 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. Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline.

- ECOG performance status (see [Appendix 4](#))

- Laboratory assessments (see Sections 5.3 and 7.1.4 for details about individual laboratory assays and reporting or abnormalities)
 - Routine safety laboratory: haematology and biochemistry, including LDH
- AE recording
- Concomitant treatments and therapies, including new anti-lymphoma treatment (if applicable)
- Clinical evidence of disease status.

5.1.3.3 Maintenance II

At the end of Maintenance I, tumour response will be assessed and compared to the patient's baseline status and patients with PR or CR (as determined by the Investigator using the Cheson response criteria¹) will be randomized to:

- **Arm A:** maintenance treatment with SC rituximab continued until progression or until EOS.
- **Arm B:** observation only with no further treatment.

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 EOS. See Section 6.1.4 for details about dose modifications, interruptions and delays.

Study visits for patients during Maintenance II will occur according to the Schedule of Assessments (Table 5) and will include the following assessments:

Maintenance II (Visits 21+), Assessments for Arm A & Arm B:

- Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline
- Tumour assessment (conducted every 6 months, at Visits 23, 26, 29, etc. until PD):
 - CT scan with contrast: neck (if clinically indicated), chest, abdomen and pelvis (if detectable by these techniques) to document nodal disease or organ involvement.
 - Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach).

The CT scan may be up to 8 weeks old. All imaging performed should be documented in the eCRF, and any changes from baseline should be documented. Tumour response, including disease progression will be evaluated by the Investigator according to Cheson response criteria for lymphoma¹ (see Appendix 1) or by the recommendations for Waldenström's macroglobulinemia² (see Appendix 2).

- Physical examination, infection assessment and vital signs (resting heart rate, blood pressure and body temperature)
- ECOG performance status (see Appendix 4)

- Laboratory assessments (see Sections 5.3 and 7.1.4 for details about individual laboratory assays and reporting of abnormalities):
 - Routine safety laboratory: haematology and biochemistry, including LDH
 - IgG, IgM and IgA quantification (every 12 months, at Visits 26, 32, etc.)
- AE recording (refer to chapter 7.1.2. Adverse Event Reporting Period and Follow-up, page 86)
- Concomitant treatments and therapies, including new anti-lymphoma treatment (if applicable)
- Clinical evidence of disease status

During Maintenance II, patients in the rituximab SC maintenance arm will be treated until PD, unacceptable toxicity, withdrawal of patient consent or until EOS.

All patients in Arm A and Arm B will be actively followed up for safety, tumour response/progression, new anti-lymphoma treatments and survival for at least 15 months after randomization.

5.1.4 Randomization Procedure

Patients cannot be randomized unless all entry criteria are fulfilled. Under no circumstances will patients who were randomized be permitted to be re-randomized in the study.

Patients will be assigned to treatment groups via a central IVRS/IWRS in a 1:1 fashion. Patient number, randomization number, date of randomization and stratification factors will be recorded. Randomization will be stratified according to the following factors:

- Indolent NHL subtype (FL, non-follicular lymphoma), and
- FLIPI (low risk, intermediate risk, high risk, not applicable).

All patient identification will be unique across the study.

5.1.5 End of Treatment Assessments

Enrolled patients who do not complete treatment per protocol for any reason will undergo the end-of-treatment assessment and enter Off-Treatment Follow-up. Patients with PD at any time during the study will come off study treatment and will start Off-Treatment Follow-Up, being followed every 6 months for survival until the end of the study. Patients with SD at the end of Induction will come off study treatment and will enter Off-Treatment Follow-Up, being followed every 6 months for PD and survival until the end of the study.

All patients discontinuing study treatments for any reason, regardless of the treatment period, should undergo end-of-treatment assessment within 4 weeks of the last study drug administration, as detailed in Schedule of Assessments (Table 5).

The End of Treatment Visit will include the following assessments:

- Physical examination, infection assessment and vital signs (resting heart rate, blood pressure and body temperature).
- ECOG performance status (see Appendix 4)

- Laboratory assessments (see Sections 5.3 and 7.1.4 for details about individual laboratory assays and reporting or abnormalities):
 - Routine safety laboratory: haematology and biochemistry, including LDH
- AE recording
- Concomitant treatments and therapies, including new anti-lymphoma treatment (if applicable).

Patients who experience tolerance or toxicity problems related to rituximab administrations and without evidence of disease progression will not be considered as patients with a study outcome event unless a new anti-lymphoma treatment is instituted (see Section 5.1.6.1).

5.1.6 Off-Treatment Follow-up

After discontinuation of study treatment or participation in observation Arm B patients will enter Off-Treatment Follow-up and will be followed every 6 months until the end of the whole study for resolution of all SAEs, survival, disease status (which might include bone marrow and tumour assessment if PD not already documented) and whether a new anti-lymphoma treatment has been started.

Ongoing follow-up will include the following assessments:

- Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline
- Tumour assessment (in patients where PD not yet documented):
 - CT scan with contrast: neck (if clinically indicated), chest, abdomen and pelvis (if detectable by these techniques) to document nodal disease or organ involvement.
 - Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach).

The CT scan may be up to 8 weeks old. All imaging performed should be documented in the eCRF, and any changes from baseline should be documented. Tumour response, including disease progression will be evaluated by the Investigator according to Cheson response criteria for lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)).

- All SAEs will continue to be followed until resolution
- New anti-lymphoma treatment (if applicable)
- Clinical evidence of disease status
- Survival.

For all visits, a 28-day off-treatment window will be permitted (i.e. ± 14 days) to allow flexibility due to holidays and patients travel arrangements.

5.1.6.1 New anti-lymphoma treatment initiation

New anti-lymphoma treatment is defined as start of any radiation therapy (even focal radiation), chemotherapy or immunotherapy, alone or in any combination of them, which is instituted for the treatment of lymphoma. Any new anti-lymphoma treatment not planned in the protocol will be considered as a study outcome event.

New anti-lymphoma treatment should be started at any time of documented disease progression if this progression is symptomatic and/or if the Investigator considers that a new treatment is necessary for the patient's benefit. Disease progression should be documented. If the new anti-lymphoma treatment was initiated during the rituximab-based Induction or Maintenance I, the patient will undergo end-of-treatment assessment and come off study treatment. Enrolled patients starting new anti-lymphoma treatment will undergo end-of-treatment assessment and will start Off-Treatment Follow-Up, being followed for survival until the end of the study.

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

5.2 CLINICAL ASSESSMENTS AND PROCEDURES

5.2.1 Tumour Response Criteria

Clinical tumour assessments will include the following:

- Clinical assessment of lymphadenopathy
- Liver and spleen size by physical examination
- CT scans with contrast: neck (if clinically indicated), chest, abdomen, and pelvis (if detectable by these techniques) to document nodal disease or organ involvement. Other diagnostic means are acceptable for lymphomas that cannot be diagnosed radiographically (e.g. gastroscopy in patients with follicular lymphoma of the stomach).
- Bone marrow assessments are required to confirm any suspected CR in patients with bone marrow involvement at baseline.

Note: Patients with bone marrow involvement at baseline will be required to receive a bone marrow biopsy to confirm a suspected CR on study. Patients with bone marrow involvement at baseline will be assessed as PR if the bone marrow biopsy at final assessment is missing.

Tumour response assessment will be conducted by the Investigator according to Cheson response criteria for indolent lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)).

Patients enrolled at sites using PET scan as part of their routine response assessment must have achieved CR, PR or SD in CT scan according to the International Working Group response criteria for lymphoma.¹ Patients with Waldenström's macroglobulinemia should be assessed for response using the definitions provided in [Appendix 2](#).

Achievement of CR after initial PR on rituximab maintenance therapy should be recorded in the eCRF.

At the end of Induction, patients with PD or SD will come off study treatment. Patients with PD will start Off-Treatment Follow-Up, being followed for survival until the end of the study. Patients with SD will enter Off-Treatment Follow-Up, being followed for PD and survival until the end of the study. Patients having a CR or PR will continue into Maintenance I.

At the end of Maintenance I, patients with PD will come off study treatment. Patients with PD will start Off-Treatment Follow-Up, being followed for survival until the end of the study. Patients having a CR or PR will be randomized and will continue into Maintenance II.

Note: At all times during the course of the study, disease progression diagnosed based on clinical examination has to be confirmed by CT scan as soon as feasible (maximum within 4 weeks) and prior to instituting non-protocol anti-lymphoma therapy.

5.2.1.1 Scheduling of tumour assessments

Tumour assessments are performed with the following frequency during the study:

- At baseline (within 8 weeks prior to the first dose of rituximab);
- At the end of Cycle 3 or Cycle 4 and end of the last Induction treatment;
- Every 6 months during Maintenance I (4 assessments);
- Every 6 months during Maintenance II (with corresponding 6-monthly assessments for patients in the observation group, **Arm B**).

If a patient inadvertently misses a prescribed tumour evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

5.2.2 Performance status

Performance Status will be measured using the ECOG Performance Status Scale (see [Appendix 4](#)). It is recommended, where possible, that a patient's performance status will be assessed by the same person throughout the study.

ECOG performance status will be assessed at baseline, at each treatment visit throughout the study and at the end of treatment visit.

5.2.3 Clinical Safety Assessments

The NCI Common Terminology Criteria for Adverse Events (CTC-AE) version **4.0** will be used to evaluate the clinical safety of the treatment in this study (see [Appendix 6](#)). Patients will be assessed for AEs at each clinical visit and as necessary throughout the study.

A complete medical history (including demographics and prior treatment of the underlying condition) will be performed at screening/baseline.

A physical examination will be performed at each treatment visit and at the end of treatment visit.

5.3 LABORATORY ASSESSMENTS

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

- Haematology (haemoglobin, haematocrit, red blood cell count, white blood cell count with differential leukocyte counts, platelet count)
- Biochemistry: sodium, potassium, calcium, phosphate, total bilirubin, serum creatinine, alkaline phosphatase, albumin, BUN, LDH, C-reactive protein, ALT (SGPT), and if possible AST (SGOT).
- IgG, IgM and IgA quantification: After baseline, IgG, IgM and IgA quantification will be completed once a year during the Maintenance I (maintenance injections #6 and #12), once a year during Maintenance II (**Arm A**) and in case of suspicious infections. The results from these assessments must be available on the day of rituximab injections. Samples can be taken up to two weeks before the date of injection. In case the results of the Ig measurements could not be obtained before the planned treatment administration, the treatment does not have to be postponed until the Ig results become available. However, the Ig results must be reviewed as soon as possible and a new sample for Ig measurement must be drawn before the next injection visit in order to have the new Ig results available for the next injection visit.

Note: patients who have clinically significant reductions in IgG levels should be considered for IgG replacement according to local procedures for immunoglobulin replacement. Patients with profound, prolonged or repeated reductions in immunoglobulin levels should be treated with IV immunoglobulins, according to the local policies.

- If clinically indicated, negative serology for hepatitis B and C, and HIV must be demonstrated at baseline.
- Serum pregnancy test for women of child-bearing potential: within 7 days prior to the first rituximab administration or within 14 days if with a confirmatory urine pregnancy test completed within 7 days prior to the first rituximab dose.

5.4 PATIENT REPORTED OUTCOME(S)

5.4.1

[REDACTED]

[REDACTED]

[REDACTED]

█ [REDACTED]
█ [REDACTED]
█ [REDACTED]
█ [REDACTED]

5.5 PHARMACOECONOMIC ASSESSMENTS

Selected sites will also participate in the Time in Motion pharmacoeconomic sub-study that will assess Medical Care Utilization parameters. Details of the sub-study will be described in a separate protocol.

5.6 POST-STUDY PROVISIONAL CARE

Not applicable.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 DOSE AND SCHEDULE OF RITUXIMAB

See Section 6.1.4 for details about dose modifications, interruptions and delays.

6.1.1 Induction

Each participating Investigator has to decide before treatment initiation which chemotherapy regimen should be used in combination with rituximab for an individual patient. During Induction, 8 cycles of rituximab will be administered in combination with 6 - 8 cycles of approved, commercially available chemotherapy (bendamustine, CHOP, CVP, FCM, MCP, CHVP-IFN, chlorambucil or any fludarabine-containing regimen including oral fludarabine, R-GIFOX; selection at the Investigator's discretion). The switch between different chemotherapy regimens is not permitted.

Cycle 1: During the first cycle, rituximab will be administered as a single IV infusion at a standard dose of 375 mg/m² BSA, followed by administration of chemotherapy (see below).

IV rituximab should be given as a slow infusion through a dedicated line with an IV infusion pump and must not be administered as an IV push or bolus. The recommended initial rate for infusion is 50 mg/hour; after the first 30 minutes it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

In the absence of IRRs, rituximab will subsequently be administered SC starting 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, must 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 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 grade a 3 or 4 IRR after the second rituximab infusion will be withdrawn from the study.

Cycles 2 to 8: Each cycle will consist of a single SC injection of rituximab 1400 mg, followed by administration of chemotherapy (see below) and repeated every 3 - 4 weeks, depending on the combination chemotherapy regimen selected.

SC rituximab injections will be administered using conventional syringes and a 27 gauge injection needle, inserted using sterile technique in the SC space in the abdomen. The injection should be manually pushed at a flow rate of approximately 2 mL/min, therefore an administration volume of 11.7 mL (corresponding to the 1,400 mg dose) should take approximately between 5 and 7 minutes.

Patients should be observed after SC administration as described in the current version of the Investigator Brochure.

During cycles 1 to 8 of Induction, rituximab will be administered in combination with one of the following chemotherapy regimens (selection at the Investigator's discretion):

- Bendamustine
- CHOP: Cyclophosphamide + doxorubicin + vincristine + prednisone/ prednisolone
- CVP: Cyclophosphamide + vincristine + prednisone/prednisolone
- FCM: Fludarabine + cyclophosphamide + mitoxantrone
- MCP: Mitoxantrone + chlorambucil + prednisone/prednisolone
- CHVP-IFN: cyclophosphamide + doxorubicin + etoposide + prednisone/ prednisolone + interferon- α
- Chlorambucil
- Any fludarabine-containing regimen including oral fludarabine
- GIFOX: gemcitabine + ifosfamide + oxaliplatin

Note:

- Rituximab is always administered prior to chemotherapy (with the exception of the corticosteroid component).
- For all Induction treatment visits, a 4-day treatment window will be permitted (i.e. ± 2 days) to allow flexibility due to holidays and patients travel arrangements.

See Section 6.1.4 for details about dose modifications, interruptions and delays.

6.1.1.1 Rituximab plus bendamustine (R-Bendamustine)

Where the Investigator selects bendamustine as combination chemotherapy, the patient will receive 8 cycles of rituximab combined with 6 cycles of bendamustine as shown in [Table 6](#).

Table 6 R-BENDAMUSTINE DOSING SCHEDULE, CYCLES 1-6, EVERY 4 WEEKS

Medication	Dose	Mode	D1	D2	D3
Rituximab					
Cycle 1	375 mg/m ²	IV	•		
Cycles 2 - 8	1,400 mg	SC	•		
Bendamustine					
Cycles 1 - 6	90 mg/m ²	IV		•	•

On Day 1 Rituximab must be given first followed by Bendamustine. According to local practice, Bendamustine may also be given on Day 1 (following Rituximab administration) then on Day 2.

Note: Allopurinol should be used with caution, please refer to Section 4.5.1.6.

6.1.1.2 Rituximab plus CHOP (R-CHOP)

Where the Investigator selects CHOP as combination chemotherapy, the patient will receive 8 cycles of rituximab combined with 6 cycles of standard CHOP, as shown in Table 7.

Table 7 R-CHOP DOSING SCHEDULE, CYCLES 1-6, EVERY 3 WEEKS

Medication	Dose	Mode	D1	D2	D3	D4	D5
Rituximab*							
Cycle 1	375 mg/m ²	IV	•				
Cycles 2 - 8	1,400 mg	SC	•				
CHOP (Cycles 1 – 6):							
Cyclophosphamide	750 mg/m ²	IV	•				
Doxorubicin	50 mg/m ²	IV	•				
Vincristine	1.4 mg/m ² (absolute 2 mg max.)	IV	•				
Prednisone / prednisolone	100 mg	PO	•	•	•	•	•

6.1.1.3 Rituximab plus CVP (R-CVP)

Where the Investigator selects CVP as combination chemotherapy, the patient will receive 8 cycles of standard CVP as shown in Table 8.

Table 8 R-CVP DOSING SCHEDULE, CYCLES 1-8, EVERY 3 WEEKS

Medication	Dose	Mode	D1	D2	D3	D4	D5
Rituximab							
Cycle 1	375 mg/m ²	IV	•				
Cycles 2 – 8	1,400 mg	SC	•				
CVP (Cycles 1 – 8):							
Cyclophosphamide	750 mg/m ²	IV	•				
Vincristine	1.4 mg/m ² (absolute 2 mg max.)	IV	•				
Prednisone/ prednisolone	40 mg/m ²	PO	•	•	•	•	•

6.1.1.4 Rituximab plus FCM (R-FCM)

Where the Investigator selects FCM as combination chemotherapy, the patient will receive 8 administrations of rituximab (given in 6 cycles; in cycle 1 and cycle 4 two administrations of rituximab are given). The 8 administrations of rituximab are combined with 6 cycles of standard -FCM as shown in [Table 9](#).

Table 9 R-FCM DOSING SCHEDULE, CYCLES 1-6, EVERY 4 WEEKS

Medication	Dose	Mode	D1	D2	D3	D15
Rituximab*						
Cycle 1 – Day 1	375 mg/m ²	IV	•			
Cycle 1 – Day 15	1,400 mg	SC				•*
Cycle 2-3	1,400 mg	SC	•			
Cycle 4	1,400 mg	SC	•			•
Cycle 5-6	1,400 mg	SC	•			
FCM (Cycles 1 – 6)						
Fludarabine	25 mg/m ²	IV	•	•	•	
Cyclophosphamide	200 mg/m ²	PO	•	•	•	
Mitoxantrone	6 mg/m ²	IV	•			

Patients who were not able to receive their full dose of rituximab infusion in Cycle 1 as a result of IRR should receive their second rituximab dose (Day 15, Cycle 1) also IV.

6.1.1.5 Rituximab plus MCP (R-MCP)

Where the Investigator selects MCP as combination chemotherapy with rituximab, the patient will receive 8 cycles of rituximab combined with 8 cycles of MCP as shown in [Table 10](#).

Table 10 R-MCP DOSING SCHEDULE, CYCLES 1-8, EVERY 4 WEEKS

Medication	Dose	Mode	D1	D1	D3	D4	D5	D6	D7
Rituximab									
Cycle 1	375 mg/m ²	IV	•						
Cycles 2 - 8	1,400 mg	SC	•						
MCP (Cycles 1 – 8)									
Mitoxantrone	8 mg/m ²	IV			•				
Chlorambucil	3 x 3 mg/m ²	PO			•	•	•	•	•
Prednisone/ prednisolone	40 mg/m ²	PO			•	•	•	•	•

6.1.1.6 Rituximab plus CHVP-IFN (R- CHVP-IFN)

In case the Investigator selects CHVP-IFN as combination chemotherapy with rituximab, the patient will receive 8 cycles of rituximab combined with 6 cycles of CHVP-IFN treatment every 4 weeks as per standard institutional practice of the study centre.

6.1.1.7 Rituximab plus chlorambucil (R-Chlorambucil)

In case the Investigator selects chlorambucil as combination chemotherapy with rituximab, the patient will receive 8 cycles of rituximab combined with Chlorambucil

treatment every 4 week as per standard institutional practice of the study centre according to the local label.

6.1.1.8 Rituximab plus fludarabine (R-Fludarabine)

Where the Investigator selects any fludarabine regimen as combination chemotherapy with rituximab, the patient will receive 8 cycles of rituximab combined with 6 cycles of fludarabine as shown in [Table 11](#).

Table 11 R-FLUDARABINE DOSING SCHEDULE, CYCLES 1-6, EVERY 4 WEEKS

Medication	Dose	Mode	D1	D2	D3	D4	D5
Rituximab							
Cycle 1	375 mg/m ²	IV	•				
Cycles 2 - 8	1,400 mg	SC	•				
Fludarabine							
Cycles 1 - 6	25 mg/m ²	IV	•	•	•		
	25 mg/m/day	oral	•	•	•	•	•

Note: in cases of severe granulocytopenia, G-CSF use is permitted.

Fludarabine may also be administered orally in combination with rituximab. The oral regimen includes daily doses of fludarabine 25 mg/m² on days 1 to 5 of each 4-week cycle, for 6 cycles, combined with 8 cycles of rituximab.⁹⁴

6.1.1.9 Rituximab plus gemcitabine, ifosfamide and oxaliplatin (R-GIFOX)

Where the Investigator selects gemcitabine, ifosfamide and oxaliplatin as combination chemotherapy with rituximab, the patient will receive 8 cycles of rituximab combined with 6 cycles of chemotherapy as shown in [Table 12](#).

Table 12 R-GIFOX DOSING SCHEDULE, CYCLES 1-6, EVERY 4 WEEKS

Medication	Dose	Mode	D1	D2	D3
Rituximab					
Cycle 1	375 mg/m ²	IV	•		
Cycles 2 - 8	1,400 mg	SC	•		
Gemcitabine					
Cycles 1 - 6	1,000 mg/m ²	IV		•	
Oxaliplatin					
Cycles 1 - 6	130 mg/m ²	IV			•
Ifosfamide					
Cycles 1 - 6	5 g/m ²	24-hr infusion			•

Note: in cases of severe granulocytopenia, G-CSF use is permitted.

6.1.2 Maintenance I

During Maintenance I, patients will receive 12 injections of SC rituximab at a fixed 1400 mg dose, administered every 8 weeks according to the SC administration method described above.

See Section 6.1.4 for details about dose modifications, interruptions and delays. For all treatment visits, a 14-day treatment window will be permitted (i.e. ± 7 days) to allow flexibility due to holidays and patients travel arrangements.

6.1.3 Maintenance II

The first visit in maintenance II must occur 8 weeks (± 7 days) after the administration of the last dose of rituximab in maintenance I. During Maintenance II, patients randomized to the experimental arm will continue the SC rituximab maintenance treatments every 8 weeks until disease progression, unacceptable toxicity, withdrawal of patient consent or until EOS, whereas patients in the control arm will receive no treatment (observation only) as follows:

- **Arm A (prolonged maintenance treatment):** rituximab SC 1400 mg (fixed dose), one injection every 8 weeks, administered according to the SC administration method described above.
- **Arm B (observation only):** no further treatment.

See Section 6.1.4 for details about dose modifications, interruptions and delays. For all visits in Maintenance II, a 14-day treatment window will be permitted (i.e. ± 7 days) to allow flexibility due to holidays and patients travel arrangements.

Enrolled patients who do not complete treatment per protocol for any reason will undergo the end-of-treatment assessment and enter Off-Treatment Follow-up. Patients with PD at any time during the study will come off study treatment and will start Off-Treatment Follow-Up, being followed every 6 months for survival until the end of the study.

6.1.4 Dose Modifications, Interruptions and Delays

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

Patients who experience a delay in the initiation of the next planned treatment cycle caused by unresolved grade 3 or 4 AEs will enter Off-Treatment Follow-up:

- Induction: 2 weeks
- Maintenance I & II: 4 weeks

Patients who experience a total delay in the initiation of the next planned treatment cycle for any reason other than grade 3 or 4 AEs will enter Off-Treatment Follow-up:

- Induction: 3 weeks
- Maintenance I & II: 6 weeks

Delays longer than those specified above for study-drug-related toxicities require discontinuation from study treatment, unless the sponsor agrees the benefit-risk assessment supports continued treatment.

No dose modification should be done for rituximab IV or rituximab SC. Dose modifications can be done for chemotherapy if necessary. If chemotherapy is delayed, rituximab administration must also be delayed. If a patient achieves CR (according to [Appendix 1](#)) prior to completing the full chemotherapy regimen, then the

chemotherapy can be stopped but the full 8 cycles of rituximab must still be administered.

6.2 PREPARATION AND ADMINISTRATION OF IMP

6.2.1 IV Rituximab Preparation and Administration

Details regarding the preparation and administration of IV rituximab will be provided in a separate Guidance Document. See also the rituximab Investigator's Brochure.

Patients receiving IV rituximab will be administered a dose of 375 mg/m² with possible rounding to the nearest 10 mg. The appropriate amount of solution to be withdrawn from the vial will be calculated as follows:

$$\text{Volume (mL)} = \frac{\text{BSA (m}^2\text{)} \times \text{dose (375 mg/m}^2\text{)}}{\text{concentration of reconstituted solution mg/mL}} \\ \text{(100 mg/10 mL and/or 500 mg/50 mL)}$$

Instructions for calculating the BSA is provided in [Appendix 5](#).

Rituximab will be administered IV in an outpatient setting if possible.

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

- paracetamol (acetaminophen)
- diphenhydramine hydrochloride or alternative antihistamine.
- steroids (prednisone/prednisolone).

Premedication with glucocorticoids should be considered if rituximab is not given in combination with glucocorticoid-containing chemotherapy. If given, these medications must be documented on the Concomitant Medications eCRF.

Institutions should follow their standard premedication procedures regarding anti-emetics and hydration.

All AEs (regardless of intensity) that commence during or shortly (within 24 hours) after the rituximab infusion/injection should be captured in the eCRF as IRRs/ARRs. Medications to treat these events should also be recorded.

6.2.2 SC Rituximab Preparation and Administration

Details regarding the preparation and administration of SC rituximab will be provided in a separate Guidance Document. See also the rituximab Investigator's Brochure.

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

6.3 FORMULATION, PACKAGING AND LABELLING

6.3.1 IV Rituximab

Rituximab for the IV administration (MabThera IV, Ro 045-2294) will be provided as 500 mg/50 mL liquid filled vials with a nominal content of 10 mg/mL rituximab. The drug product contains sodium acetate (buffer), sodium chloride (tonicity adjustment), and

polysorbate 80 (surfactant) in water for injection at a pH of 6.5. The drug product is a sterile, colourless to pale yellow liquid.

6.3.2 SC Rituximab

Rituximab for the subcutaneous administration (MabThera SC; Ro 045-2294) is supplied as a ready to use liquid formulation with a nominal content of 120 mg/mL rituximab in an 11.7 mL vial and must not be diluted prior to administration. The drug product contains 2,000 U/mL rHuPH20 (manufactured in a CHO cell line) acting as a permeation enhancer, histidine/histidine-HCl (buffer), α,α -trehalose (bulking agent), methionine (stabilizer), and polysorbate 80 (surfactant) in water for injection at a pH of 5.5. The drug product is a sterile, colourless to yellowish, clear to opalescent liquid in colourless 11.7 mL vials.

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labelling of the study medication will be in accordance with Roche standards and local regulations. All the requirements of Annex 13 of the Good Manufacturing Practices guideline for labelling investigational drug will be fulfilled.

The study drug must be stored in a refrigerator, at temperature between 2° and 8°C. For additional storage requirements refer to the drug label. It is highly recommended that the study medication will not be withdrawn from the vial until at the time of administration. For further information please refer to the most current version of the Investigator Brochure.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

6.4 BLINDING AND UNBLINDING

Not applicable, this is an open label study.

6.5 ACCOUNTABILITY OF RITUXIMAB AND ASSESSMENT OF COMPLIANCE

The Investigator is responsible for the control of drugs under investigation. Adequate records for the receipts (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the study drug must be maintained. Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records.

6.5.1 Accountability of Rituximab

IV and SC rituximab will be supplied by F. Hoffmann-La Roche Ltd and shipped to the pharmacist of each centre by the local Roche affiliate.

In accordance with the requirements of national regulatory agencies and of local health authorities, the Investigator or the responsible local pharmacist will sign a receipt for the vials of rituximab, and will be held accountable for proper storage and dispensing. All drug supplies that will be used in the study must be maintained securely. The disposal will be the responsibility of the local Roche Affiliate in accordance with local regulations.

All drugs shall be dispensed in accordance with the Investigator's prescription. The site pharmacy must **not** release rituximab if the patient's enrolment number is not on the prescription received. Under no circumstances will the Investigator supply study drug to a

third party, or allow the study drug to be used, destroyed or disposed in other ways than as directed by this protocol.

Accurate records must be kept for each study drug provided by the Sponsor. These records must contain the following information:

- Documentation of drug shipments received from the Sponsor (date received, batch number and quantity)
- Disposition of unused study drug not dispensed to patient.

All records and drug supplies must be available for inspection by the Monitor at every monitoring visit. All supplies, including partially used or empty containers and copies of the dispensing & inventory logs, must be returned to the Monitor at the end of the study, unless alternate destruction has been authorized by Roche, or required by local or institutional regulations (Section 6.6).

The eCRF and clinic records will be checked for consistency with site-administered chemotherapy agents used during Induction.

6.5.2 Assessment of Compliance

The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Any delegation of this task must be clearly documented and approved by the Investigator.

Patient compliance will be assessed by maintaining adequate study drug dispensing records. A Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the patient to whom the study medication was dispensed
- the date(s), batch number and quantity of the study medication dispensed to the patient

At each rituximab administration the Investigator will record the date, delivery rate and amount of study drug administered in the eCRF.

6.6 DESTRUCTION OF USED INVESTIGATIONAL PRODUCT

Local or institutional regulations may require immediate destruction of used investigational product for safety reasons e.g. cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers and patient numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)

- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person who discarded the investigational product in a hazardous container for destruction.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

7.1.1 Clinical Adverse Events

According to the International Conference on Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation of a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions which worsen or change in character during a study are to be reported as AEs.

Investigators will seek information on AEs and SAEs at each patient contact by specific questioning and, as appropriate, by clinical examination. All AEs and SAEs, whether spontaneously reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the AE eCRF.

7.1.1.1 Duration and intensity

Each recorded AE or SAE will be described by its duration (i.e. start and end dates), severity, regulatory seriousness criteria if applicable, suspected relationship to the investigational product, and actions taken.

Intensity of all AEs will be graded according to the NCI CTC-AE v 4.0 on a five-point scale (Grade 1 to 5) and reported in detail in the eCRF.

AEs not listed in the CTC-AE should be graded as detailed in [Table 13](#).

Table 13 Grading of Adverse Events not listed in the NCI CTC-AE

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activity of daily living including preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

7.1.1.2 Drug – adverse event relationship

The causality relationship of study drug to the adverse event will be assessed by the Investigator as either **Yes or No**.

If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, the drug-event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes**:

- Reasonable temporal association with drug administration
- It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on re-challenge

The following criteria should be considered in order to assess the relationship as **No**:

- It does not follow a reasonable temporal sequence from administration of the drug
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- It does not follow a known pattern of response to the suspected drug
- It does not reappear or worsen when the drug is re-administered

Note: during Induction, for patients receiving rituximab plus chemotherapy, the test drug relationship is assessed for the rituximab-chemotherapy combination. If the event is an SAE, more specific information will be required on the SAE Form.

7.1.1.3 Serious Adverse Events [Immediately Reportable to Roche]

Roche confirms that the proposed study **will comply with all local regulatory requirements**. The study will adhere to the full requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be adhered to (see [Appendix 7](#)).

An SAE is any adverse event that:

- Is fatal; (results in **death**)

Note: death is an outcome, not an event

- Is life-threatening

Note: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe.

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant (e.g. secondary malignancies) or requires intervention to prevent one or other of the outcomes listed above

All AEs that do not meet any of the criteria for SAE should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

7.1.1.4 Other safety findings requiring expedited reporting

Other safety findings may require expedited reporting depending on local legislation, e.g. a major safety finding from a newly completed animal study (such as carcinogenicity).

7.1.1.5 Progression of underlying malignancy

Progression or deterioration of the malignancy under study (including new lesions and death due to disease progression) will be part of the efficacy assessment and should **NOT** be reported as an AE or SAE.

Signs and **symptoms** clearly associated with the malignancy under study should **NOT** be reported as an AE or SAE unless:

- Newly emergent (i.e. not present at baseline) and association with the underlying malignancy and old/new metastatic lesions is unclear,
- the Investigator attributed deterioration of malignancy-associated signs and symptoms directly to the study drug

Should there be any uncertainty regarding the attribution of the malignancy under study to an AE, it should be reported as an AE or a SAE accordingly.

7.1.1.6 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of NHL will be recorded only on the Study Discontinuation eCRF page. All other on-study deaths, regardless of attribution, will be recorded on an AE eCRF page and expeditiously reported to the SAE responsible reporter.

When recording a death on an AE eCRF page, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF page. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the AE eCRF page.

Note:

Serious Adverse Event Reports containing the SAE terms “Death Unexplained”, “Death Cause Unknown” or “Death NOS” will be considered **unexpected** for all Safety Reference Documents. It is thus important that Investigators differentiate between the SAE terms “Death Unexplained” and “Sudden Death” when completing SAE reporting forms. The term “sudden death” should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably. “Sudden death” is considered as being labelled, listed or expected if mentioned in the safety reference document. “Death cause unknown” or “Death Unexplained” should be used as the SAE term only when the cause of death is not known at the time of reporting the SAE to Roche.

Monitors should ensure that Investigators understand the way in which the SAE reporting forms for such deaths should be completed, and should urgently follow-up “Death Unexplained” SAEs, to ensure that the Investigator provides further information regarding the cause of death as soon as possible. The Roche Guidance *Notes for Completing the SAE reporting form (gcp_for000025)* provides further clarification regarding the reporting of death as an SAE.

7.1.2 Adverse Event Reporting Period and Follow-up

Serious Adverse Events occurring during the study must be reported to Roche (or designee) immediately (i.e. within 24 hours) of the investigator becoming aware of the event. After obtaining informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to

invasive procedures such as biopsies, or medication washout). Once study treatments commence, the site must enter the SAE into the eCRF.

Patients will be followed for new or worsening AEs as detailed in [Table 14](#).

Resolution of AEs and SAEs including dates should be documented on the AE/SAE eCRF and in the patient's medical record to facilitate source data verification. Unrelated AEs and SAEs occurring in an off-study patient who has started a new anti-cancer treatment do not need to be reported.

Table 14 Duration of Reporting and Follow-up of Adverse Events

Related			Unrelated	
	Reporting Period	Follow-up	Reporting Period	Follow-up
AEs grade 1 and 2	From signing of ICF until 28 days post-treatment	Until resolution, stabilization, death or patient lost to follow-up	From signing of ICF until 28 days post-treatment	Until 28 days post-treatment
AEs \geq grade 3	From signing of ICF up to 6 months after the last dose on arm A, or the last observation visit on arm B, or EOS whichever comes first.	Until resolution, stabilization, death or patient lost to follow up	From signing of ICF up to 6 months after the last dose on arm A or the last observation visit on arm B, or until the start of new anti-lymphoma treatment, , or EOS whichever comes first.	Until resolution, stabilization, death or patient lost to follow up
SAEs	<p>From signing of ICF onwards.*</p> <p>Note: After ICF signing, but prior to initiation of any study drugs, only SAEs caused by a protocol-mandated intervention (e.g., an invasive procedure such as biopsy or medication washout) will be collected.</p> <p>Once study treatment has been permanently discontinued, all related SAEs should continue to be reported, regardless when they occur, in particular any second primary malignancy.</p>	Until resolution, stabilization, death or patient lost to follow-up	<p>From signing of ICF until 6 months after the last dose on arm A, or the last observation visit on arm B, or until the start of new anti-lymphoma treatment, or EOS whichever comes first.</p> <p>Note: After ICF signing, but prior to initiation of any study drugs, only SAEs caused by a protocol-mandated intervention (e.g., an invasive procedure such as biopsy or medication washout) will be collected.</p>	Until resolution, stabilization, death or patient lost to follow-up

AE = adverse event, ICF = informed consent form, SAE = serious adverse event.

* The Investigator should also notify the study Sponsor of any other SAEs occurring at any time after a patient terminated study participation if felt to be related to prior study treatment.

It is encouraged that any second primary malignancy events are reported, regardless of causal relationship to study drug, occurring at any time following study treatment permanent discontinuation.

For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

7.1.3 Procedures for Recording Adverse Events

Adverse Events should be recorded on an AE eCRF page. Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF. Colloquialisms and abbreviations should be avoided. Only one event should be recorded in the event field on the AE eCRF page.

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.1.3.1 Pre-existing medical conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the appropriate General Medical History and Baseline Conditions eCRF forms.

A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE eCRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

7.1.3.2 Adverse events secondary to other events

In general, AEs occurring secondary to other events should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal haemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

7.1.3.3 Persistent or recurrent adverse events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on an AE eCRF page.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an AE eCRF page.

7.1.4 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, as applicable.

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require discontinuation of study treatment, more frequent assessments, further diagnostic investigation, etc.). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal (ULN) associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the AE eCRF page.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalaemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an AE in the CRF.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

7.1.4.1 Follow-up of abnormal laboratory test values

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

7.1.5 Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or up to 12 months after the last dose of investigational product, a paper Pregnancy Reporting Form should be completed and faxed immediately (i.e. **within 24 hours**) of the investigator becoming aware of the pregnancy. The completed Pregnancy Reporting Form and Pregnancy Fax Cover Sheet should be faxed to the Roche Drug Safety Department or the Roche designee. Any actions pertaining to subsequent study drug administrations will be at the Investigator’s discretion (in consultation with the patient).

Male patients must also be instructed to immediately inform the Investigator if their partner becomes pregnant during the study or within 12 months after the last dose of investigational product. If such an event occurs, a paper Pregnancy Reporting Form should be completed and faxed immediately (i.e. **within 24 hours**) of the investigator becoming aware of the pregnancy. The completed Pregnancy Reporting Form and Pregnancy Fax Cover Sheet should be faxed to the Roche Drug Safety Department or the Roche designee.

Abortion, whether therapeutic or spontaneous, in a female patient or female partner of a male patient exposed to the investigational product, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an AE eCRF page, and expeditiously reported to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE on an AE eCRF page.

7.1.6 Interactions with other Medicinal Products and other Types of Interactions

Formal drug interaction studies have been performed with rituximab. The tolerability of the simultaneous or sequential combination of rituximab with chemotherapy agents that are liable to cause depletion of normal B cells is well defined.

Patients with human anti-mouse antibody or human anti-chimeric antibody (HACA) titres may develop allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.⁹⁵ In the integrated review of data from 356 patients, 4 patients developed a HACA response following treatment. Two of these patients were retreated without problems. No correlation was seen between HACA response and loss of, or interference with, response to treatment.

7.2 HANDLING OF SAFETY PARAMETERS

7.2.1 Reporting of Serious Adverse Events (Immediately Reportable)

This study adheres to the definition and reporting requirements of *ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2*. Complete information can be found in [Appendix 7](#).

Any clinical adverse event or abnormal laboratory test value that is *serious* and which occurs during the course of the study (as defined in Section [7.1.1.3](#) above), regardless of the treatment arm, must be reported to Roche immediately (i.e. **within 24 hours**) of the Investigator becoming aware of the event. The Investigator must complete the *SAE Reporting Form* and forward it to the designated SAE Contact.

7.2.2 Serious Adverse Events Reporting Timeframe

Related Serious Adverse Events **MUST** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

An AE qualifies as Suspected Unexpected Serious Adverse Reaction (SUSAR) when all the following conditions are met:

- The event is serious (SAE).
- There must be a certain degree of probability that the event is an adverse reaction to the study drug.

- The adverse reaction must be unexpected, i.e. not foreseen in the Investigator's Brochure.

SUSARs are reported to Investigators at each site and their associated IECs.

Unrelated Serious Adverse Events must be collected and reported during the study and for up to 6 months after the last dose of study medication or initiation of new anti-lymphoma treatment, whichever occurs first.

7.2.3 Reporting of Infusion-Related Reactions (IRRs) or Administration-Related Reactions (ARRs)

Special attention should be given to infusion related reactions (IRRs) / administration-related reactions (ARRs). Any AEs occurring within 24 hours after administration of IV rituximab and considered related to the study drug, will be considered as IRRs. Any AEs occurring within 24 hours after administration of SC rituximab and considered related to the study drug, will be considered as ARR.

IRRs/ARRs can present with one or more of the following symptoms: allergic reaction, arthralgia, bronchospasm, chills, cough, dizziness, dyspnea, headache, hypertension, hypotension, myalgia, nausea, pruritus, pyrexia, rash, tachycardia, urticarial, vomiting.

7.3 WARNINGS AND PRECAUTIONS

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the current rituximab Investigators' Brochure.⁷⁴

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 PRIMARY AND SECONDARY STUDY ENDPOINTS

8.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is PFS_{rand}. It is defined as the time from day of randomization to the first documented disease progression or death, whichever occurs first. Progression will be based on tumour assessment made by the investigator according to the Cheson response criteria for indolent lymphoma.¹

In this trial, PFS_{rand} will be used to evaluate whether rituximab maintenance therapy beyond 2 years further improves the response to treatment.

8.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are: Progression free survival (PFS) measured from the day of first rituximab Induction dose (PFS_{regist}), Event-free survival (EFS), Time to next lymphoma treatment (TNLT), Overall survival measured from day of first rituximab Induction dose (OS_{regist}) and from randomization (OS_{rand}), Overall Response Rate (ORR) at the end of the Induction Phase and PR to CR conversion rate at the end of Maintenance I.

Progression-Free Survival (PFS_{regist}): PFS_{regist} will be measured from the day of first rituximab Induction dose until the date of first documented disease progression or death by any cause. Patients who have experienced none of these events at the time of analysis (clinical-cut off) and patients who are lost to follow-up will be censored at their last clinical assessment date.

Event-Free Survival (EFS, time to treatment failure): EFS will be measured from the day of first rituximab Induction dose until the date of any treatment failure, including disease progression, or discontinuation of treatment for any reason (e.g. disease progression, toxicity, patient preference, initiation of new anti-lymphoma treatment, or death). Patients who have experienced none of these events by the end of the study and patients who are lost to follow-up will be censored at their last clinical assessment date.

Overall Response Rate (ORR): ORR will be determined by tumour response according to the Cheson response criteria for indolent lymphoma¹, and will be assessed at the end of Induction. A responder is defined as patient experiencing either a CR or PR by these criteria.

Overall Survival (OS): OS will be determined 1) from the day of first rituximab Induction dose until the date of death irrespective of cause (OS_{regist}) and 2) from the day of randomization until the date of death irrespective of cause (OS_{rand}). In both cases, patients who have not died at the time of end of the study, and patients who are lost to follow-up, will be censored at the date of the last contact.

Time to Next Lymphoma Treatment (TNLT): TNLT will be measured from the day of first rituximab Induction dose to the date of first documented intake of any new anti-lymphoma treatment (chemotherapy, radiotherapy, immunotherapy, etc.). Responding patients, and patients who are lost to follow-up, will be censored at their last visit where the start of new medication was assessed. 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 actually made.

PR to CR conversion rate: Conversion rate will be assessed at end of Maintenance I. The percentage of patients with PR prior to rituximab maintenance therapy who achieve CR while on rituximab maintenance I therapy will be assessed. Response assessment will be conducted by the Investigator according to the Cheson response criteria for indolent lymphoma¹ (see [Appendix 1](#)) or by the recommendations for Waldenström's macroglobulinemia² (see [Appendix 2](#)).

8.1.3 Exploratory efficacy endpoint

[REDACTED]

[REDACTED]

8.1.4 Safety Variables

Safety of the treatment will be evaluated by: AEs, laboratory tests, vital signs, concomitant medications, new anti-lymphoma treatments and physical examination. In addition, IgG, IgM and IgA quantification will be completed once a year during the 2-year rituximab maintenance period, once a year during randomized rituximab maintenance (**Arm A**) and in case of suspicious infections.

8.2 STATISTICAL ANALYSES

8.2.1 Primary Efficacy Analysis

The 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. Patients

who have not experienced an event at data cut-off date or patients who are withdrawn from the study without documented progression will be censored at the date of the last tumour assessment when the patient was known to be progression free.

Patients without post baseline tumour assessments but known to be alive will be censored at the time of randomization.

The difference in PFS_{rand} between the two treatment arms (**Arm A** versus **Arm B**) will be tested with a stratified log-rank test using the stratification factors as defined in Section 5.1.4.

Furthermore, for the primary endpoint PFS_{rand} a Cox regression model will be used to estimate the hazard ratio.

8.2.2 Secondary Efficacy Analyses

The analysis of the secondary efficacy variables PFS_{regist} , EFS, OS_{regist} , OS_{rand} and TNLT will be performed the same way as described for the primary variable PFS_{rand} . Descriptive statistics and Kaplan-Meier curves will be presented for non-randomized patients and for the two randomized treatment groups.

ORR (comprising CR and PR) at the end/completion of Induction treatment (measured from the day of first dose of rituximab induction dose) will be analysed in frequency tables including 95% two-sides Pearson-Clopper confidence intervals by treatment group.

Logistic regression analysis will be performed to assess the influence of baseline covariates in an exploratory manner.

The PR to CR conversion rate at the end of Maintenance I will be summarized.

All tests will be performed at a 5% alpha level. No adjustments for multiplicity will be made during the analysis of the secondary efficacy variables.

More details regarding the efficacy analyses and statistical models used will be defined in the Statistical Analysis Plan (SAP).

8.2.3 Exploratory Analyses

8.2.3.1

[REDACTED]

8.2.4 Analysis Populations

8.2.4.1 Intent-to-treat populations

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 set. 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 analysing the primary endpoint progression-free survival beyond randomization. All randomized patients will be included in this ITT_{rand} population.

In both ITT populations, patients will be assigned to treatment groups as randomized for analysis purposes.

8.2.4.2 Per-protocol population

A per protocol (PP_{rand}) analysis (patients from the ITT_{rand} population not having any major protocol violations) will also be performed.

The primary efficacy analysis will be repeated based on the PP_{rand} population to confirm the overall study results.

8.2.4.3 Safety population

All patients who received at least one dose of rituximab will be included in the safety population. Patients will be assigned to treatment groups as treated.

8.2.5 Interim Analysis

There will be no interim analysis for efficacy. However, after the first 60 patients have completed their rituximab-based Induction, an exploratory analysis of patient-assessed satisfaction and convenience with chemotherapy administration based on the RASQ will be performed.

An interim analysis of safety will be performed after approximately 200 patients have been enrolled in the study.

8.2.6 Safety Data Analysis

All patients who have received at least one dose of SC rituximab will be included in the Safety population. The safety analysis will be based on the Safety population.

All safety parameters will be summarized and presented in tables by study period, i.e. Induction, Maintenance I, Maintenance II as well as overall.

Reported AE terms will be coded according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA).

All AEs and laboratory parameters will be assessed according to the NCI CTC-AE, version 4.0 grading system.

AEs will be presented in frequency tables (overall, by intensity and by relationship to study treatment) by system organ class.

The incidence of AEs will be reported along with 95% Pearson-Clopper CIs.

Frequency tables will be generated for:

- AEs
- SAEs
- Grade 3-5 AEs
- AEs leading to treatment discontinuation
- IRRs/ARRs

Changes in the NCI CTC-AE grades from laboratory parameters assessed at baseline of will be summarized by shift tables by treatment group. An additional analysis will be performed to examine the distribution of AEs over the course of the study (i.e. Induction, Maintenance I, Maintenance II as well as overall).

Safety laboratory abnormalities will be presented in summary tables and as shift tables from baseline tables, as applicable. In addition, IgG, IgM and IgA quantification will be completed once a year during Maintenance I, once a year during Maintenance I (**Arm A**) and in case of suspicious infections.

Vital signs will be summarized over time by treatment period and arm (Maintenance II).

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

Further anti-lymphoma treatment data (chemotherapy, radiotherapy, immunotherapy) recorded in the eCRF (e.g. type of chemotherapy or site of radiotherapy) will be presented in summary tables.

The Statistical Analysis Plan (SAP) will describe the safety analyses in more detail.

8.2.7 Other Analyses

Major protocol deviations will be summarised.

8.2.7.1 Pharmacoeconomic analysis

For details on the assessments or Medical Care Utilization parameters, refer to the *Time in Motion* pharmacoeconomic Sub-study protocol.

8.3 SAMPLE SIZE

The sample size of the proposed study has been estimated based on assumptions derived from the Phase III randomized EORTC 20981 study of 465 patients with previously treated, advanced-staged, relapsed FL.³ In this study, patients were first randomized to 6 cycles of CHOP or R-CHOP. Those with an objective response underwent a second randomization to 2 years maintenance treatment with IV rituximab (375 mg/m² once every 3 months) or observation (without maintenance treatment). Median PFS from first randomization was 20.2 months after CHOP vs. 33.1 months after R-CHOP (HR 0.65; p < 0.001). Rituximab maintenance yielded a median PFS from second randomization of 51.5 months vs. 14.9 months with observation alone (HR 0.40; p < 0.001).

In the current study, all patients will undergo rituximab-based Induction followed by a SC rituximab maintenance period of 2 years (Maintenance I). After this approximately 2.5-year treatment period, patients will be randomized to **Arm A**: further receive rituximab SC until progression vs. **Arm B**: observation only (Maintenance II). Assuming around 1.5 year of enrolment, the last patient would be randomized around 4 years after first patient enrolled. Patients with PR or CR after Maintenance I can be randomized, whereas patients with PD or SD will come off study treatment and enter Off-Treatment Follow-Up.

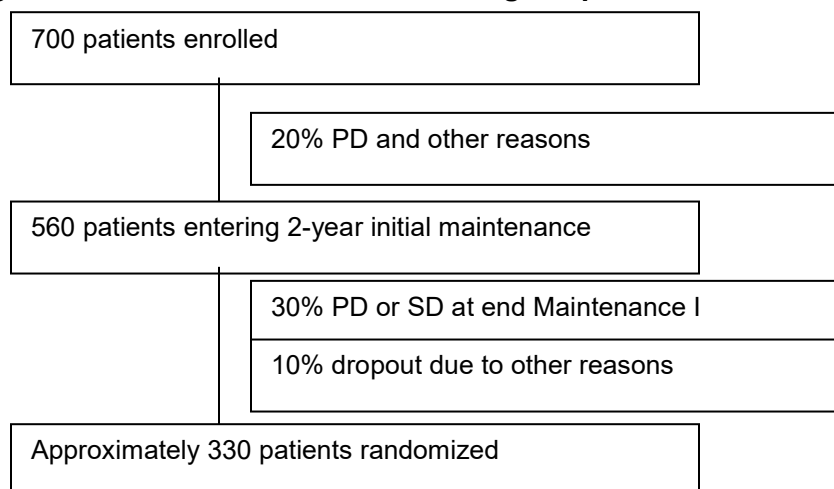
Assuming a median PFS beyond randomization of 38 months in arm A, and 23 months in arm B (corresponding to a HR of approximately 0.6), then 129 events are required to achieve 80% power for the log-rank test at a two-sided significance level of 5%.

In order to see the required events, approximately 300 patients in Maintenance II will be followed from randomization (Maintenance II treatment until PD and Off-Treatment

Follow-Up) for at least 15 months. Allowing for a drop-out rate of 10%, 330 patients should be randomized.

In total, 700 patients need to be enrolled in order to have 330 patients randomized after the 2.5-year Induction plus Maintenance I treatment period. The assumptions regarding the drop-out rates in each study phase are presented in the scheme below.

Figure 2 Estimated attrition rates during the pre-randomization phase



A summary of the sample size assumptions can be found in [Table 15](#) below.

Table 15 SAMPLE SIZE ASSUMPTIONS

Estimated HR	Estimated Median PFS beyond randomization	Duration of Follow-up Post-randomization	Total Number of Events needed	Number of patients randomized*	Total Number of Patients Enrolled (% reaching randomization)
0.6	A: 38 months B: 23 months	Minimum 15 months	129	330	700 (47%)

* Includes a +10% adjustment for post-randomization dropouts

A: Rituximab maintenance until PD

B: Observation (no treatment) after 2.5 years of rituximab-based Induction plus Maintenance I

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

Data for this study will be recorded via an Electronic Data Capture system (EDC) using electronic Case Report Forms (eCRF). Site personnel will transcribe data from the paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial. Accurate and reliable data collection will be assured by verification and cross-check of the CRFs against the Investigator's records by the study monitor (source document verification), and the maintenance of a Drug Dispensing Log by the

Investigator. A comprehensive validation check program utilizing front-end checks in the CRF and back-end checks in the Roche data base will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the CRF at the site for resolution by the Investigator. ECRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored with Sponsor and records retention for the study data will be consistent with Sponsor's standard procedures.

The Sponsor will be responsible for the data management of this trial, including quality checking of the data, according to the EDC Study Specification document. Throughout the study the Study Management Team will review data according to the Roche Data Management Plan (as described in the Data Quality Plan). Central laboratory and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

9.1 ASSIGNMENT OF PREFERRED TERMS AND ORIGINAL TERMINOLOGY

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the MedDRA terminology for adverse events and disease and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

10. STUDY COMMITTEES

10.1 INDEPENDENT DATA AND SAFETY MONITORING BOARD (DSMB COMMITTEE (iDMC))

An Independent Data Monitoring Committee (iDMC) will be formed and composed of 3 members, including a statistician. The iDMC will review all safety data pertaining to the study drug on a regular basis, at least once a year, or at F. Hoffmann-La Roche Ltd's request.

The Committee will be responsible for monitoring, on an ongoing basis, all significant safety events (SSEs).

A SSE is defined as any of the following:

- General toxicity: NCI CTC grade 3 and grade 4 AEs, SAEs
- Any AE that requires dose interruption, reduction or discontinuation of the study drug.
- A patient death.

Following each meeting, the Committee will recommend to the Sponsor that the study continues according to the protocol or suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the Committee may recommend stopping the study due to safety reasons. Further details about the definition and the role as well as the responsibility of the iDMC will be provided in a separate document, the iDMC Charter.

PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

11. ETHICAL ASPECTS

11.1 LOCAL REGULATIONS/DECLARATION OF HELSINKI

The Investigator will ensure that this study is conducted in full conformance with the principles of the “Declaration of Helsinki” or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC].

In other countries where “Guideline for Good Clinical Practice” exists, Roche and the Investigators will strictly ensure adherence to the stated provisions.

11.2 INFORMED CONSENT

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain signed informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The eCRFs for this study contain a section for documenting patient informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

For the patient not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

11.3 INDEPENDENT ETHICS COMMITTEES (IEC)

The protocol, informed consent and any accompanying material provided to the patient will be submitted to an IEC for review. For EEA member states, the Sponsor will submit to the Competent Authority and IEC, the protocol and any accompanying material provided to the patient. In the EEA member states, the accompanying material may include patient information sheets, descriptions of the study used to obtain informed consent and terms of any compensation given to the patient as well as advertisements for the trial.

An approval letter or certificate (specifying the protocol number and title) from the IEC must be obtained before study initiation by the Investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the IEC approval must also be submitted by the Investigator or by the Sponsor (in the EEA member states) in accordance with local procedures and regulatory requirements.

When no local review board exists, the Investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the Investigator in submitting the protocol to the European Ethics Review Committee.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study.

11.4 FINANCIAL DISCLOSURE

The Investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The Investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

12. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from Investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the sponsor and the Investigator (or Investigator representative[s]). Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Lead Scientific Responsible and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change[s] involves only logistical or administrative aspects of the trial (e.g. change in monitor[s], change of telephone number[s]).

13. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the Investigator will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IEC and Regulatory Agencies should be informed accordingly.

14. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

14.1 INVESTIGATOR'S FILES / RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: 1) Investigator's Study File, and 2) patient clinical source documents.

The Investigator's Study File will contain the protocol/amendments, eCRF/DCS and schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition at the end of the study the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Study File.

Patient clinical source documents [usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs] would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrollment logs. The Investigator must keep the two categories of documents as described above (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

ICH GCP guidelines require that Investigators maintain information in the study patient's records which corroborate data collected on the eCRF(s).

14.2 SOURCE DOCUMENTS AND BACKGROUND DATA

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

14.3 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

14.4 AUDITS AND INSPECTIONS

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Roche, or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

14.5 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an Electronic Data Capture (EDC) system by using eCRFs. For each patient enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

15. MONITORING THE STUDY

It is understood that the responsible monitor will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial [CRFs and other pertinent data] provided that patient confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the patient received the study drug assigned by the randomization centre (by controlling the written confirmation of the randomization by IVRS/IWRS). The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The investigator [or deputy] agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrollment log showing codes, names and addresses.

The investigator should maintain documents not for submission to Roche, e.g., Roche already maintains rigorous confidentiality standards for clinical studies by "coding" (i.e. assigning a unique patient ID number at the investigator site) all patients enrolled in Roche clinical studies. This means that patient names are not included in data sets that are transmitted to any Roche location.

17. CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and distributed to Health Authorities as required by applicable regulatory requirements.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Roche will comply with the requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Roche will generally support publication of multicentre trials only in their entirety and not as individual centre data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements. Any formal publication of the study in which input of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

19. APPENDICES

APPENDIX 1. CRITERIA FOR EVALUATION OF RESPONSE IN NON-HODGKIN'S LYMPHOMA¹

Complete Response (CR)

A complete response requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities [e.g., lactate dehydrogenase (LDH)] definitely assignable to Non-Hodgkin's Lymphoma (NHL).
2. All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes ≥ 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to < 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. Bone marrow, if positive at baseline, must be histologically negative for lymphoma.

Partial Response (PR)

A partial response requires the following:

1. $\geq 50\%$ decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. No new sites of disease.

Stable Disease (SD)

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

Progressive Disease (PD)

Progressive Disease is defined as follows:

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

APPENDIX 2. CRITERIA FOR EVALUATION OF RESPONSE IN WALDENSTRÖM'S MACROGLOBULINEMIA²

Definitions of Response

The updated recommendations for assessing response in Waldenström's Macroglobulinemia are as follows:

- Complete response (CR): categorized by a disappearance of serum and urine monoclonal protein determined by immunofixation, absence of malignant cells in bone marrow determined by histologic evaluation, resolution of adenopathy/organomegaly (confirmed by computed tomography [CT] scan), and no signs or symptoms attributable to Waldenström's macroglobulinemia. Reconfirmation of the CR status is required ≥ 6 weeks later with a second immunofixation.
- Partial response: categorized by $\geq 50\%$ reduction of serum monoclonal IgM concentration determined by protein electrophoresis, $\geq 50\%$ decrease in adenopathy/organomegaly on physical examination or on CT scan, and no new symptoms or signs of active disease.
- Minor response: categorized by $\geq 25\%$ but $< 50\%$ reduction of serum monoclonal IgM determined by protein electrophoresis and no new symptoms or signs of active disease.
- Stable disease: categorized by $< 25\%$ reduction and $< 25\%$ increase of serum monoclonal IgM determined by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms caused by disease and/or signs of Waldenström's macroglobulinemia.
- Progressive disease: categorized by $\geq 25\%$ increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings caused by disease (e.g., anemia, thrombocytopenia, leukopenia, or bulky adenopathy/organomegaly) or symptoms (e.g., unexplained recurrent fever $\geq 38.4^{\circ}\text{C}$, drenching night sweats, $\geq 10\%$ weight loss, hyperviscosity, neuropathy, or symptomatic cryoglobulinemia) attributable to Waldenström's macroglobulinemia.
- Not evaluable/delayed response: in some cases, there is insufficient data and/or time for a determination of response to treatment. A delayed response might be seen particularly after purine analogue or monoclonal antibody therapy. The panel recommended that patients must have been followed for ≥ 3 months after treatment initiation to be considered unresponsive to therapy. In addition, the best response is often exhibited several months after treatment discontinuation.

APPENDIX 3. FOLLICULAR LYMPHOMA GRADING SYSTEM (WHO CLASSIFICATION)

Follicular Cell Lymphomas: Grading and Variants⁹⁶

Grade 1	0-5 centroblasts/hpf (high power field [microscopy])
Grade 2	6-15 centroblasts/hpf
Grade 3	15 centroblasts/hpf
3a	15 centroblasts, but centrocytes are still present
3b	Centroblasts form solid sheets with no residual centrocytes

Variants

Cutaneous follicle centre lymphoma

Diffuse follicle centre lymphoma

Grade 1 0-5 CB/hpf

Grade 2 6-15 CB/hpf

APPENDIX 4. COMMON SCALES

Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	PERFORMANCE STATUS – WHO CLASSIFICATION
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more 50% of waking hours
3	Capable of only limited self-care confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed and chair.

Ann Arbor Stage

Stage I: I = Involvement of a single lymph node region.

IE = Localized involvement of a single extralymphatic organ or site.

Stage II: II = Involvement of 2 or lymph node regions on the same side of the diaphragm.

IIE = Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm.

Stage III: III = Involvement of lymph node regions on both sides of the diaphragm.

IIIE = Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site.

IIIS = Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen*.

IIIS+E = Both IIIS+IIIE *.

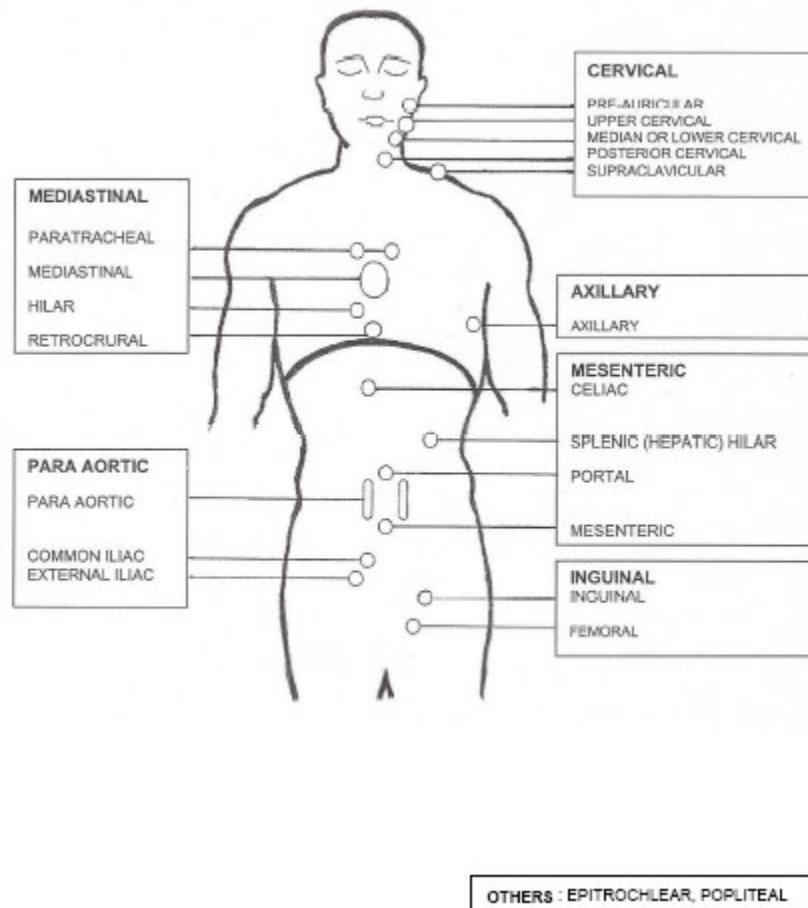
*(*Of note, in FLIPI, spleen involvement is categorized as stage IV)*

Stage IV: IV = Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.

IVE = Extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

FLIPI Score and Nodal Areas

Follicular Lymphoma International Prognostic Index (FLIPI)⁹⁷



The Follicular Lymphoma International Prognostic Index, or FLIPI, is a standardized guide on prognosis of survival rates of follicular lymphoma patients based on certain risk factors. As patients of Waldenström's macroglobulinemia or lymphoplasmacytic lymphoma, marginal zone lymphoma are non-FL patients, thus the FLIPI is not applicable.

Five adverse prognostic factors were selected:

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

Three risk groups were defined:

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

APPENDIX 5. FORMULA FOR CALCULATION OF BSA (DUBOIS)

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

Unit Conversion:

- 1 kg = 2.2 lbs
- 1 inch = 2.54 cm

Example: BSA of a subject being 1.70 m tall and weighing 80 kg:

- $\text{BSA (m}^2\text{)} = 0.20247 \times 1.7 \text{ (m)}^{0.725} \times 80 \text{ (kg)}^{0.425}$
- $\text{BSA (m}^2\text{)} = 0.20247 \times 1.469 \times 6.439 = 1.92$

The subject's standing height will be measured in bare feet standing with his/her heels and back in contact with the vertical bar of a wall mounted measuring device. The head is held so the subject looks straight forward. A level will be placed on the subject's head to ensure that the subject is looking straight forward. The point at which the lower surface of the level intersects with the vertical measuring device will be the standing height.

APPENDIX 6. NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

In the present study, toxicities will be recorded according to the National Cancer Institute (of the United States of America, NCI) Common Terminology Criteria for Adverse Events (CTC-AE), version 4.0.

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

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

APPENDIX 7. ICH GUIDELINES FOR CLINICAL SAFETY DATA MANAGEMENT, DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING, TOPIC E2

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

- is fatal; [results in death] [NOTE: death is an outcome, not an event]
- is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].
- required in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For Serious Adverse Events, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply)

- Pre-existing/Underlying disease - specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be

reported. In addition, a serious adverse event that occurs after this time, if considered related to test “drug”, should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs page of the CRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor

See attached [Protocol Administrative and Contact Information & List of Investigators Form](#), for details of administrative and contact information.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies: Clinical Operations/Clinical Science

See attached [Protocol Administrative and Contact Information & List of Investigators form](#), for details of administrative and contact information

24 HOUR MEDICAL COVERAGE

To ensure the safety of study patients, an Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with the Roche medical contact for this study and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days a week. Toll free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see “Protocol Administrative and Contact Information & List of Investigators”). **The Help Desk will be used for medical emergencies outside regular business hours.**

Medical Monitor Contact Information for All Sites:

Medical Monitor: Dr [REDACTED]
Email (preferred contact): [REDACTED]
Telephone No.: [REDACTED]
Mobile Telephone No.: [REDACTED]

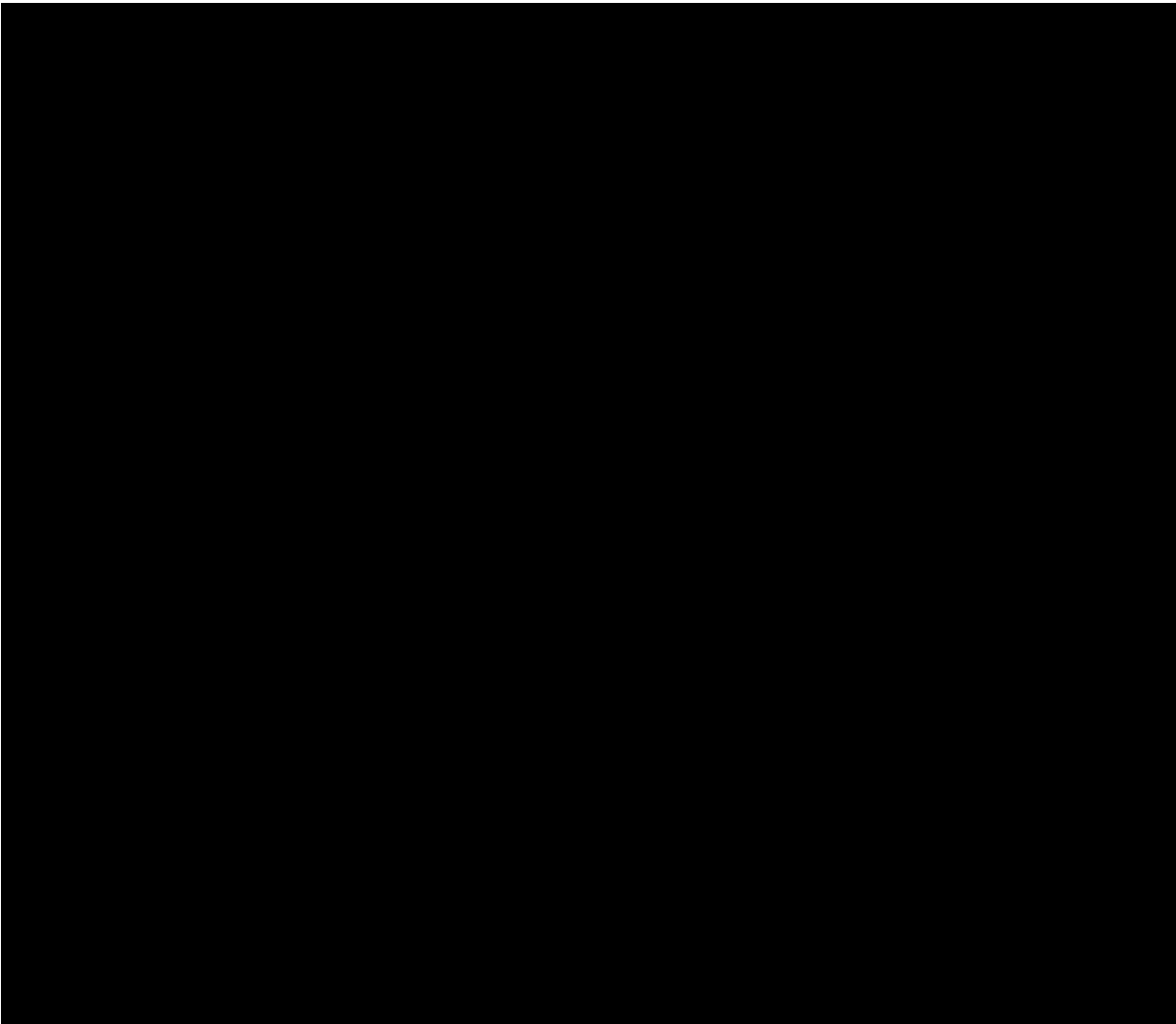
APPENDIX 8.

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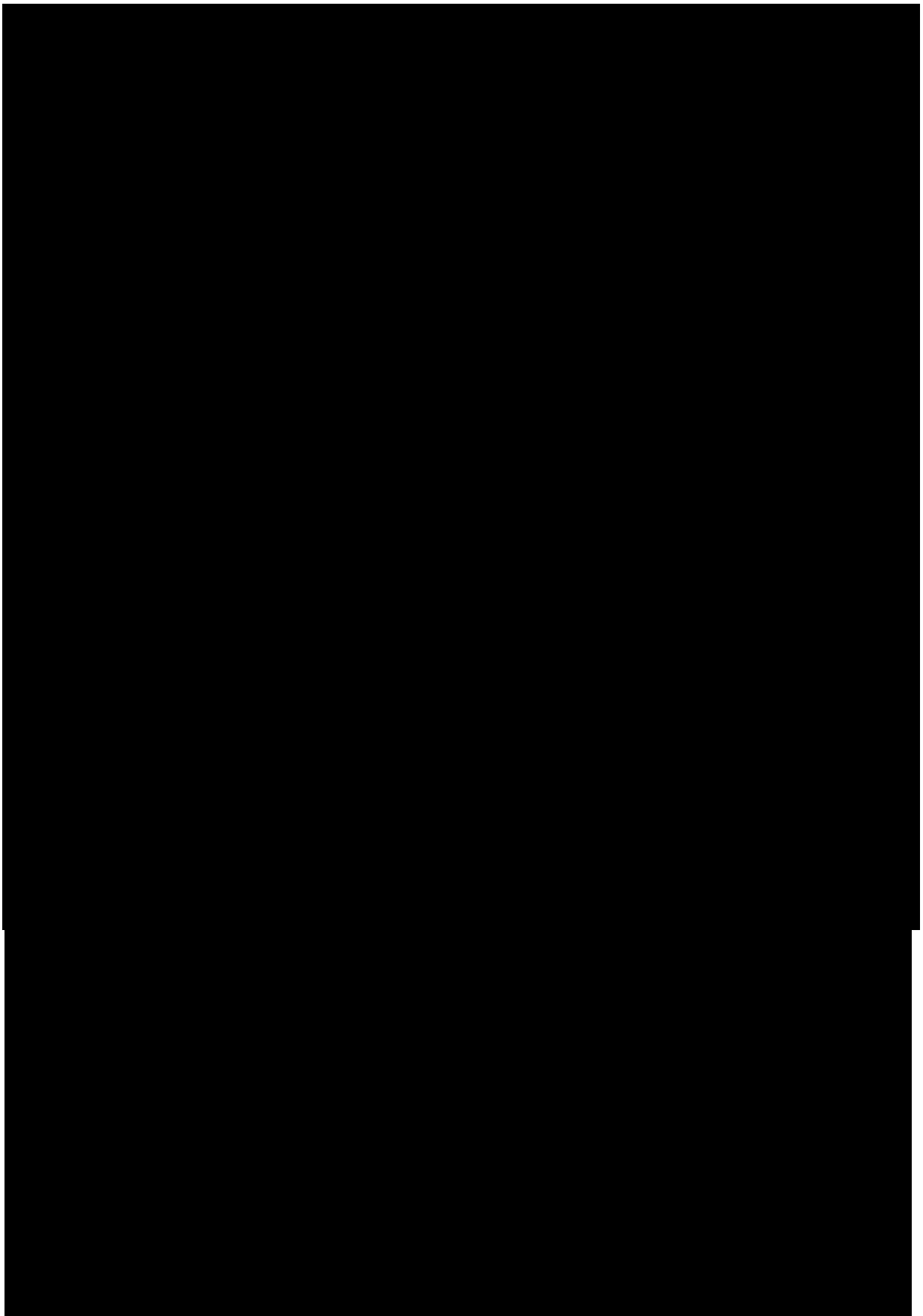
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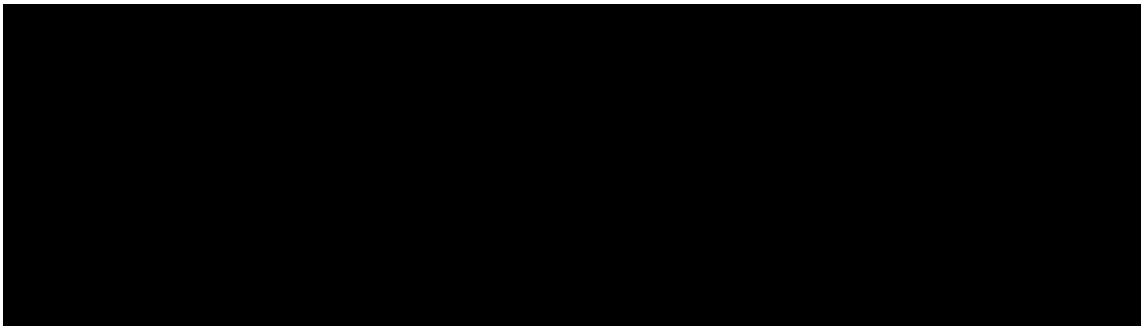
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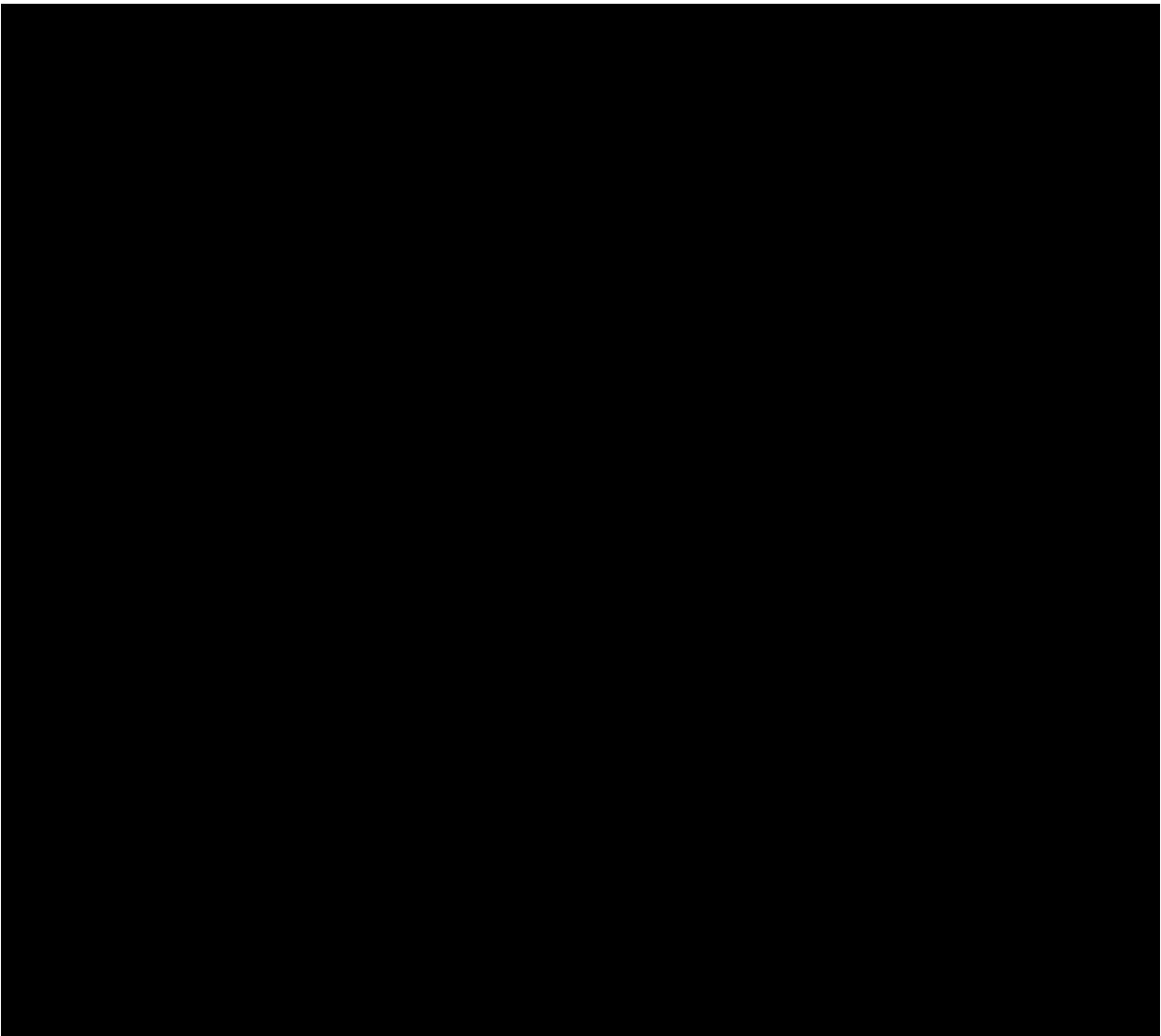
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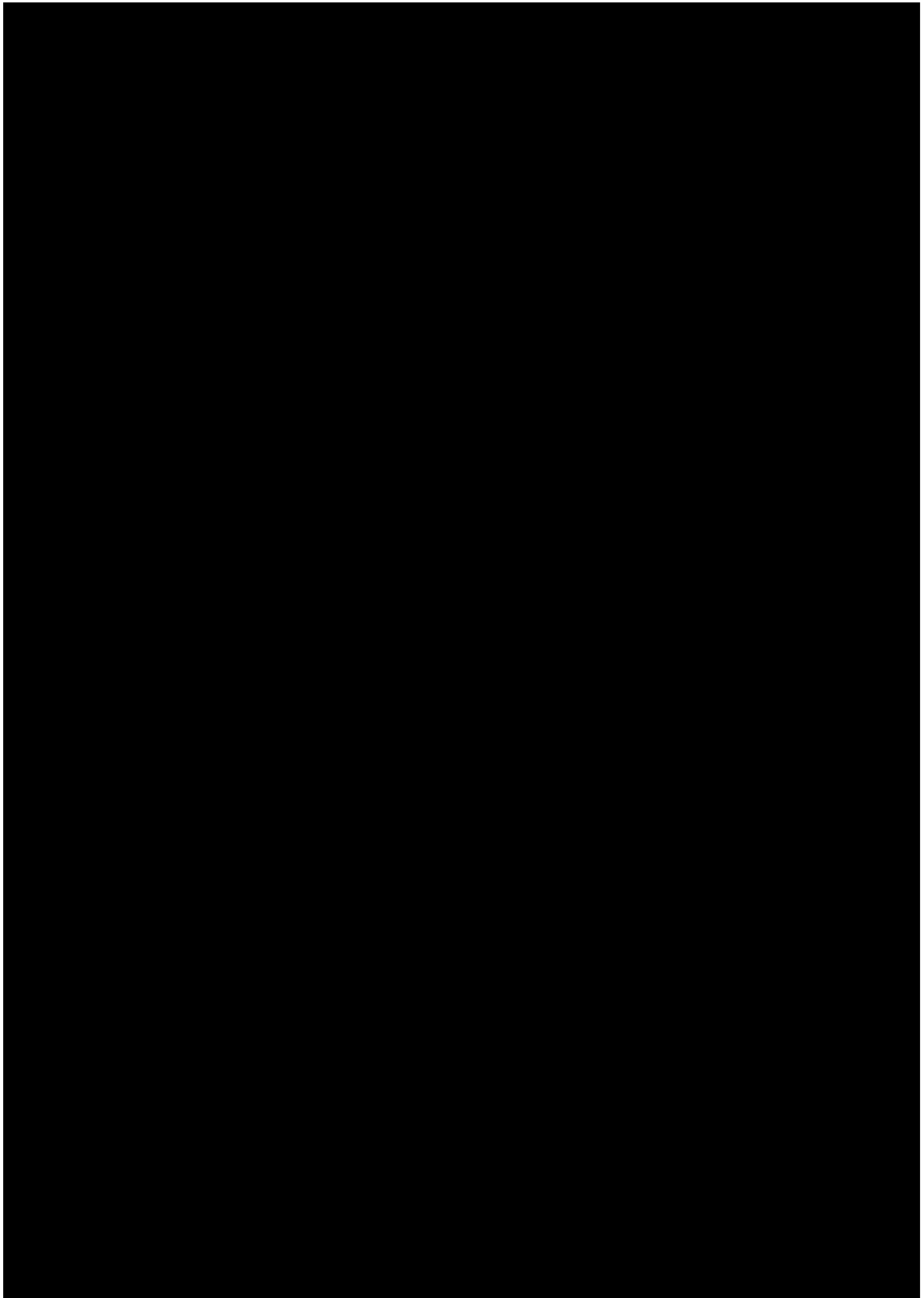
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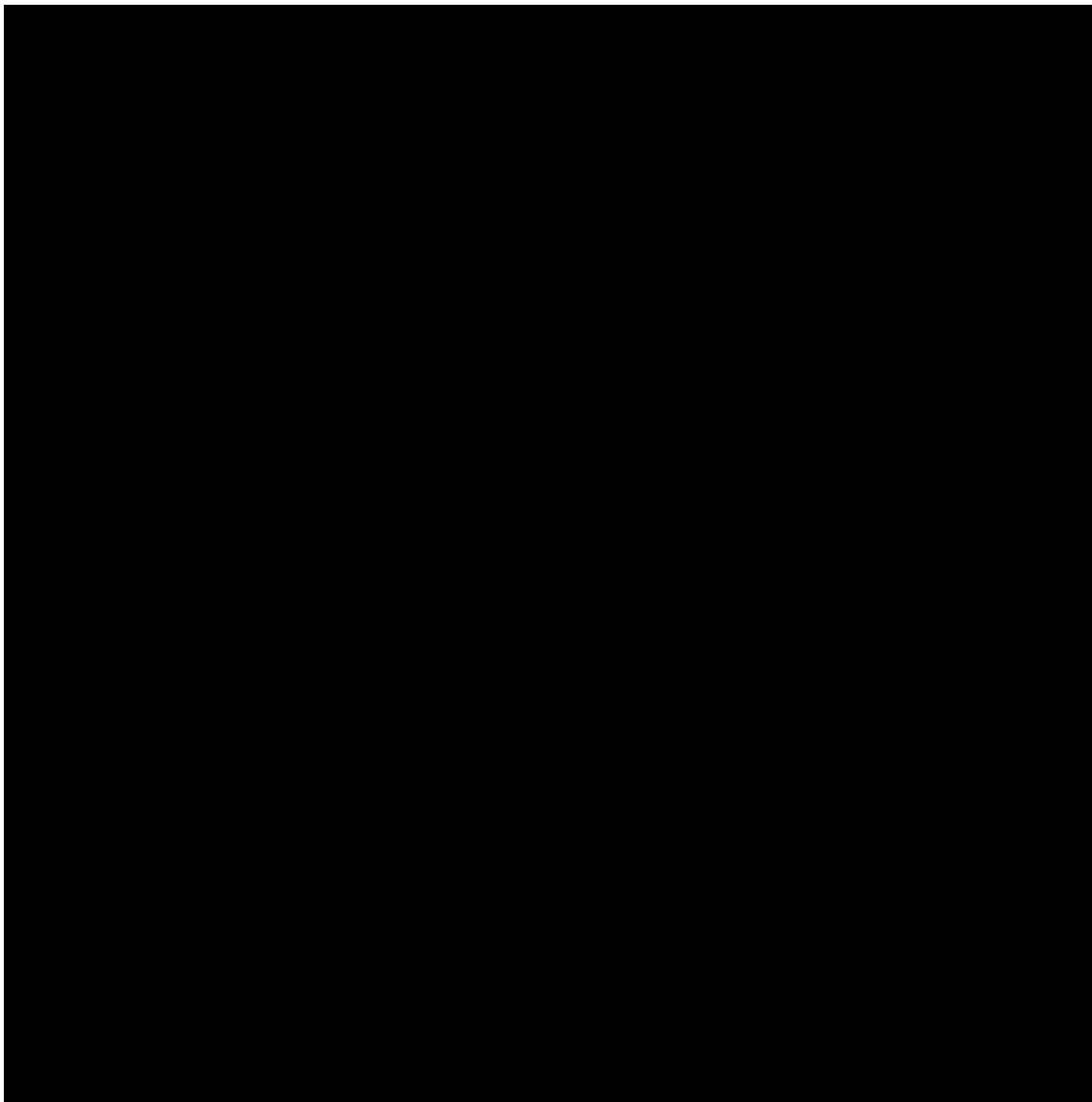






APPENDIX 9.





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