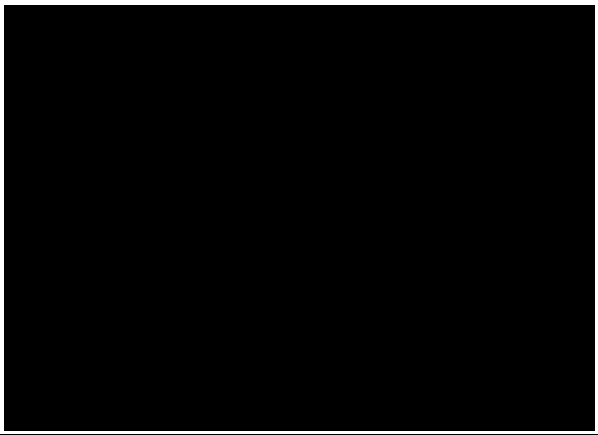
Statistical Analysis Plan

Protocol Title:	A Phase IIa, Open-Label, Multicenter Study of Single Agent MOR00208, an Fc-Optimized Anti-CD19 Antibody, in Patients with Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma
Protocol Number:	MOR208C201 (Version 6.0, including Amendment No. 4, 19 September 2017)
Compound:	MOR00208
Phase:	IIa
Sponsor:	MorphoSys AG Semmelweisstr. 7 82152 Planegg Germany
SAP Author:	
SAP Version:	Final Version 4.0
SAP Date:	03 April 2019

CONFIDENTIAL

DOCUMENT HISTORY

Version	Date	Author	Description
Final Version 1.0	20 Mar 2013	[redacted]	Final Version
Final Version 2.0	7 July 2015		Final Version 2.0
Final Version 3.0	30 November 2018		Updated to take account of protocol amendment 4
Final Version 4.0	03 April 2019		Updated to reflect further changes requested by sponsor

SIGNATURE PAGE AND APPROVALS

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

TABLE OF CONTENTS

ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-last}}$	Area under the concentration curve from dose time zero (0) to the time the last quantifiable concentration observed.
BMI	Body Mass Index
BSA	Body Surface Area
CD16	Cluster of Differentiation 16 (antigen expressed on malignant plasma cells)
CD19	Cluster of Differentiation 19
CL	Total body clearance calculated for a single dose as a first dose
C_{max}	Maximum serum concentration observed
C_{pd}	Predose serum concentration observed
CR	Complete Remission
CSR	Clinical Study Report
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DLBCL	Diffuse Large B-Cell Lymphoma
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FcγR	Fc gamma receptor

FDA	Food and Drug Administration
FDG-PET	[^{18}F]fluorodeoxyglucose-positron emission tomography
FL	Follicular Lymphoma
ICH	International Conference on Harmonisation
ITT	Intent-to-Treat
IWG	International Working Group
λ_Z	Apparent terminal rate constant
MALT	Mucosa-Associated Lymphoid Tissue Lymphoma
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MZL	Marginal Zone Lymphoma
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer
ORR	Overall Response Rate
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Remission
QTc	QT-interval for ECG corrected for heart rate
REAL/WHO	Revised European American Lymphoma/World Health Organization
RIT	Radio-immunotherapy
RT	Radiotherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Stem cell transplantation

SD	Stable Disease
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
t_{max}	Time to maximum serum concentration observed
TMF	Trial Master File
TTP	Time to Progression
$t_{½}$	Apparent terminal half-life
Vz	Apparent volume of distribution
WHO	World Health Organization

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting of data collected from MorphoSys protocol MOR208C201, Amendment 4.0, Version 6.0, dated 19 September 2017.

This Phase IIa, open-label, multicenter study is being completed to assess the antitumor activity and safety of single agent MOR00208 in adult patients with relapsed or refractory non-Hodgkin's lymphoma (NHL) who have received at least one prior therapy containing rituximab as one of the treatments.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported from this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society [3], for statistical practice.

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analysis not necessarily identified in this SAP may be performed to further examine study data and will not require updating the final SAP. Any post-hoc, or unplanned, exploratory analysis performed will be clearly identified as such and described in the final CSR.

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol MOR208C201, Amendment 4; Version 6.0, dated 19 September 2017.
- Annotated electronic Case report forms (eCRFs), Version 8 for Protocol MOR208C201, dated 10-Sep-2014.
- ICH Guidance on Statistical Principles for Clinical Trials (E9).

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objectives are

- To assess the antitumor activity of single agent MOR00208 in adult patients with relapsed or refractory NHL who have received at least one prior therapy containing rituximab as one of the treatments.

2.1.2 Secondary Objectives

- To evaluate the duration of response
- To establish safety and tolerability of MOR00208
- To assess the potential immunogenicity of MOR00208
- To evaluate the pharmacokinetics and pharmacodynamics of MOR00208 in patients with relapsed or refractory NHL

2.2 Efficacy, Safety and Pharmacokinetic/Pharmacodynamic Endpoints

2.2.1 Primary Endpoint

The primary efficacy endpoint will be the overall response rate (ORR) based on the revised IWG response criteria for malignant lymphoma as assessed by investigator [4]. The ORR for each subtype will be the rate of patients who met the criteria of partial remission (PR) or complete remission (CR) at the end of either the second or third cycle or during a response assessment in the follow-up period.

2.2.2 Secondary Endpoints

Secondary endpoints are

1. Stable disease (SD) rate
2. Duration of response (DoR)
3. Time to progression (TTP)
4. Progression-free survival (PFS)
5. Incidence and severity of AEs

6. Number and proportion of patients who potentially develop anti-MOR00208 antibodies and semiquantitative (anti-MOR00208 antibody titer determination of confirmed positive samples) anti-MOR00208 antibody assessments
7. Pharmacokinetics (C_{max}, t_{max}, C_{pd} [apparent trough serum concentration before dosing], AUC_{0-t}, λ_Z, $t_{½}$)
8. Absolute and percentage change from baseline in measurements of B-, T- and NK cell populations
9. Evaluation of AEs and ORR stratified by FcγRIIIa and FcγRIIa polymorphism
10. ORR based on central read

2.2.3 Pharmacokinetic Assessments

Concentration-time profiles and pharmacokinetic parameters will be assessed as data permit from MOR00208 serum samples collected on the following schedules (if not otherwise specified, a deviation of 10 minutes from the planned collection time point is acceptable):

For the first study drug infusion of 12 mg/kg (Cycle 1 Day1), serum samples will be collected predose, at the end of infusion, and 1 hour, 4 hours and 24 hours (± 1 hour) after end of first MOR00208 infusion.

During Cycle 1 on Days 8, 15 and 22, serum samples will be collected predose for trough level determination and then 1 hour after the end of the infusion.

During Cycles 2 and 3 on Days 8 and 22 of each cycle, serum samples will be collected predose for trough level determination and then 1 hour after the end of the infusion, a sample will also be collected on Day 28 ± 4 days.

At the 1st, 2nd and 3rd follow-up visits (± 2 days), serum samples will be collected.

The PK samples collected following the first study drug administration through the 24 hours sample will be used to characterize PK analysis to the 24 hour sample using actual elapsed sampling times with simple calculations and no terminal slope estimation. The other PK samples will only be listed and summarized by scheduled sample time except for the Day 28 samples following the last dose where the 1st, 2nd, and 3rd follow-up samples will be used to estimate a patient's terminal elimination rate. For patients receiving maintenance treatment after cycle 3, the FU1, FU2 and FU3 visits will be excluded from PK summary statistics, since the concentrations of MOR00208 at the FU1, FU2 and FU3 visits may be influenced by additional MOR00208 doses in maintenance treatment.

3. STUDY METHODS

3.1 Overall Study Design and Plan

This is a Phase IIa open-label, multicenter safety and efficacy study of MOR00208, that will enrol approximately 40 to 120 adult patients with refractory or relapsed NHL who have received at least 1 prior therapy containing rituximab.

The study will enrol patients from four different NHL subtypes: FL, DLBCL, MCL and other indolent NHL (MZL, MALT, etc). Data from the four subtypes will be presented separately, and data will also be presented for FL and other indolent NHL combined, and for all subtypes combined.

The study will employ a two-stage design where the decision to further enrol any NHL subtype in Stage 2 will depend on responses after 2 cycles in Stage 1.

Stage 1: Ten patients per NHL subtype (a minimum of 40 patients in total) will be enrolled to receive MOR00208 12 mg/kg weekly for 8 weeks. After 8 weeks of dosing, patients will be evaluated for response. If fewer than 2 of 10 patients per NHL subtype have a response of PR or better, then continued enrolment in that cohort will be stopped for futility. If at least 2 of 10 patients per NHL subtype have a response of PR or better, then additional patients will be enrolled into Stage 2 for that subtype cohort.

Any patients with a response of at least stable disease (SD) in Stage 1 will qualify for a further 4 weeks of dosing.

Stage 2: An additional 20 patients will be enrolled for each NHL cohort demonstrating a response in Stage 1. After 8 weeks, the ORR will be evaluated for each NHL cohort.

Any patients with a response of at least stable disease (SD) in Stage 2 will qualify for a further 4 weeks of dosing.

Patients who withdraw or discontinue before having received study drug on Cycle 2 Day 22 will only be replaced if the reason for withdrawal/discontinuation was not lack of efficacy.

Patients will not be replaced after they have received treatment for Cycle 2 Day 22, regardless of the reason of withdrawal or discontinuation.

3.2 Selection of Study Population

The study population will consist of adult patients with relapsed or refractory B-cell NHL who have received at least one prior therapy containing rituximab. Key inclusion criteria identified in the protocol are

1. Patients are male or female ≥ 18 years of age.
2. Patients have a histologically confirmed diagnosis according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification, of the following B-cell lymphomas:
   - Follicular lymphoma (FL)
   - Diffuse large B-cell lymphoma (DLBCL)
   - Mantle cell lymphoma (MCL)
   - Other indolent NHL (eg, marginal zone lymphoma [MZL]/ mucosa-associated lymphoid tissue lymphoma [MALT])
3. Patients' NHL must have progressed after at least 1 prior rituximab-containing regimen.
4. Patients have at least one site of measurable disease by magnetic resonance imaging (MRI) or computed tomography (CT) scan defined as at least one lesion that measures at least 1.5 × 1.5 cm,

   Exception:
   For patients with MCL only, patients with nonmeasurable disease but evaluable sites (bone marrow, spleen, peripheral blood, gastrointestinal tract) can be enrolled.
5. Patients who have previously received an autologous stem cell transplantation must be at least 4 weeks post-transplant before study drug administration and must have exhibited a full hematological recovery.
6. Patients must have discontinued previous monoclonal antibody therapy (except rituximab) or radioimmunotherapy administration for at least 60 days before study drug administration.
7. Patients should be off rituximab for at least 14 days before the screening visit and be confirmed to have either no response or have disease progression after rituximab treatment.
8. Patients with DLBCL must have a positive [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scan at baseline (Cheson 2007 response criteria).
9. Patients must have a life expectancy of > 3 months.

10. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of < 3.
11. Patients must meet the following laboratory criteria at screening:
    - Absolute neutrophil count (ANC) ≥ 1.0×10^9/L
    - Platelet count ≥ 75×10^9/L without previous transfusion within 10 days of first study drug administration
    - Hemoglobin ≥ 8.0 g/dL (may have been transfused)
    - Serum creatinine < 2.0 x upper limit of normal (ULN)
    - Total bilirubin ≤ 2.0 × ULN
    - Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
12. If a female of childbearing potential, a negative pregnancy test must be confirmed before enrolment and use of double-barrier contraception, oral contraceptive plus barrier contraceptive must be used during the study and for 3 months after the last dose, or confirmation of having undergone clinically documented total hysterectomy and/or oophorectomy, tubal ligation.
13. If a male, an effective barrier method of contraception must be used during the study and for 3 months after the last dose if the patient is sexually active with a female of childbearing potential.
14. The patients are able to comply with all study-related procedures, medication use, and evaluations.
15. The patients are able to understand and give written informed consent and comply with the study protocol.

3.3 Method of Treatment Assignment and Randomization

This is a single arm study.

3.4 Treatment Masking (Blinding)

This is an open-label study.

4. ANALYSIS AND REPORTING

Interim analyses for futility per NHL subtype are the responsibility of the sponsor; [redacted]

[redacted] will not be involved in formal interim analyses (please refer to Section 5 for further details). Decisions made at interim analysis will be described in the CSR.

4.1 Final Analysis

The analyses identified in the protocol and in this SAP will be performed after a database cutoff foreseen in July 2015. At that time, all patients will have completed the main treatment period (that is, up to 3 cycles of MOR00208 therapy), though some patients will still be receiving maintenance treatment and few other patients may be in the follow-up phase (for survival only, without maintenance treatment).

Based on the present SAP, analyses at a later point in time may be conducted, e.g., for regulatory interactions, following database lock.

Further analyses will be done after the last patient has completed the end of study visit, all data have been processed and the database has been locked. Those analyses will be used to prepare an addendum to the CSR. In addition, no database may be locked or analyses completed until this SAP has been approved and signed off by all responsible parties.

All study results will be made available to MorphoSys AG following database lock and prior to completion of the final CSR.

MorphoSys will perform further exploratory analyses to investigate correlations between different biomarker and response variables.

Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR, but will not necessitate an update of the final SAP. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

4.2 Final Pharmacokinetic Analysis

The final PK analysis will be performed on data from the clinical database combined with the concentration data from the bioanalytical lab after the database has been locked.

PK Input Files will be created using SAS® software (version 9.3 or later) from the serum concentrations reported by the bioanalytical lab combined with the dosing and sampling information from the clinical database after the database has been locked. Actual elapsed time from dose to sampling time will be used for all parameter estimation but mean concentration data will be presented in tables and figures using scheduled sampling times. Any concentration values outside acceptable time windows will be excluded from those summary statistics (see

section 10.3.2 for details). For patients receiving maintenance treatment after cycle 3, the FU1, FU2 and FU3 visits will be excluded from PK summary statistics, since the concentrations of MOR00208 at the FU1, FU2 and FU3 visits may be influenced by additional MOR00208 doses in maintenance treatment.

The PK analysis will be conducted using the Phoenix WinNonlin® version 6.3 or later software from Pharsight, Cary, North Carolina. The PK tables, listings, and figures will also be produced in SAS. Any PK tables that involve inference testing will be performed by statisticians using SAS software.

The $AUC_{0\text{-last}}$ will be produced from the first dose including samples up to the 24-hour post-infusion sample drawn just before the 2nd infusion. The last dose will provide as many as 4 samples starting at the sample drawn at Cycle 3 Day 28 and including the 3 follow-up visit samples. These samples from the last dose will be used to estimate the terminal elimination rate and its associated half-life.

5. SAMPLE SIZE DETERMINATION

A two-stage design is used to minimize exposure of NHL subtypes not showing responsiveness to MOR00208. No formal sample size estimations for determination of futility were computed for Stage 1. The number of patients to be used in this stage was determined to be the minimum number needed to adequately determine futility in any specific NHL subtype. The entire study will enroll between 40 to 120 patients, dependent upon patient response in each subtype in Stage 1.

Stage 1: Approximately 40 patients, an equal number of patients will be enrolled per NHL subtype:

- FL: 10 patients
- DLBCL: 10 patients
- MCL: 10 patients
- other indolent NHL: 10 patients

Observing less than two responses (at least PR) in 10 patients in any NHL subtype will be the criterion for discontinuing evaluation of MOR00208 in that NHL subtype. If the study drug is effective with a true ORR of 30%, the probability to stop for futility after the first stage for a specific NHL subtype is only 14.9%.

Stage 2: For those NHL subtypes with two or more responders, an additional 20 patients will be

enrolled for a total of 30 patients per subtype. Assuming that the true ORR of any NHL type is 30% and that the number of responses actually observed in the study corresponds to the expected number of responses (9 responses), N=30 would yield a lower limit of the 95% confidence interval for the ORR of 14.7%. Up to a maximum of 80 additional patients, an equal number of patients will be enrolled per "responding" NHL subtype. Some of the cohorts may have been stopped for futility after Stage 1:

- FL: 20 patients
- DLBCL: 20 patients
- MCL: 20 patients
- other indolent NHL: 20 patients

Approximately 25 to 30 centres in the United States of America and Europe are planned.

6. ANALYSIS POPULATIONS

The following analysis populations will be defined:

- Intent-to-treat (ITT) Population: Consists of all patients who received at least one dose of study drug. Patients without any post baseline assessment of NHL response will be included as non responders.
- Safety Population: Consists of all patients who received at least one dose of study drug.
- Pharmacokinetic (PK) Population: The Pharmacokinetic Population will include all patients who have at least one quantifiable serum MOR00208 concentration. (PK parameters will be calculated as data permit.)

Please note that the definition of the PK population differs slightly from that in the protocol: see section 12.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

Tables for disposition of patients and study discontinuations (see Section 8.1) will be produced for all patients enrolled. The Safety Population will be used for safety analysis and to analyze immunogenicity. The ITT Population will be used to analyze pharmacodynamic endpoints. Summaries for the analysis of response by investigator and radiology central reader will be provided for the ITT Population. Pharmacokinetic summaries will be presented for the

Pharmacokinetic Population.

If not specified otherwise, all statistical summaries will be presented by NHL subtype, for the combined subtype of FL and other indolent NHL, and overall.

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS software, Version 9.3 or later.

Continuous, quantitative variable summaries will include the number of patients (N) (with non-missing values), mean, standard deviation, median, minimum and maximum. Some of the descriptive summaries (as specified in the subsequent sections) will additionally include the 95%-confidence interval for the mean (absolute) change from baseline. The confidence interval will be calculated based on the quantiles of the t-distribution assuming normal distribution of the data. Moreover, some of the descriptive summaries (as specified in subsequent chapters) will include the 95%-confidence interval for the median (absolute or percentage) change from baseline. The 95%-confidence interval for the median will be calculated without any assumption on the distribution of the data (nonparametric confidence interval). For this calculation the SAS option CIQUANTDF in proc UNIVARIATE may be used.

Categorical, qualitative variable summaries will include the frequency and percentage of patients who are in the particular category.

For time durations in days that need to be converted to months, the number of days will be divided by factor 30.4375. For time durations in days that need to be converted to years, the number of days will be divided by factor 365.25.

Unless otherwise specified, Baseline is the last observation before the start of the study treatment, which is expected to be the Baseline Visit on Day 1, or Screening or any other unscheduled visits before the start of the study drug administration, if Baseline, Day 1 data are not available. For data such as CD16 expression on NK cells which is only recorded at Screening the Screening value will be the Baseline value, if the Screening value is missing then the baseline value will also be missing.

All data obtained on the eCRF and entered into the database will be provided in separate data listings showing individual patient values. The planning and reporting of statistical analyses will be carried out as described in the [redacted] SOPs.

Any patient who withdraws from the study will be analyzed with the data available. Imputation of missing values will not be performed, unless specified in the relevant sections of the SAP.

7.2 Handling of Missing Data for PK Analysis

Missing data can be from patients who drop out and do not complete the study or from serum concentration data that are not reported by the bioanalytical lab due to technical issues. Handling of both of these situations is described in this section.

Any patient who withdraws from the study will be evaluated for inclusion in the PK analysis based on the PK data available.

A distinction is made between a missing serum concentration due to failure to deliver the sample to the bioanalytical lab for assay, a serum concentration that was not reported by the bioanalytical lab due to a failure of the assay or handling, and a matrix concentration that is reported as being below limit of quantifiable (BLQ) of the assay. Samples that are reported with measurable concentrations are included in the PK analysis. Samples that are reported as BLQ are either assigned zero or missing depending on their location in the profile (process explained in Section 10.3.2) as this affects the calculation of AUCs. Samples that are either not reported or reported as missing will be reported as missing in the analysis.

7.3 Derived and Computed Variables

The following derived and computed variables for immunogenicity, efficacy and exposure data have been initially identified as important for the statistical analysis. Additional variables may be required. The SAP will not be amended for additional variables that are not related to the primary or secondary endpoints. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

7.3.1 Previous NHL therapy variables

Previous NHL therapies will be reviewed and assessed by a [redacted] medical monitor. The review will be conducted in line with the [redacted] SOP-MA-11 on data from the eCRF module 'Previous NHL therapies' once prior to the analysis. Clarifications on the data may be addressed by the [redacted] medical monitor to the sites directly using the Remote Data Capture portal of the database or via the responsible CRA/CM. The recorded NHL therapies will be grouped into lines of therapies taking into account all therapeutic procedures recorded (pharmacological treatment, surgery and radiotherapy), the chemotherapy regimens, response data and feedback to clarifications by the sites. Induction, consolidation, stem cell collection, preparative regimen including transplantation, and maintenance will be considered a single line

of therapy. In addition systemic therapies [systemic pharmacology therapy, systemic radiotherapy (RT), radio-immunotherapy (RIT), and stem cell transplantation (SCT),)] will be identified indicating the type of therapy (chemo, immuno, immune-chemo, SCT, RIT, systemic RT). Furthermore rituximab containing regimens will be identified and grouped into subgroups (single agent, R-CHOP or R-CHOP-like and other). The outcome of the review will be recorded in a table indicating the lines of therapy, the systemic therapies, the types of therapy and the rituximab-containing regimens) and will be reviewed by a second medic. Adjudication of cases with discrepant assessments will be performed by discussing the case with both medics involved. If the assessments remain discrepant the final decision about the case lies with the sponsor. The data and outcome of the review and related correspondence will be documented and filed in the TMF.

The following variables will be derived from this assessment:

- Number of prior lines of therapy (as continuous variable and as number of patients with 1, 2, 3, or > 3 prior lines)
- Number and type of prior systemic therapies (as continuous variable and as number of patients with 1, 2, 3, or > 3 prior therapies)
- Number (%) of patients with prior rituximab containing regimens, in total and broken down as:
    - single agent rituximab
    - R-CHOP or R-CHOP-like (R-CHOP, R-CHOEP, R-CVP, R-GEMOx, R-THP-COP)
    - Other (purine analog + rituximab, R-bendamustine, R-HyperCVAD, R -ICE, R-DHAP, R-EPOCH, R-COMP, etc.)
- Number (%) of patients with previous therapies by type (surgery, local radiation therapy, chemotherapy, immunotherapy, immune-chemotherapy, systemic radiation therapy, stem cell transplantation, or any other previous therapy)
- Previous NHL Therapies will be coded using the current version of the WHO Drug Dictionary Enhanced (WHO-DDE). Surgical and medical procedures will be coded using MedDRA. The following variables will be derived from the eCRF directly:
- Response to last therapy before study inclusion, in categories CR, PR, SD, PD, and unknown
- Response to last rituximab-containing therapy line (broken down into any rituxumab-containing therapy, rituximab containing monotherapy, and rituximab-containing

combination treatments) before study inclusion, in categories CR, PR, SD, PD, and unknown

- Classification of patients as rituximab refractory (no response or response lasting < 6 months to a prior rituximab-containing therapy; patients will be considered refractory if they are refractory to any rituximab-containing regimen, even if they had responded to another rituximab-containing regimen)
- Duration of response to last therapy, as a continuous variable (in months) and as number and % (and cumulative number and %) of patients with responses of < 6 months, 6–12 months, > 12 months, and unknown duration (if the end date of the duration of response to last therapy is not specifically recorded, it will be assumed to be the date of screening for the present study)

7.3.2 Prognostic variables

Prognostic indices will be calculated for DLBCL patients, MCL patients, and FL patients. No prognostic index will be calculated for other indolent NHL patients. Details of the prognostic indices used are given below.

7.3.2.1 Prognostic variables for DLBCL patients

The International Prognostic Index (IPI) [5] will be calculated for all DLBCL patients. This is calculated from the following items:

- Age older than 60
- Lactate dehydrogenase level higher than normal
- ECOG performance status score of 2 or greater
- Stage III or IV disease
- More than one involved extranodal disease site

The IPI gives one point for each of the above characteristics, for a total score ranging from zero to five correlating with the following risk groups :

- Low risk: 0–1 points
- Low-intermediate risk: 2 points
- High-intermediate risk: 3 points
- High risk: 4–5 points

The categories above will also be collapsed into low risk (0–2 points) and high risk (3–5 points). Subgroup analysis according to low risk and high risk IPI scores will be presented for DLBCL patients for the outcomes of overall response rate and PFS.

7.3.2.2 Prognostic variables for MCL patients

The MCL International Prognostic Index (MIPI) [6] will be calculated for all MCL patients. Points are scored for age, ECOG performance status, LDH, and leukocyte count, according to the table below, and the scores for each are added to give a total score.

Points	Age (years)	ECOG PS	LDH/ULN LDH	WBC, 10^9/L
0	< 50	0–1	< 0.67	< 6,700
1	50–69	-	0.67–0.99	6,700–9,999
2	60–69	2–4	1.00–1.49	10,000–14,999
3	≥ 70	-	≥ 1/5	≥ 15,1000

The sum of the allotted points correlates with the following risk groups:

- Low risk: 0–3 points
- Intermediate risk: 4–5 points
- High risk: 6–11 points

The categories above will also be collapsed into low risk (0–3 points) and high risk (> 3 points). Subgroup analysis according to low risk and high risk MIPI scores will be presented for MCL patients for the outcomes of overall response rate, PFS, and OS.

7.3.2.3 Prognostic variables for FL patients

The Follicular Lymphoma International Prognostic Index (FLIPI) [7] will be calculated for all FLIPI patients. This is calculated taking into account the following factors:

- Age > 60
- Serum LDH > ULN
- Hgb < 12 g/dl
- Stage III or IV
- Number of nodal sites > 4

The presence of ≤1, 2, and ≥ 3 factors define low, intermediate, and high risk.

The categories above will also be collapsed into low risk (0–2 points) and high risk (≥ 3 points). Subgroup analysis according to low risk and high risk FLIPI scores will be presented for FL patients for the outcomes of overall response rate, PFS, and OS.

7.3.3 Immunogenicity

Patient has positive anti-MOR00208 antibodies (yes/no/missing) by visit:

- yes, if a titer is available
- no, if result is reported as negative
- missing, if anti-MOR00208 measurement is not available

Patient has developed positive anti-MOR00208 antibodies during study (yes/no/transient/not evaluable/missing):

- yes, if the patient has at least one positive post-baseline sample containing positive anti-MOR00208 antibodies including a positive result for the last sample analyzed; baseline sample has to be tested negative
- no, if baseline as well as all post-baseline results are negative
- transient, if the patient has at least one positive post-baseline sample containing positive anti-MOR00208 antibodies but a negative result for the last sample analyzed; baseline sample has to be tested negative
- not evaluable, if the baseline sample of the respective patient was tested positive
- missing, if no post-baseline anti-MOR00208 measurement is available

7.3.4 Efficacy

7.3.4.1 Investigator Assessment

The Investigator will assess tumor response at specific study visits according to the criteria for NHL as defined in Section 17.4 of the study protocol. All of the criteria are based on the revised IWG response criteria [4].

The categories of overall tumor response assessment of the Investigator are as follows:

- CR - Complete remission
- PR - Partial remission
- SD - Stable disease

- PD - Progressive disease
- Missing (if response assessment is not done)

In case of progressive disease, the date of progression is given by the Investigator. In case any anti-tumor treatments other than MOR00208 are given before end of study (see also section 8.3), it is regarded as protocol non-compliance. Following a conservative approach, tumor assessments of the Investigator after start of other anti-tumor treatment which are non-PD will not be taken into account for any of the derived efficacy variables described below, whereas assessments of PD will still be taken into account. This ensures that a progression is still included in the analysis if an anti-tumor treatment has been started based on clinical progression, but the image confirming PD was done at a later time point. A response assessment provided by investigator after start of other than protocol indicated anti-tumor treatment will, however, not be counted for overall best response.

Tumor Response categories (Investigator) will be evaluated in terms of absolute and percentage frequencies by visit.

Overall best response (Investigator) will be defined as best response across the following time points: end of the second, end of third cycle, during a response assessment in the follow-up period or at an unscheduled assessment after end of second cycle.

Overall response rate (ORR) (Investigator) will be evaluated as the rate of patients who met the criteria of PR or CR at the end of either the second or third cycle or during a response assessment in the follow-up period (i.e. who have an overall best response of PR or CR).

Overall rate of SD (disease control rate) (Investigator) will be evaluated as the rate of patients who met the criteria of PR, CR or SD at the end of either the second or third cycle or during a response assessment in the follow-up period (i.e. who have an overall best response of PR, CR or SD).

Duration of response (Investigator): Duration of response will be defined as the time from date of first response (CR or PR) until first date that recurrence or progressive disease is objectively documented. The duration of response will be calculated in the subgroup of all patients showing any response; confirmation of response will not be required. Patients who showed a response but did not show PD or recurrence until end of study or before study discontinuation (i.e. patients who are at least stable at their last tumor assessment) are considered censored at the timepoint of last response assessment. Deaths due to causes other than progression of disease are to be reported as SAEs and are censored for duration of

response analysis at the date of last tumor assessment before death. The cause of death has to be recorded as free text by the Investigator on the eCRF study completion page. If the cause of death does not explicitly state whether death is related to progression of disease, a query will be raised to ask the investigator to classify the relationship to disease (yes/no). Morphosys Drug Safety will assess the causality of the SAE by reviewing the corresponding SAE documents.

Time to response (Investigator): Time to response will be defined as the time from Cycle 1, Day 1 (first administration of study drug) until the date of first response (CR or PR). Patients who do not have a response to treatment will be censored at the date of their last tumor assessment.

Time to progression (Investigator): Time to progression is defined as the time from Cycle 1, Day 1 (first administration of study drug) until date of first tumor progression (which is entered in the tumor assessment module). Patients who do not show any documented progression (which is entered in the response assessment module of the eCRF) before the end of study or before study discontinuation or before death are considered censored using the last date with a tumor assessment as censoring date (irrespective of when the patient died). Deaths due to causes other than disease progression are censored.

Progression-free survival (Investigator): Progression-free survival is defined as the time from Cycle 1, Day 1 (first administration of study drug) until date of first tumor progression (which is entered in the response assessment module of the eCRF) or date of death from any cause. If the patient does not show any documented progression (which is entered in the tumor assessment module) before death, the date of progression will be the date of death if death occurs within 2 months after the last date with a tumor assessment. If death occurs after 2 months after the last date with a tumor assessment or the patient did not progress or die until end of study or before withdrawal, the patient will be analyzed as censored using the last date with a tumor assessment as censoring date.

7.3.4.2 Central Read

Additionally a central radiology read of scans will be performed by SYNARC/BioClinica. The revised IWG criteria definitions [4] will also be applied. Details of the central read are described in the Independent Review Charter, Version 1.0, 01-JUL-2013, provided by SYNARC.

The independent reviewers (two primary radiologists) will be presented with all time points sequentially in chronological order, and will provide assessments for each time point. For the

overall tumor assessment of the central read a slightly different terminology is used:

- CR - Complete response
- PR - Partial response
- SD - Stable disease
- PD - Relapsed or progressive disease
- NE - Non-Evaluable (can be applied if repeated measurements cannot be applied for reasons such as inadequate or missing imaging and when progression/relapse cannot be assigned for the visit overall response)
- ND - No Disease (this category is used if there is no tumor and there was no tumor at baseline)

Once the independent reviews for all time points in the course of the study have taken place, all time points for a particular patient will be again reviewed together by the two independent reviewers in a global patient review over all time points. In their global patient review the two independent reviewers will determine:

- best overall response (defined as best response the subject had since treatment started taking into account scheduled and unscheduled visits)
- date of the best overall response
- duration of best overall response (calculated by the system as time from first response to progression if patient is PD at a specific visit)
- date when progression/relapse occurred

Finally, an adjudicator radiologist will perform adjudication, in case there is any discrepancy in the global patient review of the two primary radiologists. The adjudicator will review both initial readings and will record a new review that will agree with either of the duplicate reviews. Thus, the adjudicator will need to agree to the complete reading of one of the primary radiologists (all assessments by visit and all variables from corresponding global review). A mandatory comment will need to be recorded. The adjudicated reading results will be considered as the results for the involved patients.

There may be rare cases where the two primary radiologists disagree in some of the overall assessments by visit, but agree in the global patient review. In these cases no adjudication will be performed. Thus for the overall assessment by time point, descriptive tables will be based on

the following results:

- Assessment of the reader the adjudicator agrees with, in case adjudication was performed
- Worst response assessment of the two primary radiologists at each visit in case no adjudication was performed

All other variables described below are only based on the variables from global review which are adjudicated in case of discrepancies between the two primary radiologists. The term "central reviewer" used below refers to the adjudicator in case adjudication is performed or to the primary radiologists (in case global patient review of the two primary radiologists are identical and no adjudication is necessary).

In case any anti-tumor treatments other than MOR00208 are given before end of study (see also section 8.3), it is regarded as protocol non-compliance. Following a conservative approach for statistical analysis, the following steps will be implemented by [redacted] biostatistics: tumor assessments of the two primary radiologists after start of other anti-tumor treatment which are non-PD will not be taken into account, whereas assessments of PD will still be taken into account. Moreover, if the date of best overall response as provided by the adjudicator is after start of anti-tumor treatment, the date will be set to missing and the best overall response to "not evaluable". This ensures that a progress is still included in the analysis if an anti-tumor treatment has been started based on clinical progression, but the image confirming PD was done at a later time point. A response after start of anti-tumor treatment will, however, not be counted for best overall response.

Tumor Response categories (Central Read) will be evaluated in terms of absolute and percentage frequencies by visit

Best overall response (Central Read) will be directly provided by the central reviewer (SYNARC uses the terminology best overall response or best response).

Overall response rate (ORR) (Central Read) will be evaluated as the rate of patients who have a best overall response of PR or CR.

Overall rate of SD (disease control rate) (Central Read) will be evaluated as the rate of patients who have a best overall response of PR, CR or SD.

Duration of best overall response (Central Read): Duration of best overall response will be defined as the time from date of best overall response (as provided by the central reviewer) until first date that recurrent or progressive disease is objectively documented. The duration of

best overall response will be calculated in the subgroup of all patients showing any response; confirmation of response will not be required. Patients who showed a response but did not show PD or recurrence until end of study or before withdrawal (according to the central reviewer) are considered censored at the timepoint of last response assessment. Deaths without documented progression before death (according to the central reviewer) are also considered as censored at date of last response assessment.

Time to response (Central Read): Time to response will be defined as the time from Cycle 1, Day 1 (first administration of study drug) until the date of best overall response (as provided by the central reviewer) if best overall response is PR or CR. Patients who do not have a response to treatment will be censored at the date of their last tumor assessment.

Time to progression (Central Read): Time to progression is defined as the time from Cycle 1, Day 1 (first administration of study drug) until date of progression/relapse (as provided by the central reviewer). Patients who do not show any documented progression (according to the central reviewer) before the end of study or before withdrawal or before death are considered censored using the last date with a tumor assessment as censoring date (irrespectively of when the patient died).

Progression-free survival (Central Read): Progression-free survival is defined as the time from Cycle 1, Day 1 (first administration of study drug) until date of progression/relapse (as provided by the central reviewer) or date of death from any cause (as given in the eCRF). If the patient does not show any documented progression before death (according to the central reviewer), the date of progression/death will be the date of death if death occurs within 2 months after the last date with a tumor assessment. If death occurs after 2 months after the last date with a tumor assessment or the patient did not progress or die until end of study or before withdrawal, the patient will be analyzed as censored using the last date with a tumor assessment as censoring date.

7.3.5 Exposure

The following tables show the variables which will be calculated to measure exposure to MOR00208. Details regarding study drug administration are only captured from Cycle 1 to Cycle 3 in the eCRF. In the maintenance treatment phase, the only information which is captured in eCRF at the follow-up visits is whether the patient will continue to receive study drug.

Variables calculated for each study drug administration (Cycle 1 to Cycle 3)

Percentage of actual volume administered vs. planned volume [%]	Actual volume administered [mL]/250 mL*100%
Actual dose administered per kg [mg/kg]	(Actual volume administered [mL]/250 mL)*Assigned dose [mg/kg]
Actual dose administered [mg]	(Actual volume administered [mL]/250 mL)*Assigned dose [mg/kg]* Weight[kg] Note: The weight obtained at each visit before study drug administration should be used to calculate the study drug dose for the respective visit. Only in exceptional cases, e.g. due to logistical issues, the weight obtained at the previous visit can be used (provided that there is no obvious change of ± 10% compared with the previous visit).

Variables calculated on a per-patient basis:

All of the variables shown in the table below will summarize the exposure from cycle 1 to cycle 3, except the first variable “duration of exposure including maintenance treatment” which will include maintenance treatment.

Duration of exposure including maintenance treatment [weeks]	Time from Cycle 1, Day 1 to date of last study treatment (approximated) [weeks] Note: This variable can only be approximated as the date of last study treatment is not captured in the eCRF: Date of last study treatment is approximated as follows: - If patient did not receive maintenance treatment at all, the date of last study treatment is the date of last study treatment entered to the study drug administration page - If patient received (or is planned to receive) maintenance treatment, the date of last study treatment will be approximated as the minimum of the two following: o Date of follow-up visit where the question "Will the subject continue to receive treatment?" is ticked as "NO" for the first time (on the response assessment eCRF page) o End of study date (from study completion page)
Number of cycles with all infusions completed	Number of cycles with all 4 infusions completed
Total number of infusions administered	Number of all infusions
Total number of infusions administered in Cycle x	Number of all infusions in Cycle x
Total number of infusions with a duration > 2.5 h	Number of infusions with (sum of all periods (stop time – start time)) > 150 minutes

Total number of infusions with a duration > 2 h	Number of infusions with (sum of all periods (stop time – start time)) > 120 minutes
Total number of infusions with a duration of 2 to 2.5 hours	Number of infusions with (sum of all periods (stop time – start time)) >= 120 minutes, but <=150 min
Total number of infusions with a duration of < 2 hours	Number of infusions with (sum of all periods (stop time – start time)) < 120 minutes
Total number of infusions administered with any modification	Number of all infusions with any treatment modification (infusion rate reduced, infusion rate increased, infusion interrupted and restarted, infusion stopped)
Total volume administered [mL]	Sum of the variable "Actual volume administered [mL]" over all infusions
Average percentage of actual volume administered vs. planned volume [%]	Mean of the variable "Percentage of actual volume administered vs. planned volume [%]" over all infusions
Total actual dose administered per kg [mg/kg]	Sum of the variable "Actual dose administered per kg [mg/kg]" over all infusions
Total actual dose administered [mg]	Sum of the variable "Actual dose administered [mg]" over all infusions
Average actual dose administered per kg [mg/kg]	Mean of the variable "Actual dose administered per kg [mg/kg]" over all infusions

8. STUDY PATIENTS AND DEMOGRAPHICS

8.1 Disposition of Patients and Treatment Discontinuation

The following will be summarized by study population (i.e., NHL subtype) for all patients who provided an informed consent for study participation:

- Number (%) of patients enrolled (defined as having completed the Informed Consent eCRF page)
- Number (%) of patients screened
- Number (%) of screen failures including the reasons for being screen failures
- Number (%) of patients treated (as per IRT information)
- Number (%) of patients who discontinued in Cycle 1 or Cycle 2 (considering all discontinuations during the Cycles including those at the end of Cycle 2, i.e., C2D28), including the reason for discontinuation
- Number of patients who discontinued before completing Cycle 2 including the reason for discontinuation
- Number of patients completing Cycle 2
- Number of patients completing the first 2 Cycles without proceeding to Cycle 3 (i.e., PD or SD at the end of Cycle 2), including the reason for discontinuation
- Number of patients who completed Cycle 2 and entered Cycle 3 (i.e., patients who reached PR, or CR by the end of Cycle 2)
- Number of patients who discontinued in Cycle 3 (considering all discontinuations that happened in Cycle 3 including those at the end of Cycle 3, i.e., C3D28), including the reason for discontinuation
- Number of patients who discontinued in Cycle 1 or 2 or 3 (considering all discontinuations that happened during Cycle 1, 2, 3 including those at the end of Cycle 3, i.e., C3D28), including the reason for discontinuation
- Number of patients who entered the maintenance treatment phase (i.e., treatment after Cycle 3)
- Number of patients who discontinued during the maintenance treatment phase including the reason for discontinuation
-
- Number of patients still on treatment (i.e., ongoing at data cut-off; the information will be derived from entries in the IRT system)
- Number (%) of patients screened, and number (%) of screen failures including the reason for screen failure.

- Number (%) of patients screened, and number (%) of screen failures by center.

These summaries will be presented for the population of screened patients. The disposition summary will additionally be presented for all patients enrolled, including screening failures.

A listing will be provided indicating in which study stage of the trial individual patients were recruited (the listing will be generated based on information in the IRT system).

8.2 Protocol Violations and Deviations

Protocol violations and deviations will be defined in the document "Handling of Protocol Non-Compliances", current version. Protocol non-compliances (PNCs) will be categorized into minor, major or critical. The final decision on a PNC category will be taken based on data listings during data review meetings. Critical and major PNCs will be listed in the CSR and further grouped:

- PNCs related to subjects not satisfying the study entry criteria
- PNCs related to subjects who developed treatment discontinuation criteria during the study but were not withdrawn
- PNCs related to subjects receiving the wrong treatment or incorrect dose
- PNCs related to subjects receiving an excluded concomitant treatment
- Other critical or major PNCs

8.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for the populations specified above.

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics (age [both as continuous variable and as number of patients aged < 65 and aged ≥ 65], gender, race, height, weight at screening, body mass index [BMI])
- History of NHL (time since first diagnosis [months], NHL subtype, current staging)
- Medical history
- Previous NHL therapies (see section 7.3.1)
- Scores and categories on prognostic indices (see section 7.3.2)
- ECOG performance status at screening

- CD16 expression on NK cells
- Cytogenetics (tumor biopsy)
- DNA analysis of FcγR polymorphism (Mucosal cheek swab)
- Previous and concomitant medication

Medical History: Medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA Version 20.1). Incidences of findings in medical history will be summarized by system organ class (SOC) and preferred term

Time since first diagnosis of NHL [months]: Time since first diagnosis will be measured from date of first diagnosis until Screening Visit. If date of diagnosis is incomplete, time since first diagnosis [months] will be calculated based on the latest possible date for date of diagnosis:

- If the day is missing but the month is complete for date of diagnosis, the date will be imputed using day 15 of the month (or the date of screening visit in case this is earlier)
- If the day and month are missing but the year is complete for date of diagnosis, the date will be imputed using June 30 of the year *DNA analysis of FcγR polymorphism (mucosal cheek swab):* The frequency of each genotype will be summarized descriptively in a frequency table.

Prior and Concomitant medication/ therapies: All medications (prior and concomitant) and all concomitant non-drug therapies will be listed. Any prior, concomitant, or procedural medications or therapy given to or taken by the patient within 1 month before the study and up to the first follow-up visit must be recorded in the source document and the eCRF along with the indication and dosage.

Medications will be presented as prior and concomitant medications.

All medications will be coded using the WHO Drug Dictionary (March 2018). Incidences of prior and concomitant medications will be summarized by ATC level 2 and ATC level 4.

If the start date of medication is before the start date of study treatment the medication will be classified as prior medication.

Medications applied after start of study treatment will be considered as concomitant medication. Medications started before start of study treatment but are ongoing or have a stop date after the start of study treatment will be considered twice, as prior and as concomitant medications. If the start/stop dates of medication are partially or completely missing a medication will be assumed to be concomitant if it cannot be definitely shown that the medication was not administered during the treatment or follow-up period. Missing dates will

not be replaced.

Thus, the following approach will be taken for exclusion from concomitant medication because of discontinuation before start of treatment:

- If stop day is missing but month is complete, medication will only be excluded from concomitant medication if stop month is before month of treatment start.
- If stop day and month are missing but year is complete, medication will only be excluded from concomitant medication if stop year is before year of treatment start.
- If stop date is completely missing, medication will not be excluded

Additionally, concomitant medication will be split into the following two subcategories: (1) concomitant medication started before start of study treatment (and continued after start of study treatment) and (2) concomitant medication started after start of study treatment. Summary tables of concomitant medication will also be prepared within these two subcategories.

Anti-cancer Treatments: Starting from the first follow-up visit, only anti-cancer treatments and, in case of an AE, other relevant concomitant medications (according to the discretion of the investigator) should be entered to the concomitant medication eCRF module. If a patient receives anti-cancer treatment other than MOR00208, it is regarded as protocol non-compliance. Introduction of new anti-cancer treatment should result in exclusion of the patient from further study participation.

A medical review of the concomitant medication will be performed by [redacted] Medical Monitor and approved by MorphoSys Clinical Program Leader before the statistical analysis to identify anti-cancer treatments not allowed during study. All anti-cancer treatments not allowed during study will be included in the protocol violation/deviation listing and table.

The effect of anti-cancer treatments on the efficacy endpoints is described in section 7.3.4.

Previous NHL Therapies:

Information should be provided separately on any previous NHL-specific therapies since the time point of the first diagnosis of NHL. The generic or the trade name or chemo–regimen acronym may be recorded. The previous NHL therapies will be reviewed and assessed for previous lines of therapy, number of systemic therapies, type of previous therapy and rituximab-containing regiments (see section 7.3.1).

9. EFFICACY ANALYSES

All efficacy analyses will be provided for the ITT Population. All efficacy analysis will be done using both the central radiology and local (i.e., investigator) assessment. Kaplan-Meier plots will be generated for all time-to-event analyses (i.e., for the Time to Progression, Progression-Free Survival, Duration of Response).

9.1 Primary Efficacy Analysis

The primary efficacy endpoint will be ORR as determined by the Investigator by using revised IWG response criteria for malignant lymphoma [4]. The final ORR for each subtype will be the rate of patients who met the ORR definition at the end of either the second or third cycle or during the follow up period (best response) (i.e the ORR will be derived from the variable "overall best response"). The denominator for calculating the rate will be based upon the total number of patients in the ITT population, thus patients without any post baseline assessment of NHL response will be included as non-responders. Overall ORR, independent of NHL subtype, will also be summarized. Exact (Clopper-Pearson) 95% CIs for ORR for each subtype and over all subtypes will be presented.

In addition, the tumor response categories will be evaluated by visit. The corresponding number of patients in each of the response categories will be summarized in a frequency table by visit. In this summary all patients who had discontinued will be analyzed as missing for all visits after study discontinuation, also accounting for all patients in the ITT population in the denominator.

ORR will be also calculated and respective results provided based on the central review assessment (based on the variable "best overall response").

Sensitivity analysis:

The ORR will be calculated only considering patients who had at least on post-baseline response assessment. The analysis will be done using the local (investigator) assessment, and also based on the central review assessment.

Concordance rate:

The concordance rate in terms of response assessment represents the agreement in the best overall response between the central read and investigator assessment. The concordance rate is the number of patients that are concordant over the total number of patients assessed, and will be calculated across all response categories. A confusion matrix will be generated. The

concordance rate is calculated by adding the diagonal counts and dividing by the total number of patients assessed. Moreover, the agreement (%) of the investigator assessment with the central read in terms of best ORR will be calculated (i.e., the total number of patients with a best response of CR or PR by central review divided with the total number of patients with a best response of CR or PR by investigator assessment multiplied by 100).

Patients without any post-baseline response assessment will be considered as not evaluable (NE) in both the central read and investigator assessment. Patients who have been evaluated by investigator assessment, but not by central review assessment will be excluded from the concordance analysis.

The proportion (%) of patients who had at least one central review among the total number of patients who underwent at least one investigator assessment will be calculated. Moreover, the proportion (%) of the total number of central reviews among the total number of investigator assessments will be derived (i.e., the total number of central reviews across all visits and all patients divided with the total number of investigator response assessments across all visits and all patients multiplied by 100). The analysis will be conducted using the ITT population.

9.2 Secondary Efficacy Analysis

All secondary efficacy analyses will be provided twice, based on the response assessment of the Investigator and based on the central review assessment.

The analysis of ORR as described in section 9.1 will be additionally be stratified by FcγRIIIa and FcγRIIa polymorphism.

FcγR subgroups will comprise the heterozygous population and each different homozygous population, as well as the combined heterozygous plus low affinity homozygous FcγR populations. Subgroups with fewer than five patients will not be analysed.

These stratifications will be done for the overall analysis population as well as by NHL subtype.

The overall stable disease rate will be analyzed analogously to the overall response rate as described in Sect. 9.1.

Time to progression and progression-free survival will be analyzed using Kaplan-Meier methods. Kaplan-Meier tables for progression-free survival and time to progression will contain number of patients, number of patients with an event (non-censored patients), percentage of patients with an event, median time [months], 25% and 75% quantile and 95%-

confidence intervals for median (Brookmeyer and Crowley, 1982).

Moreover, the percentage of patients having an event until 2, 4, 6, and 12 months together with the corresponding 95%-confidence intervals will be retrieved.

In the main analysis of PFS, only patients with radiologically confirmed progression or death within 2 months of the last radiological assessment will be counted as having had a PFS event. A sensitivity analysis will also be done in which patients who were withdrawn from the study because of disease progression will be included as having a PFS event, even in the absence of radiological confirmation of disease progression.

Duration of response and time to response (Investigator) and duration of best overall response and time to response (Central Read) will also be analyzed using Kaplan-Meier estimates for median, 25% and 75% quantile. The analysis of duration of response will be restricted to the subgroup of responders. Moreover, the percentage of patients having an event after 2, 4, 6, and 12 months together with the corresponding 95%-confidence intervals will be retrieved from the Kaplan Meier curve.

The analysis of duration of response and time to response will be presented for all responders overall.

Kaplan-Meier plots for time to progression, progression-free survival, time to response, and duration of response will be provided.

Data on tumour lesion size will be presented with descriptive statistics and individual data listings. This will include the area of indicator lesions at baseline, the area of indicator lesions at nadir, and the difference between those two areas. The data on lesion size will be presented separately for the two central reviewers. The area of indicator lesions will be examined as follows:

1. Analysis across all points in time:

- Absolute values and both absolute and relative changes (from baseline) will be summarized for each visit:
  - Separated by NHL subtype
  - For the group of FL patients + other indolent lymphoma patients
- A graph showing the individual relative changes over time will be generated separately for all NHL subtypes and for both central readers. The best overall response of each individual will be indicated by colour coding.

2. Analysis comparing baseline and nadir:

- The area of indicator lesions will be reported at baseline and at nadir. The absolute value and both the absolute and relative difference between baseline and nadir will be reported (separated by NHL subtype, i.e., DLBCL, FL, MCL, other indolent NHL, and for the group comprising FL patients + other indolent lymphoma patients).
- A "waterfall plot" indicating the best change (%) for indicator lesions will be generated separately for both central readers. Shading of the bars will indicate the NHL subtype. The plot will be produced in the following two versions:
    - Comprising all NHL subtypes (i.e., DLBCL, MCL, FL, and other indolent NHL)
    - Comprising only DLBCL, FL, and other indolent NHL

A listing of total time on study (time from first dose of MOR208 to date of last tumour assessment), composed of time to response and duration of response, will be provided. In addition, time on study will be tabulated as a continuous variable. No censoring will be applied to total time on study.

All analyses will be provided by NHL subtype, the combined groups of FL and other indolent NHL, and overall, if not specified otherwise.

9.3 Subgroup analyses

Both ORR and PFS will be evaluated for the following subgroups:

- ORR and PFS will be presented in subgroups defined by prognostic index scores, dichotomised as high risk and low risk as described in section 7.3.2.
- ORR and PFS will be presented by FcγR subgroups as described above.
- ORR and PFS will also be presented by duration of response (≤ 12 months or > 12 months) to previous treatment.
- ORR and PFS will also be presented by the number of prior therapy lines (as 1, 2, 3, or > 3).
- ORR and PFS will be presented for the category of patients with Follicular lymphoma (FL) or other indolent lymphoma (as one group).

In addition, PFS only will be presented in further subgroups as follows:

- Baseline ECOG status (0–1 vs. 2 or more)
- Age group (<65 vs. ≥65)
- Number of prior therapy lines (as 1, 2, 3, vs >3)

- Baseline NK cells number (<100 NK cells/µl vs ≥ 100 NK cells/µl)
- Baseline NK cells number (<100 NK cells/µl vs. ≥ 100 NK cells/µl): pooled analysis across all NHL subtypes (i.e., DLBCL, FL, MCL, other indolent NHL)
- Baseline NK cells number (<100 NK cells/µl vs. ≥ 100 NK cells/µl) split by DLBCL and FL+iNHL patients (FL+iNHL patients represent one group). Thus, MCL patients will be excluded from the analysis.
- Baseline CD16 expression (< 60,000 ABCs/NK cell) vs. ≥ 60,000 ABCs/NK cell)
- Baseline CD16 expression (< 60,000 ABCs/NK cell) vs. ≥ 60,000 ABCs/NK cell): pooled analysis across all NHL subtypes (i.e., DLBCL, FL, MCL, other indolent NHL)
- Baseline CD16 expression (< 60,000 ABCs/NK cell) vs. ≥ 60,000 ABCs/NK cell): split by DLBCL and FL+iNHL patients (FL+iNHL patients represent one group). Thus, MCL patients will be excluded from the analysis.
- Rituximab refractoriness (Rituximab-refractory vs. not Rituximab-refractory; see definition below)
- Rituximab refractoriness (Rituximab-refractory vs. not Rituximab-refractory; see definition below): pooled analysis across all NHL subtypes (i.e., DLBCL, FL, MCL, other indolent NHL)
- Rituximab refractoriness (Rituximab-refractory vs. not Rituximab-refractory; see definition below): pooled analysis across all NHL subtypes excluding MCL (i.e., DLBCL, FL, other indolent NHL)

Rituximab refractoriness is defined as follows: no response (i.e., CR or PR) at all, or relapse within 6 months after completion of any rituximab-containing treatment regimen.

For the PFS subgroup analyses an estimate of the hazard ratio and a corresponding 95% confidence interval will be calculated using a Cox proportional hazards model with only one covariate in the model.

9.4 Other Efficacy Analyses

The ECOG performance status will be summarized categorically in a frequency table by visit.

10. PHARMCOKINETIC AND PHARMACODYNAMIC ANALYSIS

10.1 Pharmacodynamic Parameters Measured in Blood

Actual values and absolute and percent changes from baseline will be summarized descriptively by visit for the pharmacodynamic parameters B, T, and NK cell populations. Moreover, 95%

confidence intervals will be provided for mean and median changes in summaries of absolute changes from baseline and for median changes in summaries of percentage changes from baseline.

10.2 Pharmacodynamic Parameters Measured in Bone Marrow and Biopsy

At the Screening visit (Baseline), a bone marrow aspirate should be obtained. Results from bone marrow examination done within 4 weeks before screening are acceptable if the patient's disease has been stable since then. In this case only available data will be used and bone marrow examinations at screening for which this data are not available will not be repeated (e.g. for the sole purpose of CD19 expression).

Repeat of marrow aspirates and biopsies should be obtained at Day 28 of Cycle 2. Histological examination should be performed and the infiltration by malignant B-cells should be evaluated. Starting end of Cycle 3 and in the course of the follow up bone marrow examinations should only be repeated if response at last bone marrow examination was not CR.

On screening, CD19 expression of tumor cells in bone marrow will be determined by a central laboratory. In case CD19 expression on tumor cells can be measured in less than 15% of ITT patients the statistical analyses by baseline CD19 expression (as planned in the protocol) will not be performed. Data on baseline CD19 expression will only be listed. Other results from bone marrow aspiration and biopsy will not be available for statistical analysis.

10.3 Pharmacokinetic Analysis

10.3.1 Bioanalytical Assay of Pharmacokinetic Serum Samples.

MOR00208 concentration values (ng/mL) for each serum sample are to be processed using a validated Ligand Binding Assay. A separate bioanalytical phase plan and report will be generated that provide details on samples handling and processing, methods used for sample analysis, statements on quality control/quality assurance (QC/QA) and results of each individual sample analyzed for each patient by the bioanalytical labs.

All pharmacokinetic sample assessments will be performed at Eurofins ADME Bioanalyses, Vergèze, France.

10.3.2 Concentration Data

Pharmacokinetic concentration data will be listed as received from the bioanalytical laboratory and as used to estimate the PK parameters. The PK concentrations will be summarized based

on nominal (scheduled) sampling times. Concentration figures (linear and log y-axis) for each patient will be presented, as well as mean concentrations.

Any concentrations outside allowable windows will be excluded from summary statistics. Allowable windows are:

±15 min for the samples at the end of infusion and 1h after the end of infusion, ± 30 min for the sample 4h after the end of infusion, and ±2 h for the sample 24 h after the end of infusion. In addition, concentrations will be considered outside allowable windows if infusions after the first infusion took place outside a ±1 day window within a 28 day cycle.

Furthermore, PK samples which were analyzed outside the formally validated long-term stability will be flagged and excluded from summary statistics.

For pharmacokinetic parameter estimation, analyte concentrations that are below the limit of quantification (BLQ) will be assigned a value of zero when they precede the first quantifiable sample. The WinNonlin program automatically does this for the predose sample as it disregards any concentrations reported before the first administration of study drug.

All other BLQ samples will be treated as missing data.

When 2 or more BLQ sample values occur consecutively, all remaining concentration values will be set to missing.

No linear interpolation for these missing concentration values will be completed.

10.3.3 Pharmacokinetic Parameters estimated

Individual PK parameters will be estimated for each patient in the PK population as data permits. Pharmacokinetic parameter estimates will be completed using WinNonlin (Pharsight Corporation). Descriptive summaries (mean, SD, %CV, median, minimum, and maximum) of concentrations at each scheduled time-point and the determined or calculated PK parameters will be presented. For patients receiving maintenance treatment after cycle 3, the FU1, FU2 and FU3 visits will be excluded from PK summary statistics, since the concentrations of MOR00208 at the FU1, FU2 and FU3 visits may be influenced by additional MOR00208 doses in maintenance treatment. The categorical variable t_{max} will only report median, minimum and maximum.

The following PK parameters have been initially identified as important for the analysis of PK. Additional PK parameters may be required. The SAP will not be amended for additional PK

parameters unless the PK analysis is significantly altered. If the SAP is not amended, any additional PK parameters will be described in the CSR.

The following PK parameters are to be computed for each patient as data permit on samples obtained.

Parameter	Units	Description and Calculation Method
		Parameters Estimated from the First Dose
C_{pd}	µg/mL	Predose serum concentration observed
C_{max}	µg/mL	Maximum serum concentration observed
C_{last}	µg/mL	Last quantifiable concentration from the First Dose
t_{max}	hr	Time to maximum serum concentration observed
$AUC_{0\text{-}last}$	hr×µg/mL	Area under the concentration curve from dose time zero (0) to the time the last quantifiable concentration is observed.
		Parameters Estimated from the Last Dose
λ_Z	1/hr	Apparent terminal rate constant calculated from the regression analysis slope of the log-transformed concentrations included in the terminal phase of the concentration-time curve from the last dose
$t_{½}$	hr	Apparent terminal half-life calculated as ln(2)/ λ_Z

The parameter estimates dependent upon the regression analysis of the terminal phase (λ_Z, $t_{½}$,) will only be reported for those patients where a sufficient and meaningful number of serum concentration values are available. All possible values will be calculated and listed with a flag to indicate inclusion in the summary. Only those values that pass the following criteria will be included in the summaries:

All regression analyses must contain a minimum of 3 concentrations and characterize a descending concentration. The estimate of λ_Z from the regression analysis must have a correlation coefficient $R^2 > 0.80$ to be accepted. If these conditions fail then λ_Z and $t_{½}$, will be listed but not reported in the summary table.

The parameters λ_Z and $t_{½}$ will not be calculated for patients receiving maintenance treatment after cycle 3 if they receive any dose after the FU1 visit, since the concentrations of MOR00208 at the FU2 and FU3 visits may be influenced by additional MOR00208 doses in maintenance treatment and thus not suited to estimate these parameters. However, if patients receive maintenance treatment after cycle 3 but have blood samples taken at the FU1, FU2, and FU3 visits with no doses administered between them, then those samples may be used for estimating these parameters.

11. SAFETY AND TOLERABILITY ANALYSES

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each patient:

- Adverse Events
- Clinical Laboratory Investigations (Blood Chemistry, Hematology, Coagulation, Urinalysis, anti-MOR00208 antibodies)
- Vital Signs (Blood Pressure, Heart Rate, Respiratory Rate, Body Temperature)
- Electrocardiogram (ECG) Investigations
- Physical Examination
- Measurements of exposure

11.1 Adverse Events

The primary safety endpoint is the incidence and severity of adverse events (AEs). This endpoint will be determined based on the Safety Population. If not specified otherwise, the adverse events summary and overall table will be displayed overall, by each NHL subtype, and for the combined group of FL and other indolent NHL.

All adverse events (AEs) and serious adverse events (SAEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1.

Treatment emergent AEs are defined as AEs occurring or worsening after the start (date and time) of the first study treatment and up to 30 days after the last study treatment including all treatment cycles (treatment emergent period). However, adverse events occurring or worsening later than 30 days after the last treatment are defined as treatment emergent if these are considered to be related to the study drug.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen

during the treatment emergent period (worst case approach). Missing dates and times will not be replaced.

Thus, the following approach will be taken:

- If the start time of an AE is missing but the start date is complete, an AE will only be excluded from treatment emergent AEs if start day is before day of first treatment or start day is after end day of treatment emergent period.
- If start time and day are missing but the start month is complete, an AE will only be excluded from treatment emergent AEs if start month is before month of first treatment or start month is after end month of treatment emergent period or if stop date/time is before start of first treatment.
- If start day and months are missing but the start year is complete, an AE will only be excluded from treatment emergent AEs if start year is before year of first treatment or if start year is after end year of treatment emergent period or if stop date/time is before start of first treatment.
- If start date is completely missing, an AE will not be excluded from treatment-emergent AEs unless the stop date/time is before start of first treatment.

Time from first treatment to onset of AE [days] will be calculated for complete dates only and will be included in listings.

An AE summary table will be presented showing the incidence and frequency of any

- Treatment-emergent AEs (TEAEs)
- Serious Adverse Events (SAEs)
- Serious Adverse Events (SAEs) related to MOR00208
- MOR00208-related TEAEs
- MOR00208-related TEAEs by toxicity (according to NCI-CTC toxicity criteria)
- MOR00208-related TEAEs by severity
- Infusion related TEAEs
- TEAEs leading to any action on MOR00208
- TEAEs leading to discontinuation of MOR00208
- TEAEs leading to death

The incidence refers to the number and percentage of patient with at least one TEAE of the specified type and the frequency to the number of AEs.

The analyses by toxicity will be based on the NCI-CTC grade (per National Cancer Institute Common Toxicity Criteria, version 4.0). If the NCI-CTC grade is not available, this will be analyzed as “Missing”.

Summaries of incidence rates (number and percentage of patients) and frequencies (number of AEs) of individual TEAEs by MedDRA System Organ Class (SOC) and Preferred Term will be prepared overall and by NHL subtype. Such summaries will be displayed for all

- TEAEs
- TEAEs by toxicity according NCT-CTC
- TEAEs by severity
- TEAEs suspected to be related to MOR00208
- TEAEs leading to discontinuation of MOR00208
- Infusion related TEAEs
- Cytokine release syndromes
- Treatment-Emergent Serious Adverse Events
- TEAEs suspected to be related to MOR00208
- Serious Adverse Events suspected to be related to MOR00208 (Serious Adverse Reactions)
- TEAEs of toxicity grade 3 or higher
- MOR00208-related TEAEs of toxicity grade 3 or higher
- TEAEs of special interest (ie, infusion-related reactions of grade 3 or higher, cytokine release syndrome, allergic reaction to MOR00208 of grade 3 or higher and overdoses)
- Haematological Treatment Emergent Adverse Events
- Overdoses (defined as exceeding planned dose by more than 10%)
- Death cases (irrespective of death due to progressive disease or other reason)
- Pre-treatment AEs (based on all Screened Patients instead of the Safety Population)

A summary of all TEAEs will also be provided by FcγR polymorphisms.

In these summaries each patient will be counted only once within each preferred term to calculate the incidences.

AE listings of all adverse events with the following details will be provided for

- AEs – details
- AEs – action taken
- AEs – coding details

In the AE listings, AEs that started prior to the administration of any study drug will be flagged as pre-treatment AEs. AEs that start 30 days after the last study treatment including all treatment cycles will be flagged as post-treatment AEs.

Special AE summary listing displaying details of the event(s) captured on the eCRF in a compact format will be provided for

- AEs leading to death
- AEs leading to discontinuation of MOR00208
- AEs of toxicity grade 3 or higher
- Infusion related TEAEs
- Serious Adverse Events
- Death cases (irrespective of death due to disease progression or other reason)

Serious adverse event reconciliation will be performed as detailed in the SAE reconciliation plan.

The number and percent of patients with at least one pretreatment AE will be summarized by NHL subtype and by system organ class and preferred term.

11.2 Clinical Laboratory Evaluations

Safety monitoring for all patients enrolled in the study will include among others laboratory assessments: hematology, blood chemistry, and urinalysis, coagulation, and anti-MOR00208 antibodies. Hematology, serum chemistry, immunoglobulins, coagulation, urinalysis will be analyzed by the respective local laboratories of each involved site. Immunogenicity of MOR208 will be estimated by a central laboratory (please refer to section 11.7 for details).

The analysis of laboratory parameters will be presented separated into blood parameters (hematology, serum chemistry, immunoglobulin, coagulation) and urine parameters

(urinalysis). All data will be listed.

The blood parameters will be transformed to SI values based on SI units to make laboratory parameters comparable between different local laboratories. The relevant reference ranges supplied by each laboratory will also be transformed to SI reference ranges for each laboratory. The SI reference ranges will be presented in the listings.

Descriptive summaries of absolute values and changes from baseline will be presented for all blood parameters.

Each abnormal value will be flagged to show whether it is a value below or above the reference range. For the assessment of laboratory variables, 5 categories will be used that take into account the investigator's assessment of clinical relevance: 'clin. sign., above', 'non-clin. sign., above', 'within', 'non clin. sign., below', 'clin. sign., below'.

The assessment of laboratory variables will be tabulated by time point for each clinical laboratory analyte (frequency tables).

Additionally, for each laboratory parameter, shifts in assessments from baseline to all post administration time points will be presented.

If NCI-CTC grades are available for a clinical laboratory analyte, these will be derived according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) and used to present additional frequency and shift tables based on NCI-CTC grades.

The investigator's assessment of categorical urinalysis variables ('normal', 'abnormal, not clin. sign.', 'abnormal clin.sign.') will be tabulated by time point for each urine parameter (frequency tables).

Additionally, for each of these urine parameter shifts in assessments from baseline to all post-administration time points will be presented.

Laboratory values that are outside the reference range will also be flagged in the data listings, along with corresponding reference ranges.

Results of urine microscopy (if available), results of the pregnancy test and screening serology results will only be included in listings.

11.3 Vital Signs and Body Weight

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs (Systolic Blood Pressure, Diastolic Blood Pressure, Body Temperature, Heart Rate and

Respiratory Rate) and Body Weight and BMI. These summaries will be presented for all time points.

Each abnormal value will be flagged to show whether it is a value below or above the normal limit. The normal limits are detailed in the appendix of the study protocol (Section 17.2 of the study protocol).

11.4 Electrocardiograms

The summary ECG assessment (categories: <normal; abnormal clinically significant; abnormal not clinically significant>) will be tabulated by visit.

Each abnormal PR, QRS, and RR interval value will be flagged to show whether it is a value below or above the normal limit. The normal limits are detailed in the appendix of the study protocol (Section 17.2 of the study protocol).

Descriptive summaries of actual values and changes from baseline will be presented by visit for ECG measures of RR interval, PR interval, QRS interval, QT interval, QTc interval (both correction methods), and HR (Heart rate).

The Bazett's Correction (QTc_b) and Fridericia's Correction (QTc_f) for the QTc interval will be derived as follows:

Bazett's Correction (QTc_b) $$QTc_b = \frac{QT_{msec}}{\sqrt{RR}}$$

Fridericia's Correction (QTc_f) $$QTc_f = \frac{QT_{msec}}{\sqrt[3]{RR}}$$

where: Relative Rate: RR = 60 / HR

HR = Heart Rate obtained from the ECG.

Also, the number and percent of patients with QTc values (for both corrections) above the normal limit (451-480 ms, 481-500 ms, or > 500 ms) and the number and percent of patients who experienced a change > 30 ms or a change > 60 ms from baseline will be presented by visit.

11.5 Physical Examination

Baseline physical examination will be summarized by body system. New and worsening

abnormal physical examination findings during the study will be entered as AEs and analyzed within the AE tables

11.6 Measurement of Exposure

Variables which will be calculated to measure exposure to MOR00208 are described in section 7.3.5. All variables calculated on a per-patient basis for all cycles will be summarized descriptively. The number of cycles with all infusions completed will be presented as a continuous variable and also in categories of number of patients completing 1, 2, or 3 cycles, and the number of patients going into maintenance treatment.

11.7 Immunogenicity Analysis

Immunogenicity variables defined in section 7.3.1 will be summarized descriptively. Rates will be calculated with respect to all patients in the analysis group who have at least one post-baseline anti-MOR00208 antibody assessment. Results of semiquantitative antibody assessment will be tabulated.

12. CHANGES FROM PLANNED ANALYSIS

The PK population was originally defined in the protocol as consisting of all patients who have sufficient pharmacokinetic data to characterize the time course of MOR00208 in serum for the first study drug administration. This is changed in the SAP to include all patients who have at least one quantifiable serum MOR00208 concentration (see section 6).

The protocol did not specify ORR as a result of central read as an endpoint, but this has now been added to the secondary endpoints of the study.

The protocol specified that “Evaluation of AEs and ORR stratified by baseline CD19 expression on malignant lymphoma cells” was one of the secondary endpoints. This is no longer considered an endpoint as it has not been possible to measure CD19 expression in sufficient cases for such an analysis to be meaningful.

13. REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

13.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a CSR.
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white, unless color figures have been identified as useful for discriminating presentation in the figure. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).
- All titles will be centered on a page.
- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as DDMMMYYYY (e.g., 29AUG2001) format. A four-digit year is preferred for all dates.

- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- Time durations will be reported in HH:MM:SS notation. The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figure, and data listings will have the name of the program, location and a date stamp on the bottom of each output.

13.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "Population: <name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) AllPatients, (b) Safety Population, (c) Evaluable Population, (d) Efficacy Evaluable Population and (e) Pharmacokinetic Population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for continuous variables will include: N, mean, standard deviation, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 5%, 95% intervals, coefficient of variation (CV) or %CV) may be used as appropriate. Median and mean will be presented with one more digit than minimum and maximum, standard deviation will be presented with two more digits.
- All percentages are rounded and reported to a single decimal point (xx.x%).
- Population summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). All p-values reported on default

output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.001 should be reported as <0.001 not 0.000.

14. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999.
3. RSS. (1993) The Royal Statistical Society: Code of Conduct, August 1993.
4. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-586
5. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329:987-994
6. Hoster E, Dreyling M, Klapper W et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008; 111(2):558-565
7. Solal-Céligny P, Roy P, Colombat P et al. Follicular Lymphoma International Prognostic Index. Blood 2004; 104(5):1258-1265