PROTOCOL SYNOPSIS

Title of Study	A Phase II, Single-Arm, Open-Label, Multicentre Study to Evaluate the Safety and Efficacy of Lenalidomide Combined with MOR00208 in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL)
Investigational Drugs	MOR00208 (an Fc-engineered, humanised, monoclonal antibody targeting the B-cell surface antigen CD19) Lenalidomide (LEN: Revlimid®)
Protocol Number	MOR208C203
IND Number	114,856
EudraCT Number	**2014-004688-19**
Sponsor and CRO	**Sponsor:** MorphoSys AG Lena-Christ-Strasse 48 D-82152 Martinsried/Planegg Germany **Clinical Research Organisation (CRO):** inVentiv Health Clinical LLC 504 Carnegie Center Princeton, NJ 08540 USA
Study Phase	Phase II
Background/Study Purpose and Rationale	Diffuse large B-cell lymphoma (DLBCL) represents approximately 40% of all non-Hodgkin lymphomas (NHLs), with a rate of incidence which continues to increase and a median age range at diagnosis of 55–60 years. The addition of the CD20 monoclonal antibody (mAb) rituximab (RTX) to standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy (R-CHOP) has been shown to improve the outcome compared with CHOP alone in untreated patients with DLBCL. Despite advances in first-line treatment, 30–40% of such patients relapse. Patients progressing or relapsing after first-line treatment may be offered salvage chemotherapy followed by high-dose chemotherapy (HDC) with, if the disease is still chemosensitive, autologous stem-cell transplantation (ASCT). Several second-line combination therapies are used with variable success. However, a substantial percentage of patients will either fail to respond to salvage therapy and subsequently not be eligible for ASCT, or will progress after ASCT. Additionally, the use of HDC with stem cell support in patients with R-R DLBCL may not be appropriate for those with comorbidities or advanced

	age, restricting the benefit of this aggressive approach to a relatively small fraction of patients. R-CHOP-like regimens have become standard first-line treatment in patients with DLBCL. Those patients who have received prior RTX are less likely to respond to RTX-containing salvage treatment and therefore effective and well-tolerated new treatment modalities with manageable toxicities are needed to ameliorate prognosis in R-R DLBCL. Rational combinations of effective compounds have been shown to be active and often lead to better clinical outcomes in DLBCL than single-agent therapy. The B-lymphocyte lineage specific surface antigen CD19 is the earliest and most broadly expressed of the selective B-cell markers, and is highly expressed in the tumour cells of most patients with B-cell NHL. Because of this expression pattern, a CD19 antibody may have clinical utility as a new therapeutic approach to NHL treatment. MOR00208 is an Fc-engineered, humanised, mAb with significantly enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP) and direct cytotoxic effects (apoptosis) compared with the parental murine antibody. Monotherapy with MOR00208 has shown preliminary signs of clinical efficacy and acceptable toxicity in a phase I study in R-R chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) and a phase IIa study in R-R NHL. Additionally, MOR00208 is currently being studied as single-agent therapy in a phase IIa study in R-R B-cell acute lymphoblastic leukaemia (B-ALL). Lenalidomide (LEN) belongs to a class of immunomodulating agents (immunomodulatory drugs [IMiDs®]), which have demonstrated direct tumouricidal and immunomodulatory actions. LEN has both antiproliferative and antiangiogenic activities, modulating the tumour cell microenvironment and stimulating the activity of effector cells such as cytotoxic T-cells and natural killer (NK) cells. LEN demonstrated manageable toxicity when administered as monotherapy and in combination, as well as a synergistic effect with RTX, administered alone or as a part of an immunochemotherapeutic regimen. Preclinical data suggest that the combination of LEN with MOR00208 may increase NK cell-mediated ADCC, making this combination of interest for further study in patients with R-R DLBCL. This patient population is particularly relevant for the current study as they can usually achieve a rapid and complete lymphoma regression with second-line therapy, but invariably experience relapse, which is the principalunfavourable prognostic factor. Combining two agents with probable synergistic mechanisms of action and acceptable safety profiles could potentially contribute to significantly prolonging time to progression, and possibly overall survival (OS), in this patient population. Therefore, this open label, single-arm, prospective phase II study is designed to confirm the activity of MOR00208 combined

	with LEN in patients with R-R DLBCL who have had at least one, but no more than two prior systemic regimens and who are not eligible for HDC with ASCT at the time of study entry.
Study Objectives (Key Primary and Secondary)	**PRIMARY OBJECTIVE:** To determine the activity of a combination of LEN with MOR00208 in terms of objective response rate (ORR = complete response [CR] + partial response [PR]) in adult patients with R-R DLBCL. **SECONDARY OBJECTIVES:** 1. To determine the disease control rate (DCR = CR + PR + stable disease [SD]) 2. To determine the duration of response (DoR) 3. To determine the activity of a combination of LEN with MOR00208 in terms of progression-free survival (PFS) 4. To determine the overall survival (OS) 5. To determine time to progression (TTP) 6. To determine the time to next treatment (TTNT) 7. To determine the safety of LEN combined with MOR00208 assessed according to the frequency and severity of adverse events (AEs) 8. To assess the potential immunogenicity of MOR00208 9. To assess the pharmacokinetics (PK) of MOR00208 10. To make a preliminary evaluation of ORR, DCR, DoR, PFS, OS, TTP and TTNT in patients treated with a combination of LEN plus MOR00208 in cohorts with a “low risk”, “low-intermediate”, “high-intermediate” and “high” International Prognostic Index (IPI) 11. To compare each patient’s TTP on LEN plus MOR00208 with the TTP of their most recent prior therapy 12. To correlate efficacy parameters with certain biomarkers (e.g. baseline tumour CD19 expression level, peripheral NK cell count, constitutional FcγRIIIa and FcγRIIa polymorphism status).
Study Endpoints (Key Primary and Secondary)	**PRIMARY ENDPOINT:** 1. ORR (CR + PR) **SECONDARY ENDPOINTS:** 2. DCR, DoR, PFS, OS, TTP and TTNT 3. Incidence and severity of AEs 4. Determination and characterisation of a potential anti-MOR00208 antibody formation 5. PK analysis of MOR00208 6. Absolute and percentage change from baseline in measurements of B-, T- and NK cell populations 7. Analysis of exploratory and diagnostic biomarkers (e.g. CD19, CD20, BCL2, and BCL6 expression, CD16 expression on NK cells, ADCC capacity, and gene expression profiling

	for cell of origin subtyping) are planned to be investigated during the course of the study. Evaluation of AEs and ORR stratified by FcγRIIIa and FcγRIIa polymorphism.
Design and Methodology/Patient Population	This is a single-arm, multicentre, open-label, phase II study of LEN combined with MOR00208 in adult patients with DLBCL who have relapsed after or are refractory to at least one, but no more than two prior systemic therapies and who are not candidates for HDC and ASCT, and are thus considered to have exhausted their therapeutic options for demonstrable clinical benefit. One prior therapy line must have included a CD20-targeted therapy (e.g. RTX). Histological confirmation of the diagnosis of DLBCL will be performed by a central pathologist. Objective disease response assessments will be made by central radiology reviewers. Details will be provided in an imaging charter, outlining functions and processes. This study will consist of two parts, which will be performed sequentially, where the first part (safety run-in) will conclude with an evaluation of the safety data after six patients have completed the first cycle of treatment. The second part will commence pending the outcome of this evaluation. Approximately 80 patients will be enrolled in the study.
Key Inclusion /Exclusion Criteria	**INCLUSION CRITERIA:** **<u>Diagnosis/study population</u>** 1. Age 18–80 years old 2. Histologically confirmed diagnosis of DLBCL (not otherwise specified [NOS]) according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification 3. Fresh tumour tissue for central pathology review and correlative studies must be provided as an adjunct to participation in this study. The only exception is the availability of paraffin embedded tumour tissue acquired ≤3 years prior to screening for this protocol 4. Patients must have: a) relapsed and/or refractory disease with documented evidence of disease progression after the most recently administered anti-lymphoma regimen (according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma; Cheson et al., 2007) b) at least one bidimensionally measurable disease site. The lesion must have a greatest transverse diameter of ≥1.5 cm and greatest perpendicular diameter of ≥1.0 cm at baseline c) received at least one, but no more than two previous systemic regimens for the treatment of DLBCL and one therapy line must have included a CD20-targeted therapy (e.g. RTX)

	d) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 5. Patients not considered in the opinion of the investigator eligible, or patients unwilling to undergo intensive salvage therapy including ASCT because of, but not limited to, advanced age, comorbidities, impossibility or, refusal to perform ASCT. The documentation for reason for ineligibility must be provided in patient's source data. **Laboratory values** 6. Patients must meet the following laboratory criteria at screening: a) absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy) b) platelet count $\geq 90 \times 10^9$/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy) c) total serum bilirubin $\leq 2.5 \times$ upper limit of normal (ULN) or $\leq 3 \times$ ULN in cases of documented liver involvement d) alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AP) $\leq 3 \times$ ULN or $< 5 \times$ ULN in cases of documented liver involvement e) serum creatinine clearance must be ≥ 60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (Cockroft and Gault, 1976) 7. Females of childbearing potential (FCBP) must: a) not be pregnant as confirmed by a negative serum pregnancy test at screening and a medically supervised urine pregnancy test prior to starting study therapy b) refrain from breastfeeding and donating blood or oocytes during the course of the study and for 3 months after the last dose of study medication c) agree to ongoing pregnancy testing during the course of the study, and after study therapy has ended. This applies even if the patient practices complete and continued sexual abstinence d) commit to continued abstinence from heterosexual intercourse if it is in accordance with her lifestyle or agree to use and be able to comply with the use of double-barrier contraception without interruption during the study and for 3 months after the last dose of study medication 8. Males must use an effective barrier method of contraception without interruption, refrain from donating blood or sperm during the study participation and for 3 months after the last dose of study medication if the patient is sexually active with a FCBP 9. In the opinion of the investigator the patients must:

	a) be able and willing to receive adequate prophylaxis and/or therapy for thromboembolic events b) be able to understand, give written informed consent, and comply with all study-related procedures, medication use, and evaluations c) not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative d) be able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and give written acknowledgement of this. **EXCLUSION CRITERIA:** **<u>Exclusionary Diagnosis</u>** 1. Patients who have: a) NHL other than classical histology DLBCL e.g. including patients with DLBCL transformed from indolent lymphomas, primary mediastinal (thymic) large B-cell lymphoma (PMBL) and active central nervous system (CNS) lymphoma b) primary refractory DLBCL or relapsed within period ≤3 months of prior CD20-targeted therapy (e.g. RTX) c) a history of "double/triple hit" DLBCL characterised by simultaneous detection of *MYC* with *BCL2* and/or *BCL6* translocation(s) defined by fluorescence *in situ* hybridisation. *MYC*, *BCL2*, *BCL6* testing prior to study enrolment is not required **<u>Exclusionary Previous and current treatment</u>** 2. Patients who have, within 14 days prior to Day 1 dosing: a) not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma-specific therapy b) undergone major surgery or suffered from significant traumatic injury c) received live vaccines. d) required parenteral antimicrobial therapy for active, intercurrent infections 3. Patients who: a) have, in the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies b) were previously treated with CD19-targeted therapy or IMiDs® (e.g. thalidomide, LEN) c) have a history of previous severe allergic reactions to compounds of similar biological or chemical composition to MOR00208, IMiDs® and/or the excipients contained in the study drug formulations

	d) have undergone ASCT within the period ≤ 3 months prior to signing the informed consent form. Patients who have a more distant history of ASCT must exhibit full haematological recovery before enrolment into the study e) have undergone previous allogenic stem cell transplantation f) have a history of deep venous thrombosis/embolism, threatening thromboembolism or known thrombophilia or are at a high risk for a thromboembolic event in the opinion of the investigator and who are not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period g) concurrently use other anticancer or experimental treatments **<u>Exclusionary Patient's medical history</u>** 4. Prior history of malignancies other than DLBCL, unless the patient has been free of the disease for ≥3 years prior to screening. Exceptions to the ≥3 year time limit include a history of the following: a) basal cell carcinoma of the skin b) squamous cell carcinoma of the skin c) carcinoma *in situ* of the cervix d) carcinoma *in situ* of the breast e) carcinoma *in situ* of the bladder f) incidental histological finding of prostate cancer (Tumour/Nodes/Metastasis [TNM] stage of T1a or T1b) 5. Patients with: a) positive hepatitis B and/or C serology. b) known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV) c) history or evidence of clinically significant cardiovascular, CNS and/or other systemic disease that would in the investigator's opinion preclude participation in the study or compromise the patient's ability to give informed consent.
Investigational Drug(s) (Name, Description)	MOR00208 and LEN (Revlimid®)
Dose, Route of Administration, Treatment Regimen	Treatment consisting of **LEN** and **MOR00208** will be in 28-day cycles at specified dose levels, as scheduled, until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. **MOR00208 dose:** 12 mg/kg For the first six months of the study, each cycle will consist of a MOR00208 infusion on Day 1, Day 8, Day 15 and Day 22 of the cycle. Additionally a loading dose will be administered on Day 4 of Cycle 1. Thereafter MOR00208 will be administered on a bi-weekly (every fourteen days) basis with infusions on Days 1 and 15 of each 28-day cycle.

	LEN: Patients will self-administer a starting dose of 25 mg oral LEN daily on Days 1–21 of each cycle. Treatment with LEN may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. Detailed dose modification guidelines to manage haematologic and/or other toxicities are provided in the relevant sections of the protocol. **LEN** can be given for up to a total of 12 months and **MOR00208** for up to a total of 24 months. It is up to the investigator to decide according to the individual risk/benefit ratio if the patient should continue MOR00208 therapy in the case of 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 of 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 200 mg of MOR00208 in 5 ml of reconstituted solution. MOR00208 will be diluted into a 250 mL infusion bag containing 0.9% (w/v) sodium chloride for injection. **LEN** will be sourced from commercially available drug suppliers (Revlimid®).
Efficacy Assessments	Disease response assessments will be made according to the revised response criteria for malignant lymphoma based on the guidelines of the IWG, as reported by Cheson et al. (2007) and will be based on a central review of the radiological disease assessments. Efficacy will be evaluated in terms of ORR, DCR, DoR, PFS, OS, TTP and TTNT.
Safety Assessments	The safety and tolerability of study drug treatments will be evaluated by means of AE reports (number and severity), performance status, physical examinations, 12-lead resting electrocardiograms (ECGs), and laboratory safety evaluations. Laboratory and AE toxicities will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
Pharmacokinetics	The PK of MOR00208 will be investigated during the course of the study.
Biomarker Assessments	Blood and tumour specimens for the analysis of exploratory biomarkers will be collected throughout the study and will be characterised for markers which are important in the mechanism of action of, or could predict response to, the study drugs. Exploratory and diagnostic biomarkers (e.g. CD19, CD20, BCL2, BCL6), CD16 expression on NK cells, B-, T- and NK cell counts, ADCC capacity and gene expression

	profiling for cell of origin subtyping are planned to be investigated during the course of the study.
Statistical Methods and Data Analysis	The primary purpose of this study is to evaluate the clinical efficacy of oral LEN combined with MOR00208 administered by IV infusion in patients with R-R DLBCL. No formal statistical hypothesis testing will be performed. For the sample size determination it is assumed that the combination treatment could improve the ORR from a value of 20% (corresponding to monotherapy) to one of 35% which is achievable under combination treatment. Sample size estimation using a one-sample exact binomial test with a two-sided significance level of 5% and a power of 85% delivers a sample size of 73 patients. According to this scenario an observed ORR of 32% will lead to a statistically significant study outcome. Allowing for a drop-out rate of 10% the total required sample size comes to approximately 80 patients. All data will be summarised using appropriate statistics (counts/ percentages for discrete variables, mean, median, standard deviation, minimum, maximum, number of valid observations for continuous variables) for tabulation purposes. For specific variables, p-values and 95% confidence limits will be presented. Overall baseline and demographic data will be summarised using appropriate statistics. Patient disposition and status at the end of the study will be tabulated presenting number of patients and frequencies. General medical history and history of DLBCL, including prior cancer therapies, will be tabulated using coding systems (e.g. MedDRA, WHO-DDE), where appropriate. **PRIMARY OBJECTIVE:** **Primary efficacy endpoint: Objective response rate (ORR)** The ORR will be the percentage of patients who have met the ORR definition up until progression based on the central radiological evaluations. The denominator for calculating the rate will be based upon the total number of patients in the full analysis set (FAS) population, thus patients without any post-baseline assessment of response will be included as non-responders. Number of patients being a responder and the respective rates, as well as 95% confidence limits, will be presented. **SECONDARY OBJECTIVES:** **Disease control rate (DCR)** The DCR will be evaluated like ORR. **Duration of response (DoR) and Time to next treatment (TTNT)** Response duration by the local assessment and by the central radiological assessments will be tabulated with descriptive statistics. Time to next treatment will be descriptively analysed.

	Progression-free survival (PFS), overall survival (OS) and time to progression (TTP) Kaplan-Meier methodology will be used to evaluate median survival, presenting corresponding statistical parameters and 95% confidence limits and Kaplan-Meier survival curves. **Incidence and severity of adverse events** MedDRA coded adverse events will be used to show the incidence of all AEs by specific organ class (SOC), preferred term (PT), relationship to treatment, severity and seriousness. An AE summary table will present the number of events, number of patients and the percentage of patients having treatment-emergent AEs (TEAEs), serious AEs, adverse drug reactions, and TEAEs that led to study discontinuation. AE frequency tables will display event and patient counts/ frequency by MedDRA SOC and PT for each treatment arm, distinguishing also by severity/toxicity, relationship to study drug, seriousness and outcome. **Immunogenicity** The absolute number and percentage of patients who develop anti-MOR00208 antibodies, and the results of semi-quantitative anti-MOR00208 antibody titre determinations of confirmed positive samples assessments, will be tabulated. **Pharmacokinetics** Appropriate PK parameters for MOR00208 will be computed based on non-compartmental data analysis and summarised using descriptive statistics. Individual concentrations and mean concentrations will be visualised by figures. **Biomarker** Blood and protein biomarkers which are important in the mechanism of action of, or could predict response to, the study drugs will be descriptively tabulated, presenting absolute and change to baseline values, if applicable. **SAFETY:** Extent of exposure, clinical laboratory assessments, vital sign measurements, physical examination and results of ECGs will be summarised with appropriate descriptive statistics. Concomitant medications taken starting on the day of the screening visit through the follow-up period will be coded using appropriate coding systems and tabulated by each code system.