CLINICAL STUDY PROTOCOL
AMENDMENT NO. 5

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

Brief Description of Study	Open-label study to evaluate the preliminary efficacy and safety of MOR00208 in adult patients with refractory or relapsed non-Hodgkin's lymphoma (NHL)
Study Type:	Phase IIa
Sponsor:	MorphoSys AG
Sponsor's Address:	Semmelweisstr. 7 D-82152 Planegg GERMANY
Study Protocol Number:	MOR208C201
IND No.:	114,856
EudraCT No.:	2012-002659-41
Date of Protocol:	Final v2.0, 31 Aug 2012
Amendment No. 1:	Final v3.0, 07 Jan 2013
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Amendment No. 3:	Final v5.0, 15 Apr 2014
Amendment No. 4:	Final v6.0, 19 Sep 2017
Amendment No. 5:	Final v7.0, 26 May 2020

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Amendment No. 5: Final v7.0, 26 May 2020

Protocol Amendment No. 4: Prepared and Approved/Authorized By:

Signature:

Signature:

Coordinating Investigator's Signature

I have read the entire clinical study protocol. I agree that this protocol version contains all the information required to conduct this study.

Investigator:

Signature: ---------- **Date:** ----------
(DD, MMM, YYYY)

Printed Name: ----------

Address: ----------

Signature of Principal Investigator, Coinvestigator, or Subinvestigator

I have read the entire clinical study protocol. I agree that this protocol version contains all the information required to conduct this study. I agree to conduct the study as outlined in the study protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and the principles which have their origin in the Declaration of Helsinki, copies of both documents have been given to me by the sponsor, I will also ensure that coinvestigator(s) and other relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines and the Declaration of Helsinki to enable them to work in accordance with the provisions of these documents.

Signature: ---------- **Date:** ----------
(DD, MMM, YYYY)

Printed Name: ----------

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1 PROTOCOL SYNOPSIS

Title of Study	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
Investigational Drug	MOR00208 (an Fc-engineered humanized monoclonal antibody targeting the B-cell surface antigen CD19)
Protocol Number	MOR208C201
IND Number	114,856
EudraCT Number	2012-002659-41
Sponsor and CRO	**Sponsor:** MorphoSys AG Semmelweisstr. 7 D-82152 Planegg Germany **Clinical Research Organization (CRO):** [redacted]
Study Phase	Phase IIa
Background	Introduction of rituximab into first-line non-Hodgkin's lymphoma (NHL) regimens in recent years has improved cure rate in several NHL subtypes by at least 10%. Despite extensive use of rituximab across a range of NHL subtypes in combination with chemotherapy, as a single agent, or as maintenance therapy, there is still a high unmet medical need for patients with refractory or relapsed NHL (eg, mantle cell lymphoma [MCL], diffuse large B-cell lymphoma [DLBCL] and follicular lymphoma [FL]). The B-lymphocyte lineage specific surface antigen CD19 is the earliest and broadest of the selective B-cell markers, which is highly expressed in most patients with B-cell NHL. Because of this expression pattern, an anti-CD19 antibody may have clinical utility as a new therapeutic approach to NHL treatment. MOR00208 is an Fc-engineered humanized monoclonal antibody with significantly enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADPC) and direct cytotoxic effects (apoptosis). Preliminary data from a currently ongoing Phase I study in adult patients with relapsed/refractory CLL/SLL demonstrated that 8 weekly administrations of MOR00208 are safe and well-tolerated, with a recommended biological dose of 12 mg/kg. The most common study drug-related adverse events (AEs) reported so far are infusion-related reactions, leukopenia/neutropenia, and thrombocytopenia.

Study Purpose/Rationale	Non-Hodgkin's lymphoma accounts for approximately 5% of all new cancer cases. Non-Hodgkin's lymphoma is a heterogeneous group of lymphoproliferative malignancies which are in 90% of cases derived of B cells. Diffuse large B-cell lymphoma, an aggressive B-cell lymphoma, accounts for one-third of NHL. After standard treatment with the anti-CD20 antibody rituximab in combination with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristin, prednisone) still 30% to 40% of DLBCL patients are relapsed or refractory, requiring further treatment. Mantle cell lymphoma, like DLBCL, is an aggressive form of NHL but is far less responsive to treatment than DLBCL. Follicular lymphoma, an indolent B-cell lymphoma, accounts for 22% of NHL. Even if the overall response rate is high, standard therapy is rarely curative and nearly all patients will relapse. There is no standard-of-care treatment available for patients with advanced FL. The purpose of this study is to evaluate the preliminary efficacy and safety of MOR00208 in adult patients with relapsed or refractory NHL.
Study Objectives (Key Primary and Secondary)	**PRIMARY OBJECTIVE:** 1. 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. **SECONDARY OBJECTIVES:** 1. To evaluate the duration of response 2. To establish safety and tolerability of MOR00208 3. To assess the potential immunogenicity of MOR00208 4. To evaluate the pharmacokinetics and pharmacodynamics of MOR00208 in patients with relapsed or refractory NHL
Study Endpoints (Key Primary and Secondary)	**PRIMARY ENDPOINT:** 1. Overall response rate (ORR) (complete remission [CR] + partial remission [PR]), assessed as per the 2007 International Working Group (IWG) response criteria (see Section 17.4) **SECONDARY ENDPOINTS:** 1. Stable disease (SD), duration of response (DoR), time to progression (TTP), and progression-free survival (PFS) 2. Incidence and severity of AEs 3. 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 4. Pharmacokinetics (apparent maximum serum concentration [C_{max}], time to maximum serum concentration [t_{max}], apparent trough serum concentration before dosing [C_{pd}], area under the serum concentration versus time curve from time 0 to the time t of the last quantifiable concentration [AUC_{0-t}], area under the serum concentration versus time curve from time 0 to infinity (extrapolated) [$AUC_{0-\infty}$], apparent

	terminal rate constant [λ_Z], apparent terminal half-life [$t_{½}$], total body clearance [CL], volume of distribution during the terminal phase [Vz]), parameters determined using non-compartmental data analysis) 5. Absolute and percentage change from baseline in measurements of B, T- and natural killer (NK) cell populations 6. Evaluation of AEs and ORR stratified by baseline CD19 expression on malignant lymphoma cells 7. Evaluation of AEs and ORR stratified by (FcγR)IIIa and FcγRIIa polymorphism
Design and Methodology	This is a Phase IIa open-label, multicenter safety and efficacy study that will enrol approximately 40 to 120 adult patients with refractory or relapsed NHL who have received at least one prior therapy. The study will enrol different NHL subtypes: FL, DLBCL, MCL and other indolent NHL (marginal zone lymphoma [MZL], mucosa-associated lymphoid tissue lymphoma [MALT], etc). Efficacy will be determined with the ORR, which will be evaluated by using the revised IWG criteria (Cheson response criteria) and will be defined as the proportion of patients with CR and PR (CR+PR). The study will employ a two-stage design and may be stopped for futility (lack of efficacy) for any NHL subtype, thus potentially reducing the number of patients exposed to ineffective treatment. **Stage 1 –** At least ten patients per NHL subtype (in total a minimum of 40 patients) will be enrolled to receive MOR00208 12 mg/kg IV weekly infusions for 8 weeks. After 8 and 12 weeks of dosing (for patients having had at least SD at Week 8), patients will be evaluated to determine if it is futile to continue testing patients of a subtype. If in stage 1 fewer than 2 patients per NHL subtype have a best response of PR or better, then the subtype cohort will be stopped for futility. In other words, no more patients of that subtype will be enrolled in the next stage. If at least 2 patients per NHL subtype have a response of PR or better, then this cohort will progress to Stage 2. Regardless of futility decisions, any patients with a response of at least SD will qualify for further 4 weeks of dosing. **Stage 2** – An additional 20 patients will be enrolled for each NHL subtype cohort demonstrating a response of PR or better in 2 patients in Stage 1. After 8 weeks, the ORR per cohort will be evaluated. All patients with a response of at least SD will qualify for further 4 weeks of dosing. **Maintenance treatment** – Patients with an ongoing response of at least PR at the end of Cycle 3 (regardless of Stage 1 or 2) may receive further study drug until progression.
Population	Adult patients with refractory or relapsed B-cell NHL who have received at least 1 completed cycle of combination therapy with rituximab + chemotherapy OR at least 4 weekly administrations of rituximab as monotherapy. 1) FL 2) DLBCL 3) MCL 4) Other indolent NHL

Key Inclusion / Exclusion Criteria	**INCLUSION CRITERIA:** 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: a. FL b. Other indolent NHL (eg, MZL/MALT) c. DLBCL d. MCL NOTE: For transformed lymphomas, the subtype at screening (not at initial diagnosis) is relevant for the assignment to the respective subtype. 3. Patients' NHL must have progressed after at least one 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 haematological 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 had a positive [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scan at baseline (Cheson response criteria). 9. Patients 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: a. Absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L b. Platelet count ≥ 75 × 10^9/L without previous transfusion within 10 days of first study drug administration c. Haemoglobin ≥ 8.0 g/dL (may have been transfused) d. Serum creatinine < 2.0 x upper limit of normal (ULN) e. Total bilirubin ≤ 2.0 × ULN f. 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. **EXCLUSION CRITERIA:** 1. Previous treatment with cytotoxic chemotherapy, immunotherapy, radiotherapy or other lymphoma-specific therapy within 14 days before the screening visit or patient has not recovered from side effects of previous lymphoma-specific therapy. 2. Treatment with a systemic investigational agent within 28 days before the screening visit. 3. Previous treatment with an anti-CD19 antibody or fragments. 4. Previous allogenic stem cell transplantation. 5. Known or suspected hypersensitivity to the excipients contained in the study drug formulation. 6. Clinically significant cardiovascular disease or cardiac insufficiency (New York Heart Association [NYHA] classes III-IV), cardiomyopathy, preexisting clinically significant arrhythmia, acute myocardial infarction within 3 months of enrolment, angina pectoris within 3 months of enrolment. 7. Patients with positive hepatitis serology (see also Section 9.5.2). Hepatitis B (HBV): Patients with positive serology for HBV, defined as positivity for hepatitis B surface antigen (HBsAg) or total anti-hepatitis B core antibody (anti-HBc). Patients positive for anti-HBc may be included if HBV DNA is not detectable. Hepatitis C (HCV): Patients with positive HCV serology (defined as positive for anti-HCV antibody [anti-HCV]) unless HCV-ribonucleic acid (RNA) is confirmed negative. 8. History of human immunodeficiency virus (HIV) infection. 9. Any active systemic infection (viral, fungal, or bacterial) requiring active parenteral antibiotic therapy within 4 weeks of study drug administration. 10. Current treatment with immunosuppressive agents other than prescribed corticosteroids (not more than 10-mg prednisone equivalent). 11. Major surgery or radiation therapy within 4 weeks before first study drug administration. 12. Systemic diseases (cardiovascular, renal, hepatic, etc.) that would prevent study treatment in the investigator's opinion. 13. History or clinical evidence of central nervous system (CNS), meningeal, or epidural disease, including brain metastasis. 14. Active treatment/chemotherapy for another primary malignancy

	within the past 5 years (except for ductal breast cancer in situ, non-melanoma skin cancer, prostate cancer not requiring treatment, and cervical carcinoma in situ). 15. Pregnancy or breastfeeding in women and women of childbearing potential not using an acceptable method of birth control. 16. History of noncompliance to medical regimens or patients who are considered potentially unreliable and/or not cooperative.
Sample Size, Planned Total Number of Study Sites and Locations	The study will enrol patients in two stages. Enrolment to the stages will be consecutive. The primary objective of the study is to assess the antitumor activity as measured by ORR after two cycles of treatment with MOR00208 (two 28-day cycles). 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 enrol between 40 to 120 patients, dependent upon patient response in each subtype in Stage 1. **Stage 1:** Approximately 40 patients, a similar number of patients will be enrolled per NHL subtype: • FL: at least 10 patients • DLBCL: at least 10 patients • MCL: at least 10 patients • other indolent NHL:at least 10 patients Observing less than 2 responses (at least PR) in stage 1 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 2 or more responders, an additional approximately 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 approximately 80 additional patients, a similar number of patients will be enrolled per "responding" NHL subtype. Some of the cohorts may have been stopped for futility after Stage 1: • FL: at least 20 patients • DLBCL: at least 20 patients • MCL: at least 20 patients • other indolent NHL:at least 20 patients

	Approximately 25 to 30 centres in the United States of America and Europe are planned.
Investigational Drug(s) (Name, Description)	MOR00208
Dose, Route of Administration, Treatment Regimen	MOR00208 dose: 12 mg/kg Patients will receive up to 2 cycles for a total of 8 infusions: each 28-day cycle will consist of a MOR00208 infusion on Day 1, Day 8, Day 15 and Day 22 of the cycle. Premedication will be administered for the first 3 infusions. Patients with a response of at least SD on Day 28 of Cycle 2 will qualify for a further cycle (Cycle 3) of MOR00208 with infusions on Day 1, Day 8, Day 15 and Day 22 of that cycle. Patients who have an ongoing response of at least PR may be eligible for continued treatment every two weeks or monthly, until disease progression.
Supply, Preparation and Administration	MOR00208 DP is a lyophilisate supplied in single-use 20-mL glass vials. Each vial contains 200 mg of MOR00208 for reconstitution with 5 mL water for injection (WFI). Reconstitution yields 40 mg/mL MOR00208 in 25 mM sodium citrate, 200 mM trehalose and 0.02% (w/v) polysorbate 20 at pH 6.0. Each product vial is intended to deliver 5 mL of drug solution or 200 mg of MOR00208. MOR00208 will be diluted into a 250 mL infusion bag containing 0.9% sodium chloride for injection. MOR00208 will be administered via IV infusion using an in-line filter in all cases.
Visit Schedule and Assessments	Refer to Schedule of Assessments in Section 10.
Efficacy Assessments	Response will be determined using the revised IWG response criteria for malignant lymphoma (Cheson response criteria), evaluated in terms of ORR (CR + PR), stable disease (SD), DoR, TTP, and PFS. Response rates will also be determined using CT scan. Pharmacodynamics will be assessed by measuring B-, T- and NK cell populations; for patients with a CR, bone marrow histology will be performed.
Special Safety Assessments	Physical examination, vital signs, electrocardiograms (ECGs), haematological and biochemical tests and number and severity of AEs. Laboratory and AE toxicities will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
Pharmacokinetics	C_{max}, t_{max}, C_{pd} (trough level before dosing), AUC_{0-t}, $AUC_{0-\infty}$, λ_Z, $t_{½}$, CL, and Vz; parameters determined using non-compartmental data analysis
Biomarker Assessments	Expression levels of CD19 on B cells; FcγRIIa and FcγRIIIa genotyping; CD16 expression on NK cells; B-, T- and NK cell counts, ADCC capacity
Immunogenicity Assessments	1. Number of patients with confirmed positive anti-MOR00208 antibodies 2. MOR00208 antibody titer of confirmed positive samples

Statistical Methods and Data Analysis	The primary efficacy endpoint will be ORR as determined by using revised IWG response criteria for malignant lymphoma. The final ORR for each subtype will be 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 (best response). Patients with PD after Day 28 of the second cycle will be discontinued and classified as nonresponders. Those with SD after Day 28 of the second cycle will be allowed to continue treatment into a third cycle.

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2.1 Overall Table of Contents

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Not applicable

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cell-mediated phagocytosis
ADR	Adverse drug reaction
AE	Adverse event
ALC	Absolute lymphocyte count
ALL	Acute lymphoblastic leukaemia
ALT	Alanine transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the serum concentration versus time curve from time 0 to the time t of the last quantifiable concentration
$AUC_{0-\infty}$	Area under the serum concentration versus time curve from time 0 to infinity (extrapolated)
β-HCG	Beta-human chorionic gonadotropin
bpm	Beats per minute (heart rate)
CBC	Complete blood count
CD19	Cluster of differentiation 19
CL	Total body clearance
CLL	Chronic lymphocytic leukaemia
C_{max}	Apparent maximum serum concentration
C_{pd}	Apparent trough serum concentration before dosing
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CR	Complete remission
CRi	Incomplete count recovery
CRO	Clinical Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediamine tetraacetic acid
EMA	European Medicines Agency
EOS	End of Study
FcγR	Fc gamma receptors
FDA	Food and Drug Administration
FDG-PET	[^{18}F]fluorodeoxyglucose-positron emission tomography
FL	Follicular lymphoma
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
anti-HBc	Anti-hepatitis B core antibody
HBsAb	Hepatitis B surface antibody

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCL	Hairy cell leukaemia
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional/Independent Review Board
IV	Intravenous
IWG	International Working Group
IWRS	Interactive web response system
λ_z	Apparent terminal rate constant
LLQ	Lower limit of quantification
mAb	Monoclonal antibody
MALT	Mucosa-associated lymphoid tissue lymphoma
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NYHA	New York Heart Association
ORR	Overall response rate (complete remission + partial remission)
PEI	Paul-Ehrlich-Institut
PET	Positron emission tomography
PFS	Progression-free survival
PML	Progressive multifocal leukoencephalopathy
po	Per oral
POC	Proof-of-concept
PR	Partial remission
PR (ECG)	PR interval
PT	Prothrombin time
PVC	Polyvinyl chloride
QRS	QRS interval
QT	QT interval
QTc	QT interval corrected
RBC	Red blood cell
REAL/WHO	Revised European American Lymphoma/World Health Organization
RNA	Ribonucleic acid
rpm	Respirations per minute (respiration rate)
RR (ECG)	RR interval
SAE	Serious adverse event
SCID	Severe combined immunodeficiency
SD	Stable disease
SLL	Small lymphocytic lymphoma

SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Apparent terminal half-life
t_{max}	Time to maximum serum concentration
TNF-α	Tumour necrosis factor alpha
TTP	Time to progression
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
Vz	Volume of distribution during the terminal phase
WBC	White blood cell
WFI	Water for Injection
WHO-DDE	World Health Organization–Drug Dictionary Enhanced
WOCBP	Woman of childbearing potential

4 BACKGROUND

4.1 Overview of Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) accounts for approximately 5% of all new cancer cases. Non-Hodgkin's lymphoma is a heterogeneous group of lymphoproliferative malignancies and is in 90% of cases derived of B cells.

Diffuse large B-cell lymphoma (DLBCL), an aggressive B-cell lymphoma, accounts for one-third of NHL, and after standard treatment with the anti-CD20 antibody rituximab with the chemotherapy CHOP (cyclophosphamide, doxorubicin, vincristin and prednisone) 30% to 40% of patients are still relapsed or refractory, requiring further treatment. Mantle cell lymphoma (MCL), like DLBCL, is an aggressive NHL but is far less responsive to treatment than DLBCL.

Follicular lymphoma (FL), an indolent B-cell lymphoma, accounts for 22% of NHL. Even if the overall response rate is high, standard therapy is rarely curative and nearly all patients will relapse. There is no standard-of-care treatment available for patients with advanced FL.

Therapy with a monoclonal antibody would have the potential to improve response rates and overall survival without increasing haematologic toxicity.

This is supported by initial data from other anti-CD19 monoclonal antibodies (MDX-1342 and SAR3419) and the bispecific antibody blinatumomab (Viardot, 2011), MDX-1342 a glycoengineered fully human anti-CD19 Ab (Camacho, 2009), SAR3419 a humanized IgG1 conjugated with DM4 (a cytotoxic maytansinoid derivate) (Coiffier, 2011) published preliminary data from their Phase I studies indicating that a CD19 is a valid target and that an anti-CD19 therapy has potential clinical benefit. No significant myelosuppression was reported from these trials.

4.2 Overview of MOR00208

MOR00208 (synonym: XmAb®5574), an Fc engineered mAb that binds to the human B-cell surface antigen CD19, is being developed for the treatment of CD19+ lymphoid malignancies. The engineered antibody possesses variable modes of significantly increased tumor cytotoxicity relative to the parent, nonengineered, murine 4G7 anti-CD19 antibody. The increase in binding of MOR00208 Fc to Fc gamma receptors (FcγR) due to engineered mutations significantly enhances in vitro ADCC, ADCP, and direct cytotoxic effects (apoptosis) on tumor relative to the unmodified antibody. MOR00208 has not been shown to mediate complement-dependent cytotoxicity.

In preclinical studies, MOR00208 has demonstrated to significantly enhance in vitro ADCC, ADCP, and direct cytotoxic effects (apoptosis) on CD19+ tumor cell line spanning a broad range of human lymphomas and leukaemias (Burkitt's lymphoma, chronic lymphocytic leukaemia [CLL], hairy cell leukaemia [HCL], CD19+ chronic myeloid leukaemia [CML], DLBCL, and acute lymphoblastic leukaemia [ALL]) expressing different levels of CD19 antigen (15000 to 105000 molecules/cell). Similar effects were also noted on freshly isolated patient CLL or ALL cells and are also expected to translate to primary NHL cells since the expression range reported for ALL and CLL B cells covers the respective range observed for

NHL B cells (Ginaldi et al., 1998; Olejniczak et al., 2006). In vivo, MOR00208 has also shown a superior efficacy compared with its nonengineered version as demonstrate in xenograft models of human lymphoma inducing a significant reduction of tumor growth and increased survival.

Tissue cross-reactivity studies have shown that the pattern and distribution of MOR00208 binding to cynomolgus monkey tissues closely parallels that of human tissues. Flow cytometry experiments with MOR00208 show binding to human and cynomolgus monkey B cells. However, similar results were not observed with B cells of other common laboratory species (rat, mouse, rabbit and dog). Therefore, the range of pharmacology studies was restricted to human and cynomolgus monkey cell-based in vitro systems, CD19+ human B-cell tumor xenograft models in severe combined immunodeficiency (SCID) mice, and to cynomolgus monkeys in vivo. In cynomolgus monkeys, in vivo B-lymphocyte depletion in peripheral blood, bone marrow, spleen and in inguinal lymph nodes, the anticipated response to MOR00208, was observed. Cynomolgus monkeys were judged to be the only relevant common laboratory species for toxicity studies.

The results of studies evaluating the pharmacokinetics, pharmacodynamics and toxicity of MOR00208 are provided in the Investigator's Brochure (IB). The findings in preclinical toxicology studies were limited to the expected pharmacologic effects of MOR00208 and no unanticipated toxicity was observed. These studies include a nonclinical toxicology study conducted in cynomolgus monkeys to support the use of MOR00208 in human clinical trials. The supporting Good Laboratory Practice (GLP)-compliant, multiple-dose toxicology study involved four administrations of MOR00208 over an 8-week time period. Other than the expected dose-related decreases in B-lymphocyte level and in cellularity of spleen tissues, there were no MOR00208-related changes identified in clinical observations, food consumption, body weight, electrocardiography, ophthalmology, urinalysis, coagulation, serum chemistry, and gross anatomic pathology at doses up to 50 mg/kg. In addition, GLP-compliant tissue cross-reactivity studies were performed on normal tissue panels from human and cynomolgus monkey donors. No specific staining to structures other than the expected mononuclear leukocytes, lymphocytes and haematopoietic precursor cells was observed.

Study XmAb®5574-01, a Phase I study in patients with CLL/SLL, was the first study of XmAb®5574/MOR00208 in humans. The preliminary results of Study XmAb®5574-01 showed an acceptable safety profile as well as preliminary activity. One dose-limiting toxicity (DLT) of Grade 4 neutropenia lasting at least 7 days was observed during Study XmAb®5574-01 in one patient at the maximum-administered dose (12 mg/kg) out of 16 patients treated at this dose level.

Because the major pharmacologic effect of MOR00208 is B-cell depletion, investigators should be vigilant for adverse events (AEs) associated with the clinical use of B-cell depleting anti-CD20 mAbs as similar effects might be observed with MOR00208.

4.2.1 Clinical Experience with MOR00208

A Phase I study of MOR00208 (XmAb®5574-01) in adult patients with relapsed/refractory CLL/SLL was the first study of XmAb®5574/MOR00208 in humans. During the course of this study, 27 patients were treated in dose cohorts from 0.3 mg/kg to 12 mg/kg (n=16) intravenously on a weekly schedule for 8 weeks, with an extra dose administered on Day 4. Patients enroled in the expansion phase of Cohort 6 (12 mg/kg) received an additional

4 monthly doses of MOR00208 after completing the initial 2 cycles of therapy if there was no evidence of disease progression or intolerable drug-related toxicity.

The preliminary antitumor activity of MOR00208 observed in this Phase I study is encouraging and provides support for additional studies. Twenty of 23 patients (87%) with evaluable data in the clinical database had a reduction in their absolute lymphocyte count (ALC; range 2% to 99%), with 17 of 20 (85%) having reductions of >50% from their baseline values. Lymph node size reduction (range 4% to 89%) as assessed by CT scans were observed in 13 of 18 (72%) of patients to date. While the number of patients in this Phase I study is limited to draw definitive conclusions, there appeared to be a dose response relationship with greater reductions in ALCs and nodal size reduction in the higher dose cohorts.

The maximum-tolerated dose (MTD) was not established, since only one DLT occurred. Therefore the selected dose (12 mg/kg) from study XmAb®5574-01 will be used in this clinical trial.

4.2.2 Safety of MOR00208

MOR00208 provides a novel mechanism of action that may add to the care of NHL. Based on the available data from the completed clinical study of MOR00208 (Study XmAb®5574-01), nonclinical studies and experiments, and literature data on CD19, the sponsor is of the opinion that the potential benefit of MOR00208 outweighs the potential risks. It is expected that the potential risks will be adequately controlled by the design of this trial (eg, by the inclusion and exclusion criteria) and by frequent monitoring of potential adverse drug reactions throughout the entire study. Based on the preliminary results of the clinical study of MOR00208 in patients with CLL/SLL, anticipated possible risks associated with administration of MOR00208 include the following:

One DLT of Grade 4 neutropenia (normal absolute neutrophil count [ANC] at baseline) lasting at least 7 days was observed at the maximum-administered dose of 12 mg/kg.

As of 11 May 2012, 5 serious adverse events (SAEs) have been reported in 5 patients; 2 were considered possibly related to the study drug. One related SAE of febrile neutropenia (Grade 3) occurred in the same patient who experienced the DLT. The second related SAE of tumor lysis syndrome (Grade 3) occurred after the first dose of study drug. The other 3 SAEs were assessed as unrelated by the investigator and included rash (Grade 1), pneumococcal pneumonia (Grade 3), and sinusitis/acute bilateral otitis media (Grade 3).

The most frequent AE was infusion-related reaction in trial XmAb®5574-01, which occurred in 12 of 21 (57.1%) patients, despite premedication with antihistamine, acetaminophen and corticosteroids as mandated for the first 3 infusions of MOR00208. All infusion reactions occurred during the patient's first infusion (typically within the first 15 minutes of the start of infusion), as has been described with other B-cell depleting monoclonal antibody therapies in this patient population. Infusion reaction was more frequent in the higher dose cohorts, although infusion reaction did occur in at least one patient in every cohort. The infusion reactions were all Grade 1 or Grade 2 in severity. All patients were able to complete their dose after pausing of the infusion and symptomatic treatment, some with a reduction in the infusion rate.

Leukopenia and neutropenia has been observed in 14% and 24% of patients, respectively, with one patient experiencing Grade 4 neutropenia. Thrombocytopenia has also been reported at a frequency of 14% in patients.

Since a major pharmacologic effect of MOR00208 is B-cell depletion, risks associated with the use of approved anti-CD20 B-cell depleting therapeutics based on their labeling should be considered. These anticipated possible risks include the following: B-cell depletion, absolute lymphocyte reduction, infusion reactions, tumor lysis syndrome, neutropenia/thrombocytopenia, hepatitis B reactivation, progressive multifocal leukoencephalopathy, mucocutaneous reactions and infections.

Anticipated possible risks associated with administration of MOR00208 are described in detail in the IB for MOR00208.

5 STUDY PURPOSE/RATIONALE

MOR00208 has enhanced cytotoxicity against CD19+ tumors in both in vitro and in vivo, and it is expected to provide potent recruitment of immune effector cells as a result of the Fc engineering. MOR00208 is being developed for the treatment of CD19+ lymphoid malignancies. CLL, NHL, HCL and B-precursor ALL represent tumor types that have been well characterized in regard to expression of the CD19 antigen.

Introduction of rituximab into first-line NHL regimens in the recent years has improved cure rate in several NHL subtypes by at least 10%. Despite extensive use of rituximab across a range of NHL subtypes in combination with chemotherapy, as a single agent, or as maintenance therapy, there is still a high unmet medical need for patients with refractory or relapsed NHL (eg, MCL, DLBCL, and FL). (van Oers, 2011; Rummel, 2010; Parekh, 2011)

The B-lymphocyte lineage-specific surface antigen CD19 is the earliest and broadest of the selective B-cell markers, which is highly expressed on the malignant cells in most patients with B-cell NHL. Because of this expression pattern, an anti-CD19 antibody may have clinical utility as a new therapeutic approach to NHL treatment. MOR00208 is an Fc-engineered mAb with significantly enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADPC), and direct cytotoxic effects (apoptosis) on the tumor relative to the unmodified antibody.

Several mAbs targeting CD19 are currently being evaluated in early-phase clinical trials, demonstrating preliminary efficacy. Data from the Phase I trial in patients with relapsed/refractory CLL/SLL (study XmAb®5574-01) demonstrate that MOR00208/XmAb®5574 is well-tolerated and has potential clinical benefit. With an enhanced cytotoxicity and safety/tolerability profile, MOR00208 has the potential to be an effective therapy for patients with CD19-expressing B-cell malignancies. The purpose of this study is to evaluate the efficacy and safety of MOR00208 in adult patients with relapsed or refractory NHL.

6 OBJECTIVES

6.1 Primary Objective

- To assess the antitumor activity of single-agent MOR00208 in adult patients with relapsed or refractory NHL who have received at least 1 prior therapy containing rituximab as one of the treatments.

6.2 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

7 STUDY DESIGN

7.1 Overall Study Design and Investigational 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.).

The study will employ a two-stage design where the decision to further enrol any NHL subtype in Stage 2 will depend on best responses after 2 or 3 cycles in Stage 1.

Stage 1 – At least 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 and 12 weeks (the latter applicable only for patients with at least SD after 8 weeks) of dosing, patients will be evaluated for response. If in Stage 1 fewer than 2 patients per NHL subtype have a best response of PR or better, then continued enrolment in that cohort will be stopped for futility. If at least 2 patients per NHL subtype have a best 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 – At least 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.

Maintenance treatment - Patients with an ongoing response of at least PR at the end of Cycle 3 (regardless of Stage 1 or 2) may receive further study drug until progression (please see Sections 10.3 and 10.4). Eligible patients will receive a dose of 12 mg/kg MOR00208 either monthly or every second week.

The decision on patient eligibility and dosing frequency for this maintenance treatment will be taken jointly on a case-by-case base by the concerned investigator and the sponsor.

7.2 Study Timeframe

Each patient will participate in the active phases of the study for a minimum of 8 weeks and a maximum of 12 weeks. Patients in maintenance will be treated until progression. The anticipated overall time frame of the study will be 30 months or longer, depending on response in maintenance, until all patients have completed the end of study visit.

7.3 Study Endpoints

Primary endpoint:

1. Overall response rate (CR+PR), assessed as per the 2007 International Working Group (IWG) response criteria

Secondary endpoints:

1. Stable disease (SD), duration of response (DoR), time to progression (TTP), and progression-free survival (PFS)
2. Incidence and severity of AEs
3. 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
4. Pharmacokinetics (C_{max}, t_{max}, C_{pd} [apparent trough serum concentration before dosing], AUC_{0-t}, $AUC_{0-\infty}$, λ_z, $t_{½}$, CL, Vz)
5. Absolute and percentage change from baseline in measurements of B-, T- and NK cell populations
6. Evaluation of AEs and ORR stratified by baseline CD19 expression on malignant lymphoma cells
7. Evaluation of AEs and ORR stratified by FcγRIIIa and FcγRIIa polymorphism

8 POPULATION

The study population will consist of adult patients with relapsed or refractory B-cell NHL who have received at least 1 completed cycle of combination therapy with rituximab + chemotherapy or at least 4 weekly administrations of rituximab as monotherapy.

The planned sample size is at least 40 patients in Stage 1 (at least 10 patients per NHL subtype) and up to a maximum of 80 additional patients in Stage 2 (approximately 20 patients enrolled to each NHL subtype that continues to enrol into Stage 2). The entire study will enrol between 40 to approximately 120 patients, depending on decision to stop enrolment for futility.

The investigator or his/her designee must ensure that only patients who meet the following inclusion and exclusion criteria are offered enrolment into the study:

8.1 Inclusion Criteria

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:
   a. FL
   b. Other indolent NHL (eg, MZL/MALT) (see section 17.7)
   c. DLBCL
   d. MCL

   NOTE: For transformed lymphomas, the subtype at screening (not at initial diagnosis) is relevant for the assignment to the respective subtype.
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 haematological 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 had a positive [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scan at baseline (Cheson 2007 response criteria).
9. Patients 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:
    a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L
    b. Platelet count $\geq 75 \times 10^9$/L without previous transfusion within 10 days of first study drug administration
    c. Hemoglobin ≥ 8.0 g/dL (may have been transfused)
    d. Serum creatinine < 2.0 x upper limit of normal (ULN)
    e. Total bilirubin $\leq 2.0 \times$ ULN
    f. Alanine transaminase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ 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.

8.2 Exclusion Criteria

1. Previous treatment with cytotoxic chemotherapy, immunotherapy, radiotherapy or other lymphoma-specific therapy within 14 days before the screening visit or patient has not recovered from side effects of previous lymphoma-specific therapy.
2. Treatment with a systemic investigational agent within 28 days before the screening visit.
3. Previous treatment with an anti-CD19 antibody or fragments.
4. Previous allogeneic stem cell transplantation.
5. Known or suspected hypersensitivity to the excipients contained in the study drug formulation.
6. Clinically significant cardiovascular disease or cardiac insufficiency (New York Heart Association [NYHA] classes III-IV), cardiomyopathy, preexisting clinically significant arrhythmia, acute myocardial infarction within 3 months of enrolment, angina pectoris within 3 months of enrolment.

7. Patients with positive hepatitis serology (see also Section 9.5.2). Hepatitis B (HBV): Patients with positive serology for HBV defined as positivity for hepatitis B surface antigen (HBsAg) or total anti-hepatitis B core antibody (anti-HBc). Patients positive for anti-HBc may be included if HBV DNA is not detectable. Hepatitis C (HCV): Patients positive HCV serology (defined as positive for anti-HCV antibody [anti-HCV]) unless HCV-ribonucleic acid (RNA) is confirmed negative.
8. History of human immunodeficiency virus (HIV) infection.
9. Any active systemic infection (viral, fungal, or bacterial) requiring active parenteral antibiotic therapy within 4 weeks of study drug administration.
10. Current treatment with immunosuppressive agents other than prescribed corticosteroids (not more than 10-mg prednisone equivalent).
11. Major surgery or radiation therapy within 4 weeks before first study drug administration.
12. Systemic diseases (cardiovascular, renal, hepatic, etc.) that would prevent study treatment in the investigator's opinion.
13. History or clinical evidence of central nervous system (CNS), meningeal, or epidural disease, including brain metastasis.
14. Active treatment/chemotherapy for another primary malignancy within the past 5 years (except for ductal breast cancer in situ, non-melanoma skin cancer, prostate cancer not requiring treatment, and cervical carcinoma in situ).
15. Pregnancy or breastfeeding in women and women of childbearing potential not using an acceptable method of birth control.
16. History of noncompliance to medical regimens or patients who are considered potentially unreliable and/or not cooperative.

8.3 Definition of Woman of Childbearing Potential

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least 1 of the following criteria:

- Age at least 50 years and naturally amenorrhoeic for at least 1 year (amenorrhoea following cancer therapy does not rule out childbearing potential)
- Premature ovarian failure confirmed by a gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis

8.4 Procedures for Enrolment

A fully signed informed consent must be available before the start of screening activities.

Patients who are able to understand the study but unable to read or write may be consented in accordance with the local legislation, e.g. written confirmation by a witness.

Enrolment to treatment will be performed after all inclusion and exclusion criteria have been confirmed and the patient is found to be eligible.

Patients can be re-screened once if since the last visit (either screening or baseline visit) at least four weeks have elapsed.

In cases of re-screening, patients need to be reconsented and a new patient number will be assigned.

Re-screening procedures

Patients can be re-screened at the discretion of the investigator under certain circumstances. Re-screening is restricted to one attempt per patient and may be performed only if one of the following criteria is met:

- If the inclusion of a patient who has already consented and who met all the inclusion and has met none of the exclusion criteria is delayed due to an unexpected change in the patient's personal situation (e.g. family issues),
- If a patient previously failed to be eligible due to any event (e.g. planned surgery) that has since been resolved,
- If the allowed concomitant medication doses have stabilized,
- If laboratory values that prevented the inclusion of a patient based on the first screening attempt have changed to satisfy the inclusion and exclusion criteria outlined in the currently valid study protocol,
- If a patient who previously failed screening becomes eligible for the study, based on a change in the inclusion and exclusion criteria following a protocol amendment.
- If a patient failed screening due to non-progressed/non-relapsed disease at the time of screening and later is clinically diagnosed as having progressed/relapsed.

NOTE: A patient should only be re-screened if there is a clear indication that the patient may be eligible according to the currently valid study protocol.

In these cases, if previous screening activities were discontinued and enrollment did not occur, the following procedure should be implemented:

- the patient must sign and date a new Informed Consent Form as part of the screening procedure,
- the patient will receive a new unique inclusion/identification number and, in case of eligibility, a new unique number via the IWRS,
- a new Case Report Form (CRF) will be completed,
- the patient will be documented as re-screened in the source documents, and
- recording of medical histories, physical examinations, prior NHL treatments, adverse events, and concurrent medications will be transcribed from the previously used to the new CRF if the conditions and medications still apply to the current status of the

re-screened patient as documented in the source documents. All screening procedures must be completed again.

A re-screened patient can be enrolled if all current inclusion criteria are met and none of the exclusion criteria are met.

9 TREATMENT

Each investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor via delegated depot are correctly received, recorded, handled and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this protocol. The investigator can delegate these tasks to a dedicated pharmacist or another person (according to the national laws and regulations). Drug accountability forms will be kept by the site during the study and will be checked during monitoring visits.

For the first 5 patients in the study (irrespective of the subgroup) the first study drug infusion will be administered as in-patients (ie, these patients will remain in the hospital overnight for the first infusion). Whether subsequent patients will have to stay overnight will then be decided by the sponsor after consultation with the investigators concerned.

All study drug containers – ie, outer packing and vial - (opened, unopened, or empty) must be returned to the sponsor/sponsor's designee and will be destroyed by the sponsor or representative after the study and overall drug accountability has been completed by the sponsor or representative.

Opened or empty vials should only be returned if this is not in violation of local guidances or SOPs.

A list of study drug and other materials that have been returned or destroyed must be prepared and signed by the principal investigator or designee. If there are any discrepancies, an explanation for these should also be provided.

The IB for MOR00208 or other safety documents for study drugs will be supplied to the study sites.

9.1 Patient Numbering

This is an open-label study. Patients will not be randomized.

For each patient screened, the investigator or designee will log into the Interactive Web Response System (IWRS) and will enter the age at time of consent and the gender. The IWRS will allocate the next available screening identification (ID) number, ensuring that screening ID numbers are assigned sequentially per center. These numbers (7 digits) are made up of the country code (2 letters) (eg, PL, DE), the site number (2 digits) (01, 02), and a 3-digit number (001, 002) given to each patient in sequence as they are screened at site. Leading zeros will be used for the site and 3-digit number part of the ID number to ensure a consistent length of 7 digits. The investigator will enter the information (ie, age at time of consent and the associated screening ID number) into the confidential patient identification list. The patient will be identified by the previously assigned screening ID number throughout the study. No additional patient number will be used. For numbering of patients who were re-screened, please see Section 8.4.

Informed consent must be obtained before any study procedures are carried out.

9.2 Investigational Medicinal Products

9.2.1 Instructions for Prescribing and Taking the Study Drug

Detailed descriptions concerning correct storage conditions, handling, solution preparation, and administration will be provided in a drug preparation manual for MOR00208.

MOR00208 DP is a white to yellowish lyophilisate for reconstitution with 5 mL water for injection (WFI), supplied in single-use 20 mL glass vials. The solution after reconstitution is colorless to slightly yellow and essentially free of foreign particles; it may contain few white to whitish product-related particles. Reconstitution with 5 mL WFI yields approximately 5.4 mL of drug product that contains 40 mg/mL of MOR00208, 25 mM sodium citrate, 200 mM trehalose and 0.02% (w/v) polysorbate 20 at pH 6.0. Each product vial is intended to deliver 5 mL of drug solution or 200 mg of MOR00208. Each vial of MOR00208 is packaged in a single drug product box.

MOR00208 DP must be stored under refrigeration at 2°C to 8°C in an appropriately locked room accessible only to the pharmacist(s), the investigator, or a duly designated person.

For administration, MOR00208 will be diluted into a 250 mL infusion bag containing 0.9% sodium chloride for injection. MOR00208 DP and commercially available 0.9% sodium chloride saline for injection will be provided to investigational sites by the sponsor or delegated depot.

The individual MOR00208 infusion will be prepared and administered at the study site, according to directions of the sponsor, which will be provided in a drug preparation manual. In general, a vial of MOR00208 must be used as soon as possible after reconstitution with WFI; any solution remaining in the vial has to be discarded. After dilution for infusion, administration of MOR00208 should take place as soon as possible. Maximum allowed storage times and conditions will be detailed in the drug preparation manual.

For the first infusion, IV infusion should be started with an infusion rate of 70mL/h for the first 30 minutes and then subsequently increased to a rate of 125mL/h; the total infusion duration should ideally not exceed 2.5 hours. All subsequent MOR00208 infusions will be administered IV at a constant rate over a 2-hour period. In all cases an in-line filter has to be used. MOR00208 infusion should NOT be administered as an IV push or bolus.

Resuscitation equipment should be readily available.

9.2.2 Treatment

The dose of MOR00208 will be 12 mg/kg, which was established in study XmAb®5574-01.

For all patients, weight measurements are to be performed at each visit (except Day 2 of Cycle 1) and the values are to be entered into the eCRF recording the day of the actual measurement.

Measurements can be done up to 24 hours before study drug administration. The weight obtained at 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).

9.3 Treatment Arms

Not applicable. This is a single-arm study.

9.4 Treatment Blinding

Blinding does not apply since the study will be open label.

9.5 Treating the Patient

9.5.1 Management of Infusion Reactions

Infusion reactions will be defined according to the NCI-CTCAE, Version 4.0 definition of infusion-related reaction and cytokine release syndrome.

Table 1 Definition of an Infusion Reaction

NCI-CTCAE Version 4.0, Select Criteria: Infusion-Related Reaction and Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (eg, not rapidly responsive to symptomatic medication, brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening; consequences; pressor or ventilatory support indicated

REMARK: An acute infusion reaction may occur with an agent that causes cytokine release (eg, monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting

During Cycle 1, premedication including antipyretics (eg, acetaminophen 500-650 mg PO or IV or equivalent), histamine H1 receptor blockers (eg, diphenhydramine 25 to 50 mg IV or equivalent), and glucocorticosteroids (methylprednisolone 80 to 120 mg IV or equivalent;

please refer to Table 17.6) should be given for the first 3 infusions. In medically justified cases, the investigator may use other doses and/or formulations if this is documented thoroughly in the eCRF and the source data.

Premedication for patients who do not experience any infusion reactions during the first 3 infusions will be optional for subsequent infusions at the discretion of the investigator. Otherwise, the premedication should be continued for subsequent administrations of MOR00208. In case of development of rigor or chills treatment with meperidine is allowed.

Grade 1 or 2 infusion reactions

If a patient presents with Grade 1 or Grade 2 infusion reactions:

- Infusion should be stopped immediately
- The patient should receive appropriate further treatment with an antihistamine and/or paracetamol or methylprednisolone (or equivalent) if clinically indicated.
- Once symptoms are resolved or reduced to "mild" by investigator assessment the infusion can be continued at an infusion rate of 50%. If after one hour, the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to the baseline rate.

If a patient who developed infusion reactions (Grade 1 or 2) receives further infusions, then premedication should be given before all subsequent infusions of MOR00208.

Grade 3 infusion reactions

If a patient presents with Grade 3 infusion reactions:

- Infusion should be stopped immediately
- The patient **must** receive appropriate treatment with an antihistamine and/or paracetamol or methylprednisolone (or equivalent) and, if necessary, further medications (ie, epinephrine, bronchodilator).
- Obtain blood sample for cytokine analysis during the event and approximately 24 hours later.
- Only after complete resolution of all symptoms (less than Grade 1) and after having received appropriate prophylactic medication(s) above may the infusion be resumed at an infusion rate of 25%. If, after one hour, the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased to a maximum of 50%.
- If, after resumption of infusion, symptoms have returned (irrespective of Grade), infusion must be stopped immediately and the infusion tubing should be disconnected from the patient. Patient should not receive further study drug.

Grade 4 infusion reactions

If a patient presents with Grade 4 infusion reactions:

- Infusion should be stopped immediately and the infusion tubing should be disconnected from the patient.

- Patient should receive appropriate treatment with an antihistamine and/or paracetamol or methylprednisolone (or equivalent) and, if necessary, further medications (ie, epinephrine, bronchodilator).
- Obtain blood sample for cytokine analysis during the event and approximately 24 hours later.
- Patient must not receive further study drug.

9.5.2 Management of Patients with Positive Hepatitis B Serology

All patients will be screened for hepatitis B before dosing. Patients with a positive test for anti-HBc can only be included if HBV-DNA is not detected. In these patients, HBV-DNA should be assessed at regular intervals during treatment (see Table 2).

If HBV-DNA becomes detectable during treatment, patients should be prophylactically treated and followed-up for potential hepatitis B reactivation as per local practice or guideline for anti-CD20 antibodies like rituximab.

For ongoing patients (ie, either in treatment, follow-up, or maintenance) who were included before anti-HBc measurement was introduced with this amendment, anti-HBc should be measured at least once (see Table 2) unless a patient's anti-HBc status is known from within 6 months prior to screening. If anti-HBc is positive and HBV-DNA from within 6 months before screening is not known, then HBV-DNA should be measured. If HBV-DNA is positive, then patients can only stay in the study if they were assessed by a physician experienced in the treatment of hepatitis B and pre-emptive treatment was initiated if deemed appropriate and/or according to local practice/guideline.

9.6 Management of Treatment-Related Toxicities

If a patient develops a study drug-related Grade 3 or 4 toxicity and the toxicity has not resolved to Grade 1 or to at least the baseline grade (if the condition was pre-existing at screening) at the day of the next scheduled administration, study drug administration for that visit will be postponed.

If treatment needs to be postponed for more than 15 days for the same study drug-related toxicity, the patient's treatment should be permanently discontinued. Patients who discontinue before end of Cycle 2 proceed with the EOS visit. Patients who have had at least SD at the end of Cycle 2 and have not progressed should continue with the first follow-up visit in the study (see Section 9.10 and 10.3).

If based on medical judgment, the treating physician considers a laboratory parameter change or adverse event not to be a study drug-related toxicity, but to represent natural fluctuation or progression of the underlying disease, it is up to the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the patient should be dosed (see Section 10.8.4). The decision and rationale behind the decision should be documented in the source data.

9.7 Safety-related Criteria for the Initiation of Each New Cycle of Therapy

Patients can only enter the next treatment cycle if the following criteria are met. If at least one criterion is not met (unless this is due to the fluctuation/progression of the underlying disease or infiltration of the bone marrow by the NHL; see Section 9.6), the beginning of the cycle will be postponed until resolution to Grade 1 or at least the baseline value (for pre-existing conditions at screening). If a cycle has to be postponed for more than 15 days for the same persisting study drug-related toxicity then the patient will be withdrawn from the study (see Section 9.11.2).

1. ANC $\geq 1.0 \times 10^9$/L
2. Platelet count $\geq 75 \times 10^9$/L
3. Haemoglobin ≥ 8.0 g/dL (may have been transfused)
4. Serum creatinine $< 2.0 \times$ upper limit of normal (ULN)
5. Total bilirubin $\leq 2.0 \times$ ULN
6. Alanine transaminase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN
7. No study treatment-related Grade 3 or 4 toxicity in CNS, cardiovascular, infections or gastrointestinal system organ class (as per CTC 4.0 classification)

9.8 Prior and Concomitant Therapy

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. However, information should be provided on any previous NHL-specific therapies since the time point of the first diagnosis of NHL. The generic or the trade name may be recorded. Other than the study drug, patients should not receive any other NHL-specific therapy during the study. The patient should not receive any investigational agent other than MOR00208 during the participation in the study.

Noninvestigational medications needed to treat concomitant medical conditions may be continued during the study. Prophylactic antibiotics/antifungals are allowed at the discretion of the investigator. Any other medication for treatment of symptoms of NHL or concurrent diseases is allowed and can be prescribed at the discretion of the investigator. However, the medical monitor should be contacted to discuss the use of any NHL-related therapies before those therapies are started.

However, treatments that might potentially interfere with the study drugs should be avoided and (with the exception of treatments required in emergency situations) should be approved by the medical monitor before administration.

The investigator should instruct the patient not to take any additional medications (including over-the-counter-products) during the study without prior consultation. All medications (including over-the-counter medications) administered after the patient has signed the informed consent must be listed on the concomitant medications form in the eCRF.

All respective treatments given during the treatment period until the first follow-up visit should be recorded in the eCRF as concomitant medication. 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.

9.9 Treatment Compliance

Patients will receive MOR00208 under the direct supervision of study personnel. Each administration volume or dose will be checked and the vial/outer package code and volume or dose per administration will be recorded in each patient's eCRF as well as in the source data. Drug accountability will be checked by the field monitor during site visits and at the completion of the trial.

9.10 Treatment Postponement

Study drug administration may be postponed for medical reasons (see Section 9.6) or other reasons (eg, social reasons, weather circumstances). In case of a postponement in study drug administration, the treatment should be restarted as early as possible and continue with the postponed visit. The allowed window for each treatment visit is ± 1 day, outside this window a one-time postponement for up to 7 days is allowed. However, the period between two drug administrations should always be at least 5 days. If not, then the administration on the following visit should be skipped.

Should treatment be postponed for more than 15 days due to the same treatment-related toxicity, then the treatment should be permanently discontinued. Patients who discontinue before end of Cycle 2 proceed with the EOS visit. Patients who have had at least SD at the end of Cycle 2 and have not progressed should continue with the first follow-up visit in the study as defined in Section 10.3.

Further or longer postponements, especially during the maintenance treatment, can be allowed by the sponsor in close collaboration with the investigator if this is justified by the previous response to the treatment and the current medical condition of the patient.

9.11 End of Treatment and Study Drug Discontinuation

9.11.1 End of Treatment

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. In addition, the investigator should discontinue study drug if he or she thinks that continuation would be detrimental to the patient´s well-being.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient´s premature withdrawal from the study and record the information on the electronic Case Report Form (eCRF). If the reason for withdrawal is an AE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF.

Patients may be withdrawn from the study prematurely for one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol violation
- Subject withdrawal of consent
- Loss to follow-up
- Administrative problems
- New cancer therapy
- Disease progression
- Death
- Withdrawal of a patient at the specific request of the sponsor.

The sponsor must be notified within 24 hours if a patient is withdrawn from the study.

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.

Patients who are withdrawn for any reason may not re-enter this clinical study at any time.

9.11.2 Study Drug Discontinuation

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for the patient.

Patients who discontinue study before completing the second cycle and response assessment should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the End of Study visit should be performed. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the first 4 weeks following the last dose of study drug.

Patients who discontinue study drug should be considered withdrawn from the study after the final visit assessments are performed or when it becomes clear that the patient will not return for these assessments. The last day of study drug administration should be entered into the eCRF and the reason for discontinuing study drug should be given. Patients lost to follow-up should be recorded as such in the eCRF. Treatment after study drug discontinuation is at the discretion of the investigator.

9.12 Study or Site Termination

The investigator and the sponsor both reserve the right to terminate the study at any time at a given clinical study center. The sponsor also reserves the right to terminate the entire study or temporarily interrupt enrolment and/or dosing of already enrolled patients for further evaluation, eg, if during ongoing evaluation of the risk/benefit ratio the sponsor decides that the risks outweigh the benefits of MOR00208.

Stopping criteria for this study will include, but not be limited to:

1. Two or more patients within the first six patients enrolled experience unexpected Grade 4 or 5 toxicities of the same or related Adverse Event terms according to CTC and these events are assessed as being related to MOR00208 by the investigator or the sponsor.
2. ≥ 30% of patients following the initial six enrolled experience unexpected Grade 4 or 5 toxicities of the same or related Adverse Event terms according to CTC and these events are assessed as being related to MOR00208 by the investigator or the sponsor.

Should a termination of a given clinical study center or the whole study be necessary then the procedures will be arranged on an individual study basis after review and consultation by all involved parties. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the patients' interests. Institutional Review Boards (IRBs)/IECs and competent authorities will be notified of premature termination in accordance with applicable regulatory requirements.

10 VISIT SCHEDULE AND ASSESSMENTS

Table 2 lists all of the assessments, and indicates with an "X" the visits at which these assessments are performed. All data obtained from these assessments must be supported in the patient´s source documentation.

Table 2 Schedule of Assessments

Evaluation or Procedure	**Screening**	**Cycle 1 (28 days)**					**Cycle 2 (28 days)**					**Cycle 3** (if response is at least SD) **(2 weeks ± 1 day after Cycle 2 Day 22)**					**Follow-up**		**Maintenance Treatment Visits beyond Follow-up Visit 12[20]**	**EOS Visit**
Day	**-21 to -1**	**Day 1**	**Day 2**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**1 ± 1 day**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**28 ± 4 days**	**1 ± 1 day**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**28 ± 4 days**	**1st Follow-up + 4 weeks ± 2 days**	**Follow-up Visits 2 - 12[1]**		**+ 4 weeks ± 2 days**
Informed consent	X																			
Inclusion/exclusion criteria	X	X[2]																		
Demography	X																			
Medical history (incl. prior NHL treatments)	X																			
Staging	X																			
ECOG	X	X			X		X		X			X		X			X	X		X
Determination of CD19 on tumor cells (bone marrow)	X																			
Determination of CD19 on tumor cells (tumor biopsy/aspirate)[3]	X																			
Study drug administration		X		X	X	X	X	X	X	X		X	X	X	X				X[20]	
Premedication		X		X	X	X[4]	X[4]	X[4]	X[4]	X[4]		X[4]	X[4]	X[4]	X[4]					
"Emergency laboratory"		X[19]		X[19]	X[19]	X[19]	X[19]	X[19]	X[19]	X[19]		X[19]	X[19]	X[19]	X[19]					
Haematology	X	X[2]	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X[2]	X[2]	X[2]	X[2]	X	X	X	X	X
Serum chemistry	X	X[2]	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X[2]	X[2]	X[2]	X[2]	X	X	X	X	X
Coagulation	X	X[2]					X[2]					X[2]					X	X		X
Pharmacokinetics		X[5]		X[6]	X[6]	X[6]		X[6]		X[6]	X		X[6]		X[6]	X	X	X[7]		
Urinalysis	X	X[2]					X[2]					X[2]					X	X		X
β-HCG pregnancy test (WOCBP)	X																X[22]	X[22]		X
Urine pregnancy test (WOCBP)		X[2]					X[2]					X[2]					X[22]	X[22]	X	
Serology (Hepatitis B and C)	X					X[21]					X[21]					X[21]	X[21]	X[21]	X[21]	
B-, T- and NK cell flow cytometry		X[2]		X[2]	X[2]	X[2]	X[2]		X[2]		X	X[2]		X[2]		X				X
CD16 expression on NK cells	X																			
Anti-MOR00208 antibodies		X[2]					X[2]					X[2]					X	X[18]		
FcγR polymorphism (mucosal cheek swab)		X[2]																		

Table 2 Schedule of Assessments

Evaluation or Procedure	**Screening**	**Cycle 1 (28 days)**					**Cycle 2 (28 days)**					**Cycle 3** (if response is at least SD) **(2 weeks ± 1 day after Cycle 2 Day 22)**					**Follow-up**		**Maintenance Treatment Visits beyond Follow-up Visit 12[20]**	**EOS Visit**
Day	**-21 to -1**	**Day 1**	**Day 2**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**1 ± 1 day**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**28 ± 4 days**	**1 ± 1 day**	**8 ± 1 day**	**15 ± 1 day**	**22 ± 1 day**	**28 ± 4 days**	**1st Follow-up + 4 weeks ± 2 days**	**Follow-up Visits 2 - 12[1]**		**+ 4 weeks ± 2 days**
ADCC assessment	X																			
Tumor biopsy (cytogenetics)[3]	X																			
Serum immunoglobulin levels		X[2]				X[2]				X[2]					X[2]		X	X		X
Bone marrow aspiration & biopsy	X[9]										X					X[10]		X[10, 8]		
Body weight	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X[11]	X[2]				X					X[12]					X[12]	X[12]	X[12]	X	X
Vital signs	X	X[13]	X	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X	X[13]	X[13]	X[13]	X[13]	X	X	X	X	X
ECG	X	X[14]						X[14]		X[14]			X[14]		X[14]					X
AE assessment			----------continuous----------																	
Baseline disease and response assessment (CT/PET)[15]		X[2, 17]									X[17]					X[17]		X[8, 17]		
Additional Radiological evaluation[16]		X[17]									X[17]					X[17]		X[8,17]		
Previous/Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; AE = adverse event; β-HCG = beta-human chorionic gonadotropin; C2D22 = Cycle 2 Day 22; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; FU= Follow-up; PET = positron emission tomography; SD = stable disease; WOCBP = woman of childbearing potential.

[1] The second and third FU Visit should be scheduled 6 weeks ± 1 weeks following the previous visit, the fourth to sixth FU Visit should be scheduled 3 months ± 2 weeks following the previous visit, further FU Visits should then be scheduled every 6 months.

[2] Before study drug administration.

[3]Tumor biopsy/aspirates should be obtained if malignant lymph nodes are easily accessible.

[4] Premedication for patients who do not experience infusion reactions during the first 3 infusions will be optional at the discretion of the investigator for subsequent infusions.

[5] The PK sample will be taken before study drug administration; at the end of the infusion; and 1 hour, 4 hours, and 24 hours after end of first MOR00208 infusion. The sample taken on Day 2 (ie, 24 hours after end of first infusion) belongs formally to Day 1.

[6] The PK sample will be taken before study drug administration and 1 hour after the end of MOR00208 infusion.

[7] The PK sample will be taken at second and third follow-up visit only.

[8] Not performed at third FU (no response assessment).

[9] 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, obtaining bone marrow samples for the sole purpose of CD19 expression does not need to be repeated.

[10] Bone marrow examinations should only be repeated if response at last bone marrow examination was not CR.

[11] Including body height at screening only. Physical examination includes palpable tumor assessment, general appearance, skin, head, eyes, ears, nose, throat, lungs, breasts and axillae (if applicable including bi-dimensional measurement of cervical, supraclavicular, axillary and inguinal lymph nodes), cardiovascular system, back and spine, abdomen (if applicable including spleen size below the costal margin), extremities, infusion site, lymph nodes, and neurological examination.

[12] Physical examination will be used for response assessment.

[13] Immediately before infusion; 15, 30, and 60 minutes during infusion; at end of infusion; and every hour for two hours after completion of infusion.

[14] Performed 1 hour ± 10 minutes post dose. Additionally, for Cycle 1 Day 1 predose; 12-lead ECG recording should include determination of heart rate and RR, PR, QRS, QT, and QTc intervals. The 12-lead ECG will be recorded after 5 minutes of rest in a supine position.

[15] For all patients neck/chest/abdomen/pelvis CT is required. PET should also be performed for response assessment if tumor was PET avid at baseline.

[16] Radiographic examinations in addition to the neck/chest/abdomen/pelvis CT/PET evaluations are to be done, as appropriate. (For MRI, please see Section 10.6.) Follow-up radiographic examinations will be performed at the end of Cycle 2, Cycle 3, and at the second and subsequent follow-up visits for any procedures performed at baseline visit.

[17] Radiographic evaluations may be performed up to 3 days before the scheduled visit during Cycle 1-3 and within +/- 4 days of the planned visit during follow-up. If a patient discontinues from the study before a response assessment, an evaluation will occur approximately one month after the patient discontinues from the study. CT/PET examinations that were done up to 3 weeks before Cycle 1 Day 1 may be used as a patient's baseline assessment. (For MRI, please see Section 10.6.)

[18] Anti-MOR00208 sample will be taken at third follow-up visit only.

[19] Sample to be taken and evaluated before study drug administration.

[20] Maintenance treatment for patients with at least ongoing PR will be administered either every second week or monthly until progression. The treatment frequency during the follow up period should be maintained. Before administration, blood parameters (hematology, serum chemistry, urine pregnancy test) should be evaluated in local laboratory according to local guidelines/practice for the administration of monoclonal antibodies. Vital signs should be measured every hour or according to local practice with anti-CD20 antibodies.

[21] Hepatitic C serology only to be done at screening. HBV-DNA only to be measured during treatment and follow-up if total anti-HBc was positive. If HBV-DNA is positive, please see Section 9.5.2. Anti-HBc should be measured if an anti-Hbc status from during the study or within 6 months prior to screening is not known.

[22] Only urine pregnancy test is to be done if the regular follow-up visit coincides with the maintenance treatment visit. Otherwise, serum pregnancy test should be done.

10.1 Screening Evaluations

All patients must have signed and dated the informed consent before initiation of any study-related evaluation. However, assessments that have been performed before the signing of the informed consent and that fall within the screening period window may be used as screening assessments **only if** the assessments were performed as part of the routine standard of care visit for the patient. The investigational site must provide a note to file in the patient folder to attest to any such occurrence. The screening period lasts for up to 21 days. All patients must satisfy all of the inclusion criteria and none of the exclusion criteria listed in Sections 8.1 and 8.2.

The screening evaluations will include:

- Demography and ECOG performance status (see the appendix, Section 17.5)
- Prior and concomitant medication
- Medical history and physical examination including height, weight, palpable tumor assessment, general appearance, skin, head, eyes, ears, nose, throat, lungs, breasts and axillae (if applicable including bi-dimensional measurement of cervical, supraclavicular, axillary and inguinal lymph nodes), cardiovascular system, back and spine, abdomen (if applicable including spleen size below costal margin), extremities, infusion site, lymph nodes, and basic neurological examination)
- Staging
- Blood sampling:
    - Haematology with complete blood count (CBC) with differential and platelet count, serum chemistry, and coagulation
    - β-HCG pregnancy test for women of childbearing potential
    - Determination of CD16 expression on NK cells and ADCC assessment (Due to the exploratory nature of the ADCC assay, the sponsor may decide at any point during the study to terminate these assessments in which case the sites will be informed accordingly)
    - Hepatitis B and C screening (please see Section 9.5.2)
- Urine sampling for urinalysis
- Bone marrow aspirate and biopsy. Results from bone marrow examination done within 4 weeks before screening are acceptable, if the patient's disease has been stable since then. The following are included:
    - Histology (to be analysed locally)
    - Determination of CD19 on malignant B cells (to be done through central lab)
- Tumor aspirate and biopsy, if malignant lymph nodes are easily accessible. The following are included:
    - Histology (to be analysed locally)
    - Determination of CD19 on B cells (to be analysed through central lab)

  - Cytogenetics (if historical data are not available, to be analysed locally)
- Vital signs (pulse, blood pressure, temperature and respiratory rate)
- 12-lead ECG

10.2 Main Treatment Phase (Cycles 1-3)

Only patients fulfilling all inclusion and none of the exclusion criteria should be enrolled.

The schedule of required procedures for each treatment day is detailed in Table 2. Clinical site study days are Days 1, 2, 8, 15, and 22 for Cycle 1 and Days 1, 8, 15, 22, and 28 for Cycle 2. Patients qualifying for Cycle 3 will have visits on Days 1, 8, 15, 22, and 28 of this cycle.

During the first two 28-day cycles, patients will receive a total of 8 infusions: each 28-day cycle will consist of a MOR00208 infusion on Day 1, Day 8, Day 15 and Day 22 of the cycle.

- Patients with a response of at least SD on Cycle 2, Day 28, will qualify for 1 further cycle of MOR00208 (infusions on Day 1, Day 8, Day 15 and Day 22 of the 28-day cycle). This potential Cycle 3 should start 2 weeks ± 1 day after Cycle 2, Day 22.

Before dosing, premedication as detailed in Section 9.5 should be administered.

Clinical assessments, physical examinations and laboratory evaluations (instead of emergency lab) may be performed within 24 hours before administration of MOR00208 (except PK and anti-MOR00208 antibodies); assessments for Cycle 3 should only be performed if patient qualifies for the respective study drug administration:

- Assessment of AEs and concomitant medication at all visit days (see Section 9.8)
- Assessment of body weight at all visit days
- Physical examination including palpable tumor assessment, general appearance, skin, head, eyes, ears, nose, throat, lungs, breasts and axillae (if applicable including bi-dimensional measurement of cervical, supraclavicular, axillary and inguinal lymph nodes), cardiovascular system, back and spine, abdomen (if applicable including spleen size below the costal margin), extremities, infusion site, lymph nodes and neurological examination at Day 1 (predose) and Day 22 of Cycle 1; and Day 28 of Cycles 2 and 3.
- ECOG performance status (Day 1 and 15 of Cycles 1 to 3)
- Vital signs (pulse, blood pressure, temperature and respiratory rate): At each treatment visit immediately before infusion, 15, 30, 60 minutes (± 5 minutes) after start of infusion, at the end of the infusion, and every hour for two hours (± 10 minutes) after completion of the infusion. If the infusion is interrupted and/or subsequently restarted, vital signs should be assessed every 60 minutes after the first hour until two hours after the end of the infusion. Vital signs should be obtained once on Day 2 Cycle 1 and on Day 28 of Cycles 2 and 3.

- Baseline disease status on Day 1 of Cycle 1 and response assessment on Day 28 of Cycles 2 and 3 should include:
    - Assessment by physical examination
    - CT of neck, chest, abdomen and pelvis on Day 1 of Cycle 1 and Day 28 of Cycles 2 and 3 (for MRI, please see Section 10.6). A PET scan should also be used for response assessment if CT does not provide a clear readout and if the lymphoma is expected to be PET-avid. Results from CT and/or PET examination done within 3 weeks before Cycle 1 Day 1 are acceptable to be used for baseline. Radiographic examinations can be done up to 3 days before the treatment visit.
    - Radiological evaluation in addition to the CT/PET of neck, chest, abdomen and pelvis are to be done as appropriate on Day 1 of Cycle 1 and Day 28 of Cycles 2 and 3 (for MRI, please see Section 10.6). Results from additional radiological evaluations done within 3 weeks before Cycle 1 Day 1 are acceptable to be used for baseline. Radiographic examinations may be performed up to 3 days before the treatment visit.
    - Bone marrow aspiration and biopsy (baseline assessment should be done during screening and not on Day 1 of Cycle 1).
- Laboratory assessments from blood sampling (Day 1 preinfusion assessments will be considered baseline assessments):
    - Blood sample for “emergency laboratory” for immediate evaluation before study drug administration on all Days 1, 8, 15, 22 of Cycles 1, 2 and 3 (if Cycle 3 is applicable) if no blood sample from the 24 hours before study drug administration is available.
    - Haematology including CBC with differential and platelet count and serum chemistry before each infusion of MOR00208 and on Day 2 of Cycle 1 and Day 28 of Cycles 2 and 3.
    - Coagulation before infusion on Day 1 of Cycles 1 to 3
    - PK samples:
      Cycle 1, Day 1 : before infusion, at the end of infusion (± 10 minutes) and 1 hour (± 10 minutes), 4 hours (± 10 minutes) and 24 hours (± 1 hour) after end of first MOR00208 infusion
      Cycle 1, Days 8, 15 and 22; Cycles 2 and 3, Days 8 and 22: before infusion and 1 hour after the end of infusion (± 10 minutes)
      Cycles 2 and 3, Day 28
    - B-, T- and NK cell flow cytometry before infusion on Days 1, 8, 15 and 22 of Cycle 1 and on Days 1, 15 and 28 of Cycles 2 and 3.
    - Anti-MOR00208 antibodies before infusion on Day 1 of Cycles 1 to 3.
    - Serum immunoglobulin levels before infusion on Day 1 of Cycle 1 and Day 22 of Cycles 1 to 3.

  - If anti-HBc is positive: HBV-DNA as per assessment schedule. (Please see also Section 9.5.2.)

- Laboratory assessments from urine sampling before infusion (Day 1 preinfusion assessments will be considered baseline assessments):
  - Urinalysis on Day 1 of Cycles 1 to 3.
  - Urine pregnancy test in women of childbearing potential on Day 1 of Cycles 1 to 3.
- FcγRIIIa and FcγRIIa polymorphism (mucosal cheek swab) before infusion on Day 1, Cycle 1 (optional, see Section 10.9.7)
- 12-lead ECG on Day 1 of Cycle 1, and on Days 8 and 22 of Cycles 2 and 3

10.3 Follow-up Phase until Follow-up Visit 12

All patients who performed treatment Cycle 3 should have a follow-up visit 4 weeks after end of the last treatment cycle (4 weeks ± 2 days after Cycle 3 Day 28). Patients should return for further follow-up visits until relapse of the lymphoma or for a maximum of 4 years. The second and third follow-up visit should be scheduled 6 weeks ± 1 week following the previous visit, the fourth to sixth follow-up visit should be scheduled 3 months ± 2 weeks following the previous visit, further follow-up visits should then be scheduled every 6 months. If not otherwise indicated, the following assessments should be performed at every follow-up visit:

- Patients with an ongoing response of at least PR after Cycle 3 may receive maintenance treatment with MOR00208 (12 mg/kg either every second week or monthly). Before administration, blood parameters (hematology, serum chemistry) should be evaluated in the local lab according to local guidelines/practice for the administration of monoclonal antibodies. A urine pregnancy test should be performed for women of childbearing potential. These lab results will only be captured in the eCRF if the administration visits coincide with the planned follow-up visits.
- Assessment of AEs and concomitant medication (see Section 9.8)
- Assessment of body weight
- Physical examination including palpable tumor assessment (general appearance, skin, head, eyes, ears, nose, throat, lungs, breasts and axillae (if applicable including bi-dimensional measurement of cervical, supraclavicular, axillary and inguinal lymph nodes), cardiovascular system, back and spine, abdomen (if applicable including spleen size below the costal margin), extremities, infusion site, lymph nodes, and neurological examination).
- ECOG performance status
- Vital signs (pulse, blood pressure, temperature and respiratory rate)

- Response assessment should be repeated at 2nd, 4th, 5th and all subsequent follow-up visits and include:
    - Assessment by physical examination
    - CT of neck, chest, abdomen and pelvis. A PET scan should also be used for response assessment if CT does not provide a clear readout and if the lymphoma is expected to be PET-avid. Follow-up radiographic evaluations may be performed any time ± 4 days of the planned visit.
    - Radiological evaluation in addition to the CT/PET of neck, chest, abdomen and pelvis are to be done as appropriate (for MRI, please see Section 10.6). Radiological evaluations for response assessment should be performed at least for any procedure performed at baseline.
    - Bone marrow aspiration and biopsy (only to be repeated if previous response was not CR)
- Laboratory assessments from blood sampling:
    - Haematology including CBC with differential and platelet count and serum chemistry
    - Coagulation
    - PK sample at the 1st, 2nd and 3rd follow-up visit only
    - Anti-MOR00208 antibodies at the 1st and 3rd follow-up visit only
    - Serum immunoglobulin levels
    - β-HCG pregnancy test for women of childbearing potential (only urine pregnancy test is to be done if regular follow-up visit coincides with maintenance treatment visit; otherwise, serum pregnancy test should be done)
    - If anti-HBc is positive: HBV-DNA as per assessment schedule. (Please see also Section 9.5.2.)
- Laboratory assessments from urine sampling: Urinalysis

10.4 MOR00208 Treatment and Study Procedures after Follow-up Visit 12

Patients who have not progressed after four years of treatment with MOR00208 (ie, after Follow-up Visit 12 as described above) may continue receiving the IMP thereafter, until progression, based on the decision of the treating physician. The treatment frequency (during the follow-up period as described above) should be maintained.

Prior to each administration of MOR00208, the following assessments should be performed at a local laboratory:

- Assessment of body weight
- Haematology including CBC with differential and platelet count and serum chemistry

- β-HCG urine pregnancy test for women of childbearing potential (only urine pregnancy test is to be done if regular follow-up visit coincides with maintenance treatment visit; otherwise, serum pregnancy test should be done)
- Vital signs (pulse, systolic and diastolic blood pressure, body temperature, and respiratory rate) hourly
- Physical examination
- If anti-HBc was positive earlier: HBV-DNA should be measured every six months. (Please see also Section 9.5.2.)

Only the data on AEs, SAEs, and concomitant medications will be collected in the study database during this period.

10.5 End of Study Visit

Patients will have their EOS 4 weeks (± 2 days) following:

- The last administration of MOR00208 in Cycle 2 if the response after 2 cycles was not at least SD
- The visit where a relapse (or disease progression) was diagnosed or decision to stop treatment was made in patients qualifying for Cycle 3 of MOR00208

If patient terminates the study early (ie, before end of Cycle 2), the EOS will be performed on the day of termination.

The assessments that will be performed at the EOS include the following:

- Assessment of AEs and concomitant medication
- Assessment of body weight
- Physical examination including palpable tumor assessment, general appearance, skin, head, eyes, ears, nose, throat, lungs, breasts and axillae (if applicable including bi-dimensional measurement of cervical, supraclavicular, axillary and inguinal lymph nodes), cardiovascular system, back and spine, abdomen (if applicable including spleen size below costal margin), extremities, infusion site, lymph nodes, and neurological examinations
- ECOG performance status
- Vital signs (pulse, blood pressure, temperature, respiratory rate)
- Response assessment includes:
    - Assessment by physical examination
- Laboratory assessments from blood sampling:
    - Haematology including CBC with differential and platelet count and serum chemistry
    - Coagulation

  - B-, T- and NK cell flow cytometry
  - Serum immunoglobulin levels
  - β-HCG pregnancy test for women of childbearing potential
- Laboratory assessments from urine sampling: Urinalysis
- ECG

Patients who were positive for anti-HBc at screening should be followed up for potential HBV reactivation as per local practice (refer to Section 9.5.2).

10.6 Efficacy

Efficacy will be evaluated in terms of the ORR, SD, DoR, TTP, and PFS. The ORR will be evaluated using the revised IWG criteria (Cheson, 2007) and will be defined as the proportion of patients with CR and PR (CR+PR).

The DoR will be the time from first meeting of criteria for response (ie, CR or PR) to first documentation of relapse or progression.

The TTP is defined as the time from study entry (first dosing) until documented lymphoma progression or death as a result of lymphoma. Deaths from other causes are censored at the time of death.

PFS is defined as the time from study entry (first dosing) until lymphoma progression or death as a result of any cause.

Response criteria are provided in Section 17.4.

CT or PET Examination, or Further Radiological Examinations

CT: For all patients, CT neck/chest/abdomen/pelvis is required as indicated in the schedule of assessments at baseline and at all time points when a radiographic response assessment is performed.

PET: For patients with DLBCL and patients known or expected to have PET-avid lymphomas, a PET scan should be performed at baseline in addition to the CT scan. At the subsequent visits, PET should be done in DLBCL patients or if at baseline the lymphoma was PET-avid, but can be omitted if PET definitely would not change the reponse assessment according to the clinical judgement of the investigator (eg, CT already shows progressive disease).

MRI may be used in lieu of CT for subjects with contraindications to administration of contrast agents or due to other medical reasons (at the same time windows as CT), or in addition to CT at the discretion of the investigator (in this case, MRI may be performed as/when appropriate). The method used at baseline should be used throughout the study unless otherwise medically indicated.

Additional radiographic evaluations: are to be done, as appropriate. Follow-up radiographic evaluations will be performed for any procedures performed at baseline visit at the end of Cycle 2 and 3 (if applicable) and at the second, fourth and every further follow-up visit. Follow-up radiographic evaluations may be performed anytime ± 4 days of the planned visit. If

a patient discontinues from the study before any response assessment, if possible a response evaluation will occur approximately one month after the patient discontinues from the study.

CT, PET or additional radiological examinations (eg, MRI) that were done up to 3 weeks before Cycle 1 Day 1 may be used as a patient's baseline assessment at the investigator's discretion.

Physical Examination

The response assessment will be supported by the palpation of lymph nodes from the physical examination (see Section 10.2)

Bone Marrow

At the Screening visit (Baseline), a bone marrow aspirate and a biopsy 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 performed. Repeat of marrow aspirates and biopsies should be obtained at Day 28 of Cycles 2 and 3. Histological examination should be performed and the infiltration by malignant B-cells should be evaluated.

If bone marrow has been obtained within 4 weeks before screening and disease has been stable, the bone marrow biopsy does not need to be repeated solely to obtain samples for determination of CD19 expression.

10.7 Pharmacokinetic Assessments

Concentration-time profiles and pharmacokinetic parameters will be assessed for MOR00208 from 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 administration (Cycle 1 Day1), serum samples will be collected predose and then 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 Cycle 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.
- During Cycle 2 and 3 on Day 28
- At the 1st, 2nd and 3rd follow-up visit

Serum samples for pharmacokinetic analysis will be handled and stored as specified in the lab manual at the study site until shipment on dry ice to an external analytical laboratory. Per sample 2 aliquots (primary and back-up) should be obtained. At the analytical laboratory, the samples will also be stored as specified in the lab manual until analysis. Detailed instructions for handling of serum samples will be provided in the laboratory-specific documentation. Pharmacokinetic sample assessment of MOR00208 will be performed at a specified central laboratory.

10.8 Safety Assessments

Safety monitoring for all patients enrolled in the study will include laboratory safety assessments (haematology, blood chemistry, and urinalysis, coagulation, and anti-MOR00208 antibodies) and clinical evaluations (physical examinations, vital signs, 12-lead ECG) as detailed in the Schedule of Assessments (Section 10) and Section 10.8.4. All AEs and serious adverse events (SAEs) will be recorded.

Laboratory and AE toxicities will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Patients who experience any toxicity should be followed until the toxicity has stabilized, the toxicity returned to the baseline level, or a new treatment has commenced.

Safety monitoring is detailed in Section 11.

10.8.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical subject administered a medicinal product, which does not necessarily have a causal relationship to this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered related to that study drug.

Temporally associated means after signing the informed consent form until 30 days after last administration of the study drug.

For screening failure patients only SAEs will be recorded in the eCRF.

AEs include any clinically significant deterioration of a patient's medical status after the signing of the informed consent form. Also an increase in frequency or intensity of a preexisting episodic event or conditions and events resulting from protocol mandated procedure (eg, invasive procedures) fall under the definition of AE. In addition, overdoses (defined as exceeding planned dose by more than 10%) should be recorded as AEs.

As far as possible, each AE should be evaluated to determine the following:

- Relationship to study drug (suspected/not suspected)
- Duration (start and end date or if continuing at end of study)
- Intensity: The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:
    - Mild: Tolerable
    - Moderate: Interferes with normal activity
    - Severe: Incapacitating (causes inability to perform usual activity or work)

- Toxicity grade: The toxicity grade of AEs will be graded according to the NCI-CTC (CTCAE version 4.0 of May 28, 2009) using the following definitions:
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
    - Grade 4: Life-threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.
- Outcome
- Action taken (no action taken; study drug temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- Seriousness: Whether it is serious, where a serious adverse event (SAE) is defined as one that:
    - Results in death.
    - Is life-threatening.
    - Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization signifies that the patient was inpatient for at least one overnight stay) unless hospitalization is for
        - Routine treatment or monitoring of the studied indication, not associated with deterioration of symptoms related to NHL
        - Elective or preplanned treatment for a preexisting condition that is unrelated to NHL and has not worsened since signing of the informed consent
        - Social reason and respite care in the absence of any deterioration in the patient's general condition
        - Hospitalization signifies that the patient was in-patient for at least one overnight stay.
    - Results in persistent or significant disability or incapacity.
    - Is a congenital anomaly or birth defect.
    - Is medically significant, ie, defined as an event that jeopardizes the patient or may require medical intervention to prevent one of the outcomes listed previously.

NOTE: The term "life-threatening" refers to an event in which the patient was, in the view of the reporting investigator, at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical judgment should be exercised in deciding whether an AE is serious in other situations: Important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definitions should also be considered serious.

Unlike routine safety assessments, SAEs and AEs of special interest are monitored continuously and have special reporting requirements (see Section 11.1).

The investigator should determine the causality (relation to the study drug) based on his/her clinical experience and on the information given in the IB. The causal relationship of all AEs to the study drug will be judged as either suspected or not suspected. A suspected causal relationship means at least a reasonable possibility that the event is caused by the study drug. If no relationship has been provided by the investigator, the event will be considered as related to study drug.

Information about adverse drug reactions already known about the investigational study drug can be found in the IB, or will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent form and should be discussed with the patient during the study as needed.

10.8.2 Physical Examination

A qualified physician (or nurse practitioner or physician's assistant under the supervision of a physician, if permitted by local legislation and medical practice) will conduct physical examinations before study drug administration. The physical examination will include an assessment for the presence of abnormalities of the following: general appearance, skin, head, eyes, ears, nose, throat, lungs, breasts and axillae (if applicable including bi-dimensional measurement of cervical, supraclavicular, axillary and inguinal lymph nodes), cardiovascular system, back and spine, abdomen (if applicable including spleen size below costal margin), extremities, infusion site, lymph nodes, and basic neurological examination (general motor and sensory systems, mental status, cranial nerves, and coordination).

In the event that new and worsening abnormal physical examination findings are encountered during the study, these terms are defined as follows: A new abnormal physical examination finding is defined as one that occurs when a patient's normal baseline physical examination becomes abnormal post baseline, based on clinical grounds. A worsening abnormal physical examination finding is defined as one that occurs when a patient's abnormal baseline physical examination becomes worse post baseline, also based on clinical grounds. Any new findings, worsening findings, or both should be recorded as AEs.

10.8.3 Vital Signs

Vital signs will be measured at the various pre- and posttreatment time points described in the Schedule of Assessments in Table 2. Vital sign parameters include measurements of heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature. Before vital signs are measured, the patient should be resting for at least 5 minutes (if possible). The same

position will be used each time vital signs are measured for a given patient, and blood pressure will be measured from the arm contralateral to the site of study drug administration whenever possible. Body temperature should be measured using normal hospital practice.

The actual time for measurement of vital signs should not deviate more than 10 minutes from the planned time but the actual time should be recorded accurately. If the infusion is interrupted and/or subsequently restarted, vital signs should be assessed every 60 minutes after the first hour until two hours after the end of the infusion.

10.8.4 Laboratory Evaluations

Clinical laboratory parameters to be assessed in this study are displayed in Table 3.

Table 3 Laboratory Evaluations

Evaluation	Analysis	Sample Collection (approximate amount per collection)
"Emergency laboratory" (EDTA blood and serum sample)	Serum creatinine, haemoglobin, white blood cells (WBC), platelets, sodium, potassium, AST, ALT, total bilirubin	Same sample as for chemistry and haematology
Haematology (EDTA blood)	WBC with differential, haematocrit, hemoglobin, mean corpuscular volume, platelet count, red blood cell (RBC) count At screening, will include a peripheral blood smear.	5 mL blood
Serum chemistry (Serum sample)	Alanine aminotransferase (ALT), albumin, alkaline phosphatase, amylase, aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen, calcium, chloride, creatinine, creatine kinase, gamma-glutamyltransferase (GGT), glucose, lactate dehydrogenase, lipase, phosphorus, potassium, protein (total), sodium, uric acid	10 mL blood
Coagulation parameters (Sodium citrate blood)	Activated partial thromboplastin time (aPTT), prothrombin time (PT)	3 mL of blood
Serology parameters (Serum sample)	Hepatitis B: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) and hepatitis B surface antibody (anti-HBs). HBV-DNA if anti-HBc positive, optional Hepatitis C: HCV antibody (HCV RNA quantification if anti-HCV-positive)	Same sample as for chemistry (for HBV please see also Section 9.5.2)
Pregnancy test (Serum sample)	β-HCG serum, females of childbearing potential only	Same sample as for chemistry
Pregnancy test (Urine)	β-HCG urine, females of childbearing potential only	30 mL (midstream urine)
Urinalysis	pH, semiquantitative "dipstick" evaluation of glucose, protein, bilirubin (optional), ketones, leucocytes, RBCs, and microscopic evaluation if abnormal findings	30 mL (midstream urine)
Serum immunglobulin levels	IgG, IgM, IgE	Same sample as for chemistry
Immune cells (EDTA blood) (exploratory assay)	B-, T- and NK cell population (flow cytometry)	2 mL of blood
Genotyping	FcγRIIa and FcγRIIIa polymorphism	Mucosal cheek swab, optional
Flow cytometry (Heparinized blood) (Exploratory assay)	CD16 expression on NK cells	8 mL of blood
Immunogenicity (Serum sample)	Anti-MOR00208 antibodies	4 mL of blood
Pharmacokinetics (Serum sample)	MOR00208	3 mL of blood
ADCC assessment (Heparinized blood) (Exploratory assay)	ADCC with PBMCs	Same sample as for the CD16 flow cytometry
Flow Cytometry (BM+LN)	CD19 expression, % of total malignant B cells	4 mL aspirate of BM+LN

The signed and interpreted laboratory results will be kept as supplemental pages to the patient's eCRF. The laboratory results should be reviewed, dated and signed in a timely manner by the investigator.

With the exception of PK samples (see Section 10.7), anti-MOR00208 antibodies, CD19 and CD16 expression, and the ADCC assessment, all clinical laboratory parameters (see Table 3) will be analyzed at the local hospital laboratories. All blood samples will be processed and handled according to standard laboratory procedures. Anti-MOR00208 antibody assessments, the ADCC assessment, CD19 and CD16 expression assessment will be performed at a specified laboratory.

Serum samples will be collected for anti-MOR00208 antibodies and stored at the study site as specified in the lab manual until shipment on dry ice to the external analytical laboratory. At the analytical laboratory, the samples will also be stored according to the lab manual until analysis. Detailed instructions for handling of plasma and serum samples will be provided in the laboratory manual.

For all study drug administrations, the following parameters should be evaluated in a blood sample taken within 24 h predose on the day before study drug administration or on the day of study drug administration ("emergency laboratory"); if outside the limits described below, depending on the individual risk-/benefit ratio of the patient, IMP administration should be postponed (see Sections 9.6, 9.7, and 9.10):

Table 4 Pre-dose Limits for Laboratory Parameters

Value	**Subject should only be dosed if the value is:**
ANC	$\geq 1.0 \times 10^9$/L (unless this neutropenia is due to infiltration of bone marrow)
Platelet count	$\geq 75 \times 10^9$/L (unless this thrombocytopenia is due to infiltration of bone marrow)
Haemoglobin	≥ 8 g /dL (unless anemia is due to infiltration of bone marrow) (may have been transfused)
Serum creatinine	< 2.0 × upper limit of normal (ULN)
Total bilirubin	≤ 2.0 × ULN
Alanine and aspartate transaminase (ALT and AST)	≤ 2.5 × ULN
Potassium	< 6.0 mmol/L
Sodium	< 155 mmol/L

Blood (CD16 expression, ADCC) or bone marrow samples and lymph node samples (CD19 expression) will be shipped to the external laboratory at room temperature by overnight courier for analysis. At the laboratory, samples will be handled as detailed in the respective laboratory manuals.

Urine will be collected at the various pre- and posttreatment time points described in the Schedule of Assessments in Table 2 and analyzed at the local hospital laboratory. In the case of any abnormal result, a microscopic urine examination should be conducted.

A pregnancy test will be performed for women of childbearing potential at various pre- and posttreatment time points either by urine pregnancy test or β-HCG test of a serum sample. The pregnancy test assay should have a minimum sensitivity of 25 IU/mL. On dosing days, the result should be available before study drug administration.

If an abnormal laboratory value of Grade 4 or an abnormal laboratory value judged to be clinically significant that was not present at baseline is not reported as an AE, then the investigator should clearly document the rationale for not doing so in the source documentation.

Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the patient's condition (eg, ordering a WBC differential count to help characterise a high or low WBC count, or ordering a determination of RBC indices to help characterise a low haematocrit).

Detailed instructions and amounts of blood needed for the respective laboratory measurement, as well as details of which local or central laboratory is involved for the respective laboratory measurements, will be summarized in site-specific laboratory manuals.

Blood samples will be obtained for assessment of serum chemistry, haematology, and coagulation parameters at the various pre- and posttreatment time points described in the Schedule of Assessments in Table 2. The time of blood collection should be documented in the eCRF.

10.8.5 Electrocardiogram

A standard 12-lead ECG will be obtained at the various pre- and posttreatment time points described in the Schedule of Assessments in Table 2. A 12-lead ECG will be recorded after 5 minutes of rest in a supine position. Heart rate and RR, PR, QRS, and QT intervals will be determined. All ECG recordings will be reviewed on an ongoing basis at the investigational site. The investigator will evaluate the clinical significance of each value outside the reference ranges according to the nature and degree of the observed abnormality. Any new abnormal values considered to be clinically significant should be reported as AEs.

10.9 Other Variables

10.9.1 Demographic Data

Demographic variables to be recorded will include age, gender, race, ethnicity, body height, and body weight. Weight and height should be measured while the patient is without shoes, but dressed.

10.9.2 Relevant Medical History and Current Medical Conditions

Relevant medical history and current medical conditions will be recorded until the start of the study drug administration.

The medical history of NHL should be documented in detail. This should include the date of first diagnosis, details on NHL subtype, previous treatments, and best response and duration of response to these treatments. Any previous therapy (eg, chemotherapy, immunotherapy, or radiation therapy) for the NHL-specific therapy should be recorded in the eCRF.

Also, examinations leading to the diagnosis of the latest progression of NHL should be documented in the patient's source documents. This may include, for example, results of laboratory examinations, imaging results, or clinical symptoms related to the NHL. The baseline assessment of the lymphoma should include a staging.

10.9.3 Prior and Concomitant Medication and Examinations

All respective treatments given during the treatment period until the first follow-up visit should be recorded in the eCRF as concomitant medication. 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.

Further examinations that constitute standard measures and are not covered by the protocol are left to the discretion of the investigator. However, such examinations performed during the study should be documented in the patient's source documents as well.

10.9.4 Immune Cells

For evaluation of the status of the immune system, B-, T- and NK cells in peripheral blood will be measured frequently throughout the study (exploratory assay) on sites selected for this assay by the sponsor. The absolute and percentage changes from baseline will be evaluated.

CD16 expression on NK cells in peripheral blood will be evaluated at baseline (exploratory assay).

10.9.5 Immunogenicity

Number and proportion of patients who develop anti-MOR00208 antibodies will be summarized. In addition, summarization of a semiquantitative antibody assessment will be based on anti-MOR00208 antibody titres of confirmed positive samples.

10.9.6 B Cells

CD19 expression on malignant B cells in bone marrow and/or tumour aspirate (if malignant lymph node is easily accessible) will be evaluated at baseline (exploratory assay). The CD19 expression at baseline will be correlated with safety and response. Tumor and/or lymph node aspirates will be evaluated centrally. Biopsies (eg, trephine) to evaluate histology will be done locally.

If a tumour biopsy is available at screening, cytogenetics from malignant cells should be obtained if no historical data are available. In case bone marrow is affected, cytogenetics can be obtained from these samples.

10.9.7 Genotyping

A mucosal cheek swab will be used for DNA analysis of FcγRIIa and FcγRIIIa polymorphism. The evaluation will be performed at a specified laboratory.

Genotyping is optional, it will be only performed if the patient agrees. A patient can participate in the study regardless of consent to undergo genotyping.

11 SAFETY MONITORING

The patients will be closely observed and questioned for any kind of AE during the study procedures and at follow-up appointments throughout the study period with nonleading questioning (eg, "How do you feel?"). AEs also may be detected when they are volunteered by the patient during or between study visits or through physical examination, laboratory tests, or other assessments.

Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel who are trained in the acute management of infusion-related reactions, cytokine release syndrome, anaphylaxis, and other emergencies and who have access to appropriate clinical supplies must be immediately available from start of infusion until no less than 30 minutes after dosing.

All AEs should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an AE is detected, it should be followed up, and an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

11.1 Adverse Event and Serious Adverse Event Recording and Reporting

All AEs (except non-serious AEs for screening failures) that occur after the signing of informed consent and up to 30 days after last drug administration will be recorded in the eCRF and in the patient's medical records, whether or not considered by the investigator to be related to the study drug. Thereafter only AEs assessed as related should be recorded. All AEs should be recorded using acceptable diagnoses, if possible. For screening failure patients the non-serious adverse events will not be recorded in the e-CRF but only in the patient's medical records.

In addition all SAEs will be recorded on the SAE Report Form. Study centres are instructed to report all SAEs and AEs of special interest (ie, infusion-related reactions and allergic reactions to study drug grade 3 or higher, cytokine release syndrome, overdoses) to United Bio Source within 24 hours using the study-specific SAE report form.

Infusion-related reactions and allergic reactions to study drug grade 3 or higher, or cytokine release syndrome, which are AEs of special interest in this study, should be reported along with their respective symptoms (eg, hives, chill, and fever for infusion reaction). Equally, for overdoses the symptoms caused by the overdose should be reported. If an AE has already been reported, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine phosphokinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial infarction was not diagnosed, then each event would be reported as an AE.

All nonserious AEs must be followed up for a final outcome. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for nonserious AEs at the end of a patient's participation in a study. All SAEs must be followed up for a final outcome until resolution or, if resolution becomes unlikely, until stabilization or death. The follow-up for SAEs that are a progression of NHL only until the end of a patient's participation in a study is acceptable. This includes obtaining information on recovery and any sequelae and, in case of a fatal outcome, the cause of death.

Notification of initial or follow-up SAE information (by using the standard SAE form provided by the sponsor) must be sent by email to [redacted] at the following address:

[redacted]

Or via fax to:

[redacted]

For any safety-related or protocol related questions, please contact the [redacted] Medical Monitor (24/7 coverage):

Europe:

Medical Monitor

[redacted]

United States:

Medical Monitor

[redacted]

11.2 Pregnancies

As detailed in the Schedule of Assessments (Table 2) and Section 10.8.4, serum pregnancy testing will be carried out at the Screening, Follow-up, and End of Study visits. During the treatment period of the study, urine pregnancy testing will be performed locally and can be

repeated if required. Any pregnancy that occurs during study participation should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety, each pregnancy of a study patient or a female partner of a study patient must also be reported within 24 hours of learning of its occurrence to [redacted]

[redacted]

Female study patients who become pregnant must be withdrawn from the study.

A newly diagnosed pregnancy in a patient or female partner of a study patient who has received trial medication is not considered an SAE unless it meets any criteria of seriousness or it is suspected that the trial medication interacted with a contraceptive method and led to pregnancy. If the pregnancy results in clinical consequences/complications in mother or child, eg, if the child is born with a birth defect, this should be reported as an SAE of mother or child as applicable.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities or maternal and newborn complications. Every infant has to be followed up for 2 months after delivery.

11.3 Data Monitoring Board

Not applicable.

12 PROTOCOL AMENDMENTS AND OTHER CHANGES IN STUDY CONDUCT

12.1 Protocol Amendments

Any changes to the protocol will be made in the form of an amendment.

12.2 Other Changes in Study Conduct

Changes in the study conduct are not permitted. Any unforeseen changes in the study conduct will be recorded in the clinical study report.

13 DATA HANDLING AND ARCHIVING

13.1 Completing and Signing Case Report Forms

Electronic CRFs will be used in this study. Data will be entered by trained site personnel, with reasons given for any missing data. Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided. The investigator will receive a copy of their eCRF in a readable format after database lock for archiving.

13.2 Clinical Data Management

The contract research organization (CRO) will be responsible for the processing and quality control of the data according to the CRO's SOPs. Data management will be carried out by CRO. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

Details for data validation and edit checks will be described in appropriate data management documents. Queries will be handled via the eCRF system. Data cleaning will continue until all queries are resolved.

Medical coding will use MedDRA for AEs and the WHO-DDE/drug dictionary enhanced for medication.

13.3 Archiving and Filing

All study documentation at the investigator site and sponsor site will be archived in accordance with International Conference on Harmonisation (ICH) E6 GCP and the sponsor's quality standards and SOPs in the relevant current version.

14 STATISTICAL METHODS AND PLANNED ANALYSIS

14.1 Populations for Analysis

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 postbaseline assessment of NHL response will be included as nonresponders.

Safety Population: Consists of all patients who received at least one dose of study drug.

Pharmacokinetic Population: The Pharmacokinetic Population will consist of all patients who have sufficient pharmacokinetic data to characterize the time course of MOR00208 in serum for the first study drug administration.

The Safety Population will be used for safety analysis and to analyze immunogenicity. The ITT Population will be used to analyze immunogenicity and the pharmacodynamic endpoints. Summaries for the analysis of response will be provided for the ITT Population. Pharmacokinetic summaries will be presented for the Pharmacokinetic Population.

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software.

Continuous, quantitative variable summaries will include the number of patients (N) (with nonmissing values), mean, standard deviation, median, minimum, maximum, and first and third quartiles.

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

The last preadministration observation will be used as the baseline value for calculating postadministration changes from baseline. 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 CRO's SOPs.

14.2 Patient Characteristics

A table will be provided with the following information:

- Number of patients enrolled.
- Number of patients included in each analysis population.
- Number of patients withdrawn from the study and the reason for withdrawal.

Demographic information (age, height, weight, and body mass index) will be summarized for the Safety and ITT Populations using descriptive statistics. Gender, ethnicity and race will be summarized by counts and percentages.

Medical histories will be summarized by counts and percentages. Concurrent medications will be recorded and coded using the WHO Drug Dictionary and grouped by different classes, if applicable.

The NHL-specific medical history will be summarized for the duration of disease, number of previous therapies, type of previous therapy, and best response following previous NHL-specific therapy.

14.3 Immunogenicity Analysis

One of the secondary endpoints will be to evaluate the potential immunogenicity of MOR00208 in the Safety Population. This analysis will be based on both absolute (number and percentage of patients who develop anti-MOR00208 antibodies) and semi-quantitative (anti-MOR00208 antibody titer determination of confirmed positive samples) assessments.

The number of patients who develop confirmed anti-MOR00208 antibodies will be summarized descriptively by means, standard deviations and ranges.

14.4 Primary Objective

The primary efficacy endpoint will be ORR as determined by using revised IWG response criteria for malignant lymphoma. 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). The denominator for calculating the rate will be based upon the total number of patients in the ITT population, thus patients without any postbaseline assessment of NHL response will be included as nonresponders. Overall ORR, independent of NHL subtype, will also be summarized; 95% CI for ORR for each subtype and over all subtypes will be summarized.

All efficacy analyses will be provided for the ITT Population.

14.5 Secondary Objectives

The secondary efficacy variables will be analyzed using the ITT Population. For all safety analyses, the Safety Population will be used.

14.5.1 Secondary Efficacy Variables and Analyses

The proportion of patients in each subtype with stable disease (SD) will be summarized after the second cycle.

The DoR will be the time from first meeting of criteria for response (ie CR or PR) to first documentation of relapse or progression.

The TTP is defined as the time from study entry (first dosing) until documented lymphoma progression or death as a result of lymphoma. Patients not experiencing a progression will be censored at the last NHL assessment. Deaths from other causes are censored at the time of death. The data will be summarized using Kaplan-Meier estimates.

Progression-free survival is defined as the time from study entry (first dosing) until lymphoma progression or death as a result of any cause. Patients not experiencing a progression or death will be censored at the last NHL assessment. The data will be summarized using Kaplan-Meier estimates.

14.6 Pharmacokinetic Analysis

Concentration and pharmacokinetic data will be collected and analyzed for this study.

The following pharmacokinetic parameters will be computed based on non-compartmental data analysis and summarized by means, standard deviations and ranges:

C_{max}	Maximum serum concentration observed
t_{max}	Time to maximum serum concentration observed
C_{pd}	Apparent trough serum concentration before dosing
AUC_{0-t}	Area under the concentration curve. The time curve from time zero (0) to the time that the last concentration above the lower limit of quantification (LLQ) is observed.
$AUC_{0-\infty}$	Area under the concentration curve. The time curve from time zero (0) to infinity (∞), where infinity is computed from $AUC_{0-t} + [C_t/\lambda_Z)]$. C_t is calculated from the concentration at the last sampling time at which the sample is above LLQ.
λ_Z	Apparent terminal rate constant calculated from the regression analysis (slope) from the log-transformed measured concentrations on the terminal phase of the time-point concentration curve
$t_{½}$	Apparent terminal half-life calculated from $\ln(2)/\lambda_Z$
CL	Total body clearance calculated for single or multiple doses: dose(s)/$AUC_{0-\infty}$
Vz	Apparent volume of distribution during the terminal phase, calculated from

	dose/($AUC_{0-\infty}$*λ_Z)

$AUC_{0-\infty}$, λ_Z, $t_{½}$, CL and Vz will only be calculated for those patients where a sufficient and meaningful number of serum concentration values are available. More detailed information on the methodology of PK analysis will be supplied in the statistical analysis plan.

14.7 Safety Analysis

14.7.1 Adverse Events

The primary endpoint is the incidence and severity of adverse events (AEs). This endpoint will be determined based on the Safety Population.

Adverse events will be coded according to MedDRA (version 15.1) system organ class (SOC) and preferred term. Incidence of all AEs will be summarized by SOC, preferred term, relationship to treatment, severity and seriousness. Adverse events will be summarized overall and by each NHL subtype.

An AE summary table will be presented showing the incidence and frequency of treatment emergent AEs (TEAEs), SAEs, MOR00208-related TEAEs, MOR00208-related TEAEs by severity/toxicity (according to NCI-CTC toxicity criteria), and infusion reactions. The incidence refers to the number and percentage of patients and the frequency to the number of AEs. Exact 95% confidence intervals for the incidence rates will be included for overall population.

The number and percentage of patients with one or more treatment-emergent AEs will be summarised by NHL subtype and by MedDRA system organ class and preferred term. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity/toxicity, and TEAEs by relationship to study drug.

The sponsor will describe other AEs of special interest (for the definition please see Section 11.1), in addition to those reported as SAEs.

The number and percentage of patients with one or more pretreatment AEs will be summarised by NHL subtype and by system organ class and preferred term.

14.7.2 Clinical Laboratory Evaluations

The analysis of laboratory parameters will be presented as separated into blood parameters (haematology, serum chemistry, endocrinology, coagulation) and urine parameters (urinalysis). All data will be listed.

For haematology and serum chemistry, the laboratory values will be transformed into 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 into SI reference ranges for each laboratory.

Descriptive summaries of actual (absolute) values and change-from-baseline values will be presented for haematology and serum chemistry for the Safety Population.

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 into account

the investigator's assessment of clinical relevance: 'clin. rel., above', 'non-clin. rel., above', 'within', 'non clin. rel., below', 'clin. rel., below'.

The assessment of laboratory variables will be tabulated by time point for each clinical laboratory analyte for the Safety Population (frequency tables). Additionally, for each laboratory parameter, shifts in assessments from baseline to all postadministration time points will be presented (shift tables).

If NCI-CTC grades are available for a clinical laboratory analyte, they will be derived according to NCI CTCAE, Version 4.0, and used to present additional frequency and shift tables based on NCI-CTC grades.

The assessment of categorical urinalysis variables will be tabulated by time point for each urine parameter for the Safety Population (frequency tables). Additionally, for each of these urine parameter shifts in assessments from baseline to all postadministration time points will be presented (shift tables).

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

14.7.3 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.

14.7.4 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs. These summaries will be presented for the Safety Population at 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 (Section 17.2).

14.7.5 Electrocardiograms

Electrocardiogram data will be summarized as change from baseline. The summary ECG assessment (categories: "normal; abnormal clinically significant"; "abnormal not clinically significant") will be tabulated by time point for the Safety Population.

Each abnormal PR (ECG), 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 (Section 17.2).

Summary statistics for all time points will be displayed for QT and both QTc correction methods, side-by-side. The Bazett's corrections method for QTc will be applied as follows:

Bazett's Correction (QTc_b)

$$QTc_b = \frac{QT_{msec}}{\sqrt{RR}}$$

where: Relative Rate: RR = 60/HR

Also, the number and percentage of patients with QTc values above the normal limit (441-480 ms, 481-500 ms, or > 500 ms) and the number and percentage of patients who experienced a change > 30 ms or a change > 60 ms will be presented by time point.

14.8 Biomarkers

Biomarker assessments will include expression levels of CD19 on malignant B cells, FcγRIIa and FcγRIIIa genotyping, CD16 expression on NK cells, and B-, T- and NK cell counts.

In addition, the ADCC capacity of the patient will be assessed.

Due to the exploratory nature of these assays, the sponsor may decide at any point during the study to terminate these assessments, in which case the sites will be informed accordingly.

14.9 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 enrol between 40 to 120 patients, dependent upon patient response in each subtype in Stage 1.

Stage 1: Approximately 40 patients, a similar 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 2 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 2 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.

14.10 Significance Level

No interference testing will be performed in the study. However, 95% CI of the ORR after Stage 2 will be calculated.

14.11 Procedures for Missing, Unused, and Spurious Data

Missing values will not be substituted by estimated values but will be treated as missing in the statistical evaluation. All data from all patients dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

14.12 Rules for Excluding Patients from Analysis

All dosed patients will be included in the analyses unless otherwise specified. The sponsor will make any decisions regarding whether any patients will be excluded from the evaluations when the protocol noncompliance is considered to have a negative impact on the scientific aspects and interpretation of the study results. If the patient has received any MOR00208, all available safety data will be used. The reason(s) for any exclusion will be described in the report.

14.13 Procedures for Reporting Deviations from Original Statistical Plan

Details of the analyses to be performed on data from this study will be provided in a separate SAP. Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final clinical study report.

15 SPECIAL REQUIREMENTS AND PROCEDURES

15.1 Institutional Review

Before starting this study, the protocol (authorized by the sponsor) will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and to the IEC/IRB for evaluation. The protocol will also be signed by the principal investigators before submission to the IEC/IRB and to regulatory authorities where applicable. The study will not start at the concerned study site before the respective IEC/IRB gives written approval or a favourable opinion in accordance with ICH E6 GCP and all applicable regulatory bodies/local health authorities give approval or a favourable opinion as required.

No substantial changes to the final approved (authorized) protocol will be initiated without the IEC's/IRB's prior written approval or favourable opinion and approval by the regulatory bodies/local health authorities of a written amendment, except when necessary to eliminate immediate hazards to the patients or when the change involves only logistics or administration. The sponsor will authorize and the principal investigator(s) will sign the protocol amendment before submission to the IECs/IRBs. Protocol amendments should be submitted to the IEC/IRB without delay. Any significant deviation from the protocol when no approved amendment

exists will be regarded as a protocol noncompliance, and will be addressed as such during the reporting of the study.

15.2 Ethical Considerations

15.2.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be conducted and reported in accordance with the protocol, with ICH E6 GCP, with applicable local regulations, and with the ethical principles laid down in the current version of the Declaration of Helsinki.

15.2.2 Responsibilities of the Investigator and IRB/IEC

The protocol and the proposed patient information/informed consent form must be reviewed and approved by a properly constituted IRB/IEC before study start. A signed and dated statement that the protocol and informed consent form have been approved by the IRB/IEC/Regional Surveillance authority must be given to the sponsor before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his or her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol.

The IRB/IEC must be informed of all substantial subsequent protocol amendments and of reportable suspected unexpected serious adverse reactions (SUSARs) and other unexpected safety issues occurring during the study that are likely to affect the safety of the patients or the conduct of the study. Approval for such changes must be transmitted in writing to the sponsor by the investigator.

The IRB/IEC should be provided with all updates of the IB. Also, written reports should be provided to the IRB/IEC annually or more frequently if requested on any change significantly affecting the conduct of the study and/or increasing risk to the patients. A final report of study outcome, if required, should also be submitted to the IRB/IEC.

15.3 Investigator's Responsibilities

15.3.1 Overall Responsibilities

The investigator is responsible for conducting the study in full accordance with the protocol and the current version of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigational centres participating in this study that do not comply with these standards will be documented, and noncompliant sites should be excluded.

The investigator is accountable for the performance of the study (treatment of the patient and the documentation). If any responsibilities are delegated, the investigator should maintain a list of appropriately qualified persons to whom he or she has delegated significant study-related duties.

A "Delegation of Authority Log" will be filled in and signed by the responsible investigator. In accordance with this authority log, study site staff (eg, subinvestigators, nurses) will be authorized to perform study-related tasks and to enter specific data into the eCRF.

The CRO or designee is responsible for IRB/IEC submission, monitoring, biometry, data management, pharmacovigilance, and part of project management. The relevant submissions to the Competent Authorities are being handled by the sponsor in close cooperation with the CRO.

Most clinical laboratory tests will be done locally. Each investigator will receive detailed written instructions on the laboratory samples to be taken and laboratories to be used.

15.3.2 Patient Informed Consent

The investigator will obtain a freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study that is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

The investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The investigator or delegate should complete the informed consent section of the eCRF for each patient enrolled.

Each patient will be informed that his or her source records may be reviewed by the study monitor, a quality assurance auditor, a health authority inspector (eg, FDA, Paul-Ehrlich-Institut [PEI]), or other individuals in accordance with applicable regulations, and that these persons are bound by confidentiality obligations. The investigator will protect any personal information not related to the study and will assure that these persons are bound by confidentiality obligations.

15.3.3 Direct Access to Source Data/Documents

The monitors, auditors, authorized personnel of the sponsor, health authority inspectors or their agents, and authorized members of IECs/IRBs will be given direct access to source data and documentation medical charts/records, laboratory results, printouts, videotapes, etc) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

15.3.4 Confidentiality Regarding Study Patients

The investigators must assure that the privacy of the patients, including their personal identity and all other personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the sponsor, patients will not be identified by their names but by an identification code (eg, initials and study patient number).

Personal medical information may be scrutinized for the purpose of verifying data recorded in the eCRF. This may be done by the monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential. Should the need arise that the investigator forwards a copy of personal medical information (ie laboratory report) to the sponsor or delegate, then the investigator is responsible for obliterating all patient details revealing their personal identity.

15.3.5 Relevant Protocol Noncompliances

Noncompliances from the protocol should not occur. If noncompliances occur, the investigator should promptly inform the medical monitor or the monitor for nonclinical aspects and the implication of the deviation must be reviewed and discussed. Any noncompliances must be documented, stating the reason and date, the action taken, and the impact on the patient and/or the study. The documentation must be kept in the investigator's study file and the sponsor's file.

Examples of relevant protocol noncompliances that will be addressed (but are not limited to these) are as follows:

- Patients who enter the study even though they did not satisfy the entry criteria
- Patients who develop withdrawal criteria during the study
- Patients who receive the incorrect dose
- Patients who receive an excluded concomitant treatment (eg, another mAb).
- Noncompliance with protocol setting that puts the safety of the patient or the scientific validity of the study at risk

In case of any major protocol noncompliances, the investigator will decide on the further participation of the patient in this study, after having discussed all relevant aspects with the medical monitor. The sponsor may, however, request the exclusion of such a patient from further participation in the study.

A list of all included patients with all deviations from the intended study procedures and other criteria that may affect the patient's validity for statistical analysis will be prepared upon clinical completion of the study. This will then be discussed by a panel consisting of the clinical project manager, a medical expert of the sponsor, the data manager, and the study biometrician. This panel will decide upon the membership of the patient in the patient populations for statistical analysis.

15.4 Study Monitoring

Study monitoring will be performed in accordance with ICH E6 GCP, the CRO's SOPs, the protocol, and applicable local regulations.

15.5 Audit and Inspection

According to ICH E6 GCP, the sponsor or regulatory authorities may audit the investigational sites. The sponsor's Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study. The investigator must accept such audits by sponsor's Quality Assurance Unit and ensure access to source documentation.

The investigator must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP. If informed that a regulatory inspection will take place, the investigator must inform the sponsor without delay.

15.6 Insurance

This study is covered under the sponsor's Liability Insurance Policy covering damage to patients according to applicable legal requirements. A copy of the Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage will be provided to the investigator as required by Regulatory Authorities, IRBs or IECs.

The investigator must inform the patients accordingly and must also point out that the patients are allowed to undergo other medical treatment (except in an emergency) only with the investigator's prior approval or to receive additional medication only with the investigator's prior approval.

15.7 Study Report and Publication Policy

The results of this clinical study will be documented in an integrated clinical study report according to ICH E3 Note for Guidance on Structure and Content of Clinical Study Reports, which will be signed by the authors, sponsor, and coordinating investigator. Reports will also be generated for IEC/IRB review and for regulatory reporting as required.

Any presentation or publication of data from this study will be intended as a joint publication by the investigator(s)/appropriate study centre personnel and appropriate sponsor personnel. Authorship will follow the ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals and will be defined prior to the first publication. All other investigators, coinvestigators, and study coordinators will be listed in an acknowledgement.

For multicenter studies, it is mandatory that the first publication be based on data from all centres, and that data are analyzed and submitted as stipulated in the protocol by a statistician assigned by the sponsor. The authors have the final responsibility for the decision to submit their manuscript and shall be given full access to the data resulting from the study. The coordinating investigator and/or authors shall coordinate any intended publication of study results with the sponsor, to enable the sponsor to ensure that results are presented in a responsible and coherent manner. The sponsor reserves the right to review all manuscripts and abstracts before their submission for publication or presentation. This is not intended to restrict or hinder publication or presentation, but is to allow the sponsor to protect the confidentiality of information and to provide comments that may not yet available to the investigator. In the rare event that such publication would affect the patentability of any invention to which the sponsor has rights, the sponsor has the right to request an additional delay to the proposed publication of no more than 90 days so as to allow the sponsor to protect its intellectual property rights.

The results of the study may be used by MorphoSys AG for the purposes of national and international registration, publication, and information for medical professionals. If necessary, the authorities will be notified of the investigators' names, addresses, qualifications, and extent of involvement.

16 REFERENCES

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17 APPENDICES

17.1 Information on Investigational and Registered Products

The Investigator's Brochure for MOR00208 will be supplied to the study sites.

17.2 Normal Limits for Vital Signs, Weight, Height, and Electrocardiogram Intervals

Table 5 Criteria For Normal Limits For Vital Signs, Height, And Weight

Body Weight, Body Height, Vital Signs Parameter	Normal Limits	
	Low	High
Systolic BP (mm Hg)	85	139
Diastolic BP (mm Hg)	60	89
Heart rate (bpm)	60	100
Respiration rate (rpm)	12	22
Body temperature (°C)	36.4°C	37.7°C
Oxygen saturation (%)	93	100
Body weight (kg)[a]	41	113
Body mass index (kg/m²)[b]	18.5	24.9

[a] Changes in body weight are evaluated by the investigator (without taking height into account), because body mass index is not collected on the electronic case report form.

[b] Body mass index is calculated and analyzed retrospectively by the sponsor, at which time height is taken into account.

Table 6 Criteria For Normal Limits For Electrocardiograms

ECG Variable	Normal Limits (msec)	
	Low	High
PR interval	120	200
QRS interval	50	100
RR interval	600	1000
QT interval (gender not specified)	-	≤440
QTc interval[a] (gender not specified)	-	≤440

[a] No lower boundary will be set for QTc.

17.3 New York Heart Association Functional Classification

Table 7 Criteria For NYHA Functional Classification

NYHA Class	Criteria
I	No symptoms and no limitation in ordinary physical activity; shortness of breath when walking, stair climbing, etc.
II	Mild symptoms (mild shortness of breath and/or angina pain) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (eg, walking short distances, approximately > 20 – 100 meters); comfortable only at rest
IV	Severe limitations; patient experiences symptoms even while at rest, mostly bedbound

Abbreviation: NYHA, New York Heart Association

17.4 Response Criteria

The response criteria in this study are those defined in the table below. All of them are based on the International Working Group Response Criteria (2007).

Table 8 Response Criteria

Response	Definition	Nodal masses	Spleen, liver	Bone marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variable FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohisto-chemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size on CT a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b) Variable FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variable FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease

17.5 ECOG Performance Status

Table 9 ECOG Performance Status Grades

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Published in *Am J Clin Oncol:* Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5:649-655, 1982.

Credit: the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

17.6 Equivalent Doses for Corticosteroids

Name (INN)	Example	Equivalent doses for 80 – 100- 120 mg methylprednisolone	Potency
Hydrocortisone	Hydrocortone®	400 – 500- 600 mg	1
Prednisone	Decortin®	100 - 125 – 150 mg	4
Prednisolone	Decortin® H	100 - 125 – 150 mg	4
Methylprednisolone	Urbason®	80 – 100 – 120 mg	5
Dexamethasone	Fortecortin®	14- 16 - 20 mg	30

17.7 List of Indolent B-cell Lymphomas

Below are listed the indolent lymphomas that can be included in the indolent lymphoma subtype. Please note that for FL, gradings 1 and 2 belong to the group of indolent lymphomas but will be included in their particular subtype.

a. Chronic lymphocytic leukemia/small lymphocytic lymphoma
b. Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia)
c. Extranodal marginal zone B-cell lymphoma (MALT lymphoma)
d. Nodal marginal zone B-cell lymphoma (monocytoid B-cell lymphoma)
e. Splenic marginal zone lymphoma (splenic lymphoma with villous lymphocytes)
f. Hairy cell leukemia