1 SYNOPSIS

Title of Study	A Phase I/IIa, Open-Label, Multicentre, Dose-Escalation Study to Evaluate the Safety and Preliminary Efficacy of the Human Anti-CD38 Antibody MOR03087 as Monotherapy and in Combination with Standard Therapy in Subjects with Relapsed/Refractory Multiple Myeloma
Investigational Drug	MOR03087, a fully human monoclonal antibody targeting the CD38 membrane protein
Protocol Number	MOR202C101
EudraCT Number	2009-015942-50
Sponsor and CRO	**Sponsor:** MorphoSys AG Lena-Christ-Strasse 48 D-82152 Martinsried/Planegg GERMANY **Clinical Research Organization (CRO):** Premier Research Germany Ltd. Birkenweg 14 D-64295 Darmstadt GERMANY
Study Phase	Phase I/IIa
Background	Despite the recent approval of the novel therapeutic agents bortezomib and lenalidomide for relapsed disease, multiple myeloma remains an incurable malignancy. One of the most strongly and uniformly expressed antigens on malignant plasma cells is CD38, which is found in all multiple myelomas. Because of this expression pattern, an anti-CD38 antibody may have clinical utility as a new therapeutic approach to multiple myeloma treatment. MOR03087 is a fully human monoclonal antibody directed to CD38 that has demonstrated in vitro and in vivo efficacy in preclinical multiple myeloma models. Relapsed and refractory myeloma, associated with median survival rates of less than 30 months in most studies and progressively lower response rates to therapy, remains an unmet medical need. Further improvements in overall response, duration of clinical benefit, progression-free survival (PFS), and overall survival (OS) are desirable, and even minimal responses to therapy may be associated with symptomatic benefit. Novel synergistic combinations of anti-myeloma drugs with different modes of action may be warranted to overcome drug resistance and improve patient outcome. In preclinical studies, the combination of bortezomib or lenalidomide with MOR03087 demonstrated increased cytotoxicity compared with either agent alone in multiple myeloma cell lines, supporting the combination of these therapies clinically.
Study Purpose/Rationale	The purpose of this study is to characterise the safety profile and preliminary efficacy of MOR03087 and establish the maximum tolerated dose (MTD) or recommended dose of MOR03087 as monotherapy and in combination with standard therapy in adult subjects with relapsed or refractory multiple myeloma.

Study Objectives (Key Primary and Secondary)	**PRIMARY OBJECTIVES:** 1. To assess the safety profile and to establish the MTD or recommended dose of MOR03087 in subjects with relapsed or refractory multiple myeloma: a. As monotherapy b. In combination with bortezomib c. In combination with lenalidomide 2. To assess the immunogenicity of MOR03087 **SECONDARY OBJECTIVES:** 1. To evaluate the pharmacokinetics and pharmacodynamics of MOR03087 in subjects with relapsed or refractory multiple myeloma: a. As monotherapy b. In combination with bortezomib c. In combination with lenalidomide 2. To evaluate the preliminary efficacy of MOR03087 in subjects with relapsed or refractory multiple myeloma: a. As monotherapy b. In combination with bortezomib c. In combination with lenalidomide
Study Endpoints (Key Primary and Secondary)	**PRIMARY ENDPOINTS:** 1. Determination of the MTD and/or recommended dose of MOR03087 2. Incidence and severity of adverse events (AEs) 3. Immunogenicity of MOR03087 based on both absolute (number and percentage of subjects who develop anti-MOR03087 antibodies) and semi-quantitative (anti-MOR03087 antibody titer determination of confirmed positive samples) assessments **SECONDARY ENDPOINTS:** 1. Pharmacokinetics (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λ_Z, $t_{½}$, CL, Vz) 2. Absolute and percent change from baseline in measurements of B, T, and natural killer (NK) cell populations 3. Overall response rate (complete response [CR] + partial response [PR] + minimal response [MR]), further tumour response rates (CR, PR, MR, very good partial response [VGPR]), and stable disease (SD) rate 4. Duration of response, time to progression (TTP), and PFS 5. Absolute and percent change from baseline in serum and urine M-protein levels 6. Absolute and percent change from baseline in serum free light chain (FLC) levels and serum FLC ratio 7. Absolute changes from baseline in laboratory parameters (serum chemistry, haematology, urinalysis) and clinically relevant abnormal values 8. Absolute change from baseline in overall quality of life scores 9. Change in cytokines from baseline

Design and Methodology	This is an open-label, multicentre, dose-escalation study designed to characterise the safety profile and preliminary efficacy of MOR03087 in adult subjects with relapsed or refractory multiple myeloma as monotherapy and in combination with standard therapy. This study will consist of 2 parts: **Part 1** The first part of the trial is a Phase I dose escalation to establish the recommended dose/MTD of MOR03087 and evaluate the confirmatory safety of the recommended dose/MTD in an open-label Phase IIa monotherapy arm. The dose level proposed for the Phase I part of the study range from 0.01 mg/kg to 8.0 mg/kg administered by IV infusion. A standard 3 + 3 dose escalation design will be used. **Part 2** The second part of the study will evaluate the recommended dose/MTD of MOR03087 in combination with both bortezomib and lenalidomide in 2 open-label dose escalation arms. Further subjects will be enrolled at the established recommended dose/MTD of the combination regimen to confirm safety.
Population	Adult subjects with relapsed or refractory multiple myeloma (after at least 2 prior regimens).
Key Inclusion / Exclusion Criteria	**INCLUSION CRITERIA:** 1. Male or female subjects ≥ 18 years of age 2. Relapsed or refractory multiple myeloma defined as: • Failure of at least 2 previous therapies including an immunomodulatory agent and a proteasome inhibitor (unless the patients were not eligible or refused to receive those treatments) 3. Presence of serum M-protein ≥ 1 g per 100 mL (≥ 10 g/L) and/or urine M-protein ≥ 200 mg per 24-hour period and/or serum FLCs ≥ 10 mg per 100 mL (≥ 100 mg/L) combined with an abnormal ratio of lambda and kappa chains 4. Life expectancy of > 3 months 5. Karnofsky performance status ≥ 60% 6. Absolute neutrophil count (ANC) ≥ 1.0 (1,000/mm^3) and platelets ≥ 80×10^9/L without previous transfusion within the last 4 weeks before first study drug administration 7. Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault equation) 8. Total bilirubin ≤ 2 × ULN 9. Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN 10. Hemoglobin ≥ 8 g/dL 11. If a female of childbearing potential, confirmation of a negative pregnancy test before enrollment and use of double-barrier contraception, oral contraceptive plus barrier contraceptive, or confirmation of having undergone clinically documented total hysterectomy and/or oophorectomy, tubal ligation 12. If a male, use of an effective barrier method of contraception during the study and for 3 months after the last dose if sexually active with a female of childbearing potential

	13. Ability to comply with all study-related procedures, medication use, and evaluations 14. Ability to understand and give written informed consent, and comply with the protocol **EXCLUSION CRITERIA:** 1. Primary refractory multiple myeloma 2. Previous treatment with cytotoxic chemotherapy or large-field radiotherapy or other myeloma-specific therapy within 28 days prior to the screening visit (radiation to a single site as concurrent therapy is allowed) 3. Treatment with a systemic investigational agent within 28 days prior to the screening visit 4. Solitary plasmacytoma or plasma cell leukaemia 5. Previous allogenic stem cell transplantation 6. Known or suspected hypersensitivity to the excipients contained in the study drug formulation 7. Significant uncontrolled cardiovascular disease or cardiac insufficiency (New York Heart Association [NYHA] classes III-IV) 8. Prior therapy with other monoclonal antibodies 9. Clinical or laboratory evidence of active hepatitis B (positive HBsAg with negative HBsAb) or hepatitis C (positive HCV antibody and detectable HCV RNA with ALT above the normal range) 10. History of positive HIV test result (ELISA or Western blot) 11. History of significant cerebrovascular disease or sensory or motor neuropathy of toxicity grade 3 or higher (per National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], version 4.0) 12. Presence of diarrhoea of grade 2 or higher (per NCI CTCAE, version 4.0) 13. Any active systemic infection 14. Any antibiotic therapy due to infections 2 weeks prior to first study drug administration 15. Current treatment with immunosuppressive agents other than prescribed corticosteroids (not more than 10 mg prednisone equivalent) 16. Major surgery $\leq$ 4 weeks prior to first study drug administration or ongoing side effects of such surgery 17. Systemic diseases (cardiovascular, renal, hepatic, etc) that would prevent study treatment 18. Multiple myeloma with central nervous system (CNS) involvement. 19. Active treatment/chemotherapy for another primary malignancy within the past 3 years (except for non-melanoma skin cancer, prostate cancer not requiring treatment, and cervical carcinoma in situ) 20. Pregnancy or breastfeeding in women and women of childbearing potential not using an acceptable method of birth control 21. History of non-compliance to medical regimens or subjects who are considered potentially unreliable and/or not cooperative

	ADDITIONAL EXCLUSION CRITERIA FOR THE COMBINATION ARM OF MOR03087 AND BORTEZOMIB: 1. Known or suspected hypersensitivity to bortezomib, boron, or any of the excipients 2. During previous treatment with bortezomib, refractoriness or relapse of multiple myeloma within 60 days after end of treatment 3. Peripheral neuropathy > grade 2 4. Acute diffuse infiltrative pulmonary (eg, interstitial pneumonia, acute respiratory distress syndrome) or pericardial disease **ADDITIONAL INCLUSION AND EXCLUSION CRITERIA FOR THE COMBINATION ARM OF MOR03087 AND LENALIDOMIDE:** **Inclusion Criteria** 1. Ability to understand the reason for and understand the special conditions of the pregnancy prevention and give written acknowledgement of these 2. Ability and willingness to comply with the special conditions of the pregnancy prevention 3. Creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault equation) **Exclusion Criteria** 1. Known or suspected hypersensitivity to lenalidomide or to any of the excipients 2. During previous treatment with lenalidomide, disease progression within 60 days after start of treatment
Sample Size, Planned Total Number of Study Sites and Locations	**Part 1:** Up to 34 subjects • Up to 24 subjects in the dose escalation part • 10 subjects in monotherapy arm **Part 2:** 40-48 subjects • 20-24 subjects in MOR03087 and bortezomib combination therapy arm • 20-24 subjects in MOR03087 and lenalidomide combination therapy arm Approximately 4 centres (Part 1) and approximately 10-15 centres (Part 2) in Germany and Austria (including the 4 centres from Part 1).
Investigational Drug(s) (Name, Description)	MOR03087, bortezomib, lenalidomide, dexamethasone
Dose, Route of Administration, Treatment Regimen	**Part 1:** ***MOR03087 dose escalation:*** - Dose level 1: 0.01 mg/kg - Dose level 2: 0.04 mg/kg - Dose level 3: 0.15 mg/kg - Dose level 4: 0.5 mg/kg - Dose level 5: 1.5 mg/kg - Dose level 6: 4.0 mg/kg - Dose level 7: 8.0 mg/kg Subjects in all cohorts will receive 2 cycles for a total of 5 infusions: each

	28-day cycle will consist of a MOR03087 infusion on Day 1 and Day 15 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle. At least 48 hours will pass between the first study drug administration to the subjects within a cohort in order to observe for AEs. After the first administration of study drug, the subjects will remain at the site until the end of Day 2 for safety monitoring. The subjects will not stay overnight at the site after the 4 subsequent administrations. ***MOR03087 monotherapy extension:*** The final recommended doses will be based on consideration of the incidence of severe AEs at all dose levels. Subjects will receive up to 4 cycles: each 28-day cycle will consist of a MOR03087 infusion on Day 1 and Day 15 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle. After the first administration of study drug, the subjects will remain at the site until end of Day 1 for safety monitoring. The doses will be administered every 2 weeks. The subjects will not stay overnight at the site after the administrations. **Part 2:** ***MOR03087 combined with bortezomib:*** Dose level 1: MOR03087 50% MTD/recommended dose + 1.0 mg/m^2 bortezomib IV bolus Dose level 2: MOR03087 50% MTD/recommended dose + 1.3 mg/m^2 bortezomib IV bolus Dose level 3: MOR03087 100% MTD/recommended dose + 1.3 mg/m^2 bortezomib IV bolus Each treatment cycle will consist of 2 IV infusions of MOR03087 on Day 1 and Day 11 of the cycle and 4 IV bolus injections of bortezomib on Days 1, 4, 8, and 11 of the cycle, followed by a treatment-free period until Day 21. • Dexamethasone (20 mg, orally, on Days 1, 2, 4, 5, 8, 9, 11, and 12) may be added for subjects who develop PD or have SD after Cycle 2 or Cycle 3. • Study treatment will be discontinued if subjects have disease progression despite treatment with dexamethasone. At least 48 hours will pass between the first study drug administration to the subjects within a cohort in order to observe for AEs. After the first administration of study drug, the subjects will remain at the site until the end of Day 2 for safety monitoring. The subjects will not stay overnight at the site after the subsequent administrations. ***MOR03087 combined with lenalidomide:*** Dose level 1: MOR03087 50% MTD/recommended dose + 15 mg lenalidomide orally once daily on Days 1-21 + dexamethasone 40 mg orally once daily on Days 1, 8, 15, and 22. Dose level 2: MOR03087 50% MTD/recommended dose + 25 mg lenalidomide orally once daily on Days 1-21 + dexamethasone 40 mg orally once daily on Days 1, 8, 15, and 22.

	Dose level 3: MOR03087 100% MTD/recommended dose + 25 mg lenalidomide orally once daily on Days 1-21 + dexamethasone 40 mg orally, once daily on Days 1, 8, 15, and 22. Each treatment cycle will consist of 2 IV infusions of MOR03087 on Day 1 and Day 15 of the cycle; lenalidomide orally once daily on Days 1-21; and dexamethasone 40 mg orally once daily on Days 1, 8, 15, and 22 of each cycle. At least 48 hours will pass between the first study drug administration to the subjects within a cohort in order to observe for AEs. After the first administration of study drug, the subjects will remain at the site until the end of Day 2 for safety monitoring. The subjects will not stay overnight at the site after the subsequent administrations. Anticoagulation medication (acetylsalicylic acid or low-molecular-weight heparin) is mandatory during combination treatment with lenalidomide and dexamethasone. ***Modification or interruption of bortezomib and lenalidomide treatment*** If upon treatment with bortezomib or lenalidomide subjects present with protocol-defined dose limiting toxicities (DLTs) or conditions described in the corresponding Summary of Product Characteristics (SmPC), treatment must be modified or interrupted accordingly. For nonhaematological toxicities (excluding neuropathies in the bortezomib arm) upon bortezomib or lenalidomide treatment, only protocol-defined DLT rules should be applied. Neuropathies in the bortezomib arm should be handled as described in the SmPC.
Supply, Preparation and Administration	MOR03087 antibody is formulated in a histidine buffer ready for IV administration. MOR03087 will be presented in a labelled glass vial at a concentration of 8-12 mg/mL and an extractable volume of 5 mL (40-60 mg/vial). The appropriate number of vials will be supplied to each respective investigational site. MOR03087 must be stored at -20°C. MOR03087 will be administered after dilution by slow IV infusion over approximately 2 hours in 100 mL or 250 mL 0.9% sodium chloride solution. Bortezomib is formulated as a powder for reconstitution in solution for injection. Bortezomib will be presented in a vial containing 3.5 mg of drug. After reconstitution, 1 mL of solution for injection will contain 1 mg bortezomib. The appropriate number of vials will be supplied to each respective investigational site. Bortezomib should not be stored at temperatures above 30ºC and should be kept in the outer carton in order to protect from light. The reconstituted solution should be administered as a 3- to 5-second bolus IV injection. Lenalidomide is formulated as hard capsules containing 10 mg, 15 mg, or 25 mg of lenalidomide. The appropriate strength will be supplied to the subject. Lenalidomide will be supplied in polyvinyl chloride (PVC)/polychlorotrifluoroethylene (ACLAR) blisters with push-through aluminium foil. The appropriate number of blisters will be supplied to each respective investigational site. Lenalidomide requires no special storage conditions. It will be administered orally. Dexamethasone is a corticosteroid and will be used in the study as tablets

	containing 4.0 mg or 8.0 mg dexamethasone and excipients. Each subject will receive the respective number of tablets. Dexamethasone should be stored below 25°C and protected from light. It will be administered orally.
Visit Schedule and Assessments	Refer to Schedules of Assessments in Section 7.1
Efficacy Assessments	Efficacy will be evaluated in terms of overall response (CR + PR + MR), further tumour response rates (CR, PR, MR, VGPR), SD, duration of response, TTP, and PFS, using the modified European Group for Blood and Marrow Transplantation (EBMT) criteria plus the International Myeloma Working Group Uniform Response Criteria. Pharmacodynamics will be assessed in terms of B, T, and NK cell populations; serum and urine M-protein levels; serum FLC levels (if applicable); and for subjects with CR also, bone marrow histology.
Special Safety Assessments	Safety will be assessed in terms of physical examination, vital signs, electrocardiograms, haematological and biochemical tests, AEs, cytokines and immunogenicity. Laboratory and AE toxicities will be graded according to NCI CTCAE, version 4.0, with a DLT defined as an AE or abnormal laboratory value assessed as having a suspected or unknown relationship to the study drug (MOR03087, bortezomib, or lenalidomide) and meeting one of the following criteria: • Nonhaematologic DLT: o Liver Any grade 3 AST/ALT that does not resolve to grade 1 within 14 days or any grade 4 elevation in liver function tests (AST/ALT) o Gastrointestinal ≥ Grade 3 vomiting or grade 3 nausea despite the use of standard antiemetics ≥ Grade 3 diarrhoea despite the use of optimal antidiarrhoeal treatment o All other events ≥ grade 3 (excluding hypersensitivity reactions and fatigue) • Haematologic DLT: o Grade 4 thrombocytopaenia, anaemia, or neutropaenia that does not resolve to grade 2 or less within 14 days o All other treatment-related grade 4 events • Any AE that delays treatment with study drug for more than 14 days Subjects experiencing DLTs in Part 1 of the study should not receive further study drug.
Subject-Reported Outcomes/Quality of Life	Quality of life will be evaluated using the QLQ-30 and the QLQ-MY20, an instrument for use in subjects with multiple myeloma.
Pharmacokinetics	Concentration-time profiles and pharmacokinetic parameters will be assessed from serum samples collected on the following schedules (if not otherwise specified, a deviation of 5 minutes from the planned collection time point will be acceptable):

	Part 1: ***MOR03087 dose escalation*** • For the first investigational medicinal product (IMP) administration, serum samples will be collected predose and then 1, 2, 4, 8, 14 ± 2, 22 ± 2, and 28 ± 2 hours after start of first infusion. • For the second to fourth IMP administrations, serum samples will be collected predose for trough level determination and then 2 hours after start of infusion. • For the last IMP administration, serum samples will be collected predose for trough level determination and then 2 hours after start of infusion, and 1 week and 3 weeks later. ***MOR03087 monotherapy*** • For the first IMP administration, serum samples will be collected predose; at 1, 2, 4, and 8 hours after start of first infusion. • For the second to penultimate IMP administrations, serum samples will be collected predose for trough level determination and then at 2 hours after start of infusion. • One sample each will be taken in the period between Day 17 and Day 20 and the period between Day 22 and Day 25. • For the last IMP administration, serum samples will be collected predose for trough level determination and then at 2 hours after start of infusion and 3 weeks later. **Part 2:** ***MOR03087 combined with bortezomib*** Pharmacokinetics for MOR03087 and bortezomib will be determined: • For the first IMP administration, serum samples will be collected predose before administration of bortezomib and then 1, 2, 4, 8, 14 ± 2, 22 ± 2, and 28 ± 2 hours after start of first infusion of MOR03087. • For the second and third bortezomib administration on Day 4 and Day 8, a sample for determination of bortezomib and MOR03087 will be collected predose. • For the second, third, and fourth administration of MOR03087 (Cycles 1 and 2), serum samples will be collected predose before administration of bortezomib for trough level determination and then 1 hour and 2 hours after start of infusion. • For both administrations of MOR03087 in Cycle 3 and the second administration of MOR03087 in Cycles 4 and 5, serum samples will be collected predose before administration of bortezomib for trough level determination and then 1 and 2 hours after start of infusion. • A predose sample will be taken before the second injection of bortezomib in Cycle 3. • For the last administration of MOR03087, serum samples will be collected predose before administration of bortezomib for trough level determination and then 1 hour and 2 hours after start of infusion and 3 weeks later. ***MOR03087 combined with lenalidomide*** Pharmacokinetics for MOR03087 and lenalidomide will be determined: • For the first IMP administration, serum samples will be collected

	predose before administration of lenalidomide and then 1, 2, 4, 8, 14 ± 2, 22 ± 2, and 28 ± 2 hours after start of first infusion of MOR03087. • A predose sample for the determination of lenalidomide and MOR03087 will be taken on Day 8 before the intake of lenalidomide. • For the second administration of MOR03087 in Cycle 1 and both MOR03087 administrations in Cycle 2, serum samples will be collected predose before administration of lenalidomide for trough level determination and then 1 hour and 2 hours after start of infusion. • For the second administrations of MOR03087 in Cycles 3 to 5, serum samples will be collected predose before administration of lenalidomide for trough level determination and then 1 and 2 hours after start of infusion. • For the last administration of MOR03087, serum samples will be collected predose before administration of lenalidomide for trough level determination and then 1 hour and 2 hours after start of infusion and 3 weeks later.
Biomarker Assessments	CD38 expression on malignant plasma cells in the bone marrow; CD16 expression on NK cells and FcγR phenotype
Immunogenicity Assessments	Absolute (number of subjects with anti-MOR03087 antibody development) and semiquantitative (antibody MOR03087 antibody titer determination of confirmed positive samples) assessments of MOR03087 immunogenicity
Other Biomarker Studies on Additional / Remaining Samples	Cytokine evaluation will be performed before (predose) and 2 hours after the end of the first dose administration. A bone marrow sample will be collected at screening for potential DNA or RNA analysis at a later stage to allow for potential identification of biomarkers that could influence the pharmacokinetics and the pharmacodynamics of MOR03087. Determinations of translocations t(4;14) and t(14;16) and deletions Del 13 and Del17p13 will be made at baseline for use as prognostic markers.
Data Monitoring Committee	An independent data monitoring committee (DMC) is planned for this study. The DMC will operate according to a charter and will consist of 3 independent members (2 haematologists, 1 clinical pharmacologist). This independent DMC will review • Data obtained during the dose-escalation Part 1 of the study from each cohort after the first cycle of MOR03087 infusion. • Cumulative data from Part 1 of the study (dose-escalation) • Cumulative data from Part 1 of the study (dose-escalation) and the first 6 subjects from the Phase IIa monotherapy arm). • Data obtained during the dose-escalation phase of the combination therapy arms in Part 2 of the study for each cohort. • Cumulative data from the dose escalation phase of the combination therapy arms in Part 2 of the study.
Statistical Methods and Data Analysis	One of the primary endpoints will be to determine the MTD or recommended dose for monotherapy (Phase I) and the recommended dose combination for the 2 different combination therapies (Phase Ib). This primary endpoint will be determined in the evaluable population. The

	evaluable population will consist of all enrolled subjects who have received at least 1 cycle of MOR03087 (monotherapy or combination therapy) and who have minimum safety evaluations, including the first cycle and AEs reported from Day 1 after the start of the first infusion until Day 1 of the second cycle (before start of infusion), or who are withdrawn before having received the minimum number of infusions and safety evaluations due to DLT. The recommended dose for the final cohort in Phase IIa (monotherapy) will be determined after review of all available safety data from the Phase I dose-escalation portion of the study and based on the recommendation of the DMC. The recommended dose may be the MTD or a dose below the MTD. Analogously, the recommended dose combination for the final cohort in the Phase Ib (combination therapy) portion of this study will be determined after review of all available safety data from the Phase Ib dose-escalation cohorts and the Phase IIa monotherapy arm of the study and based on the recommendation of the DMC. The other primary and secondary endpoints will be analysed descriptively using summary statistics for continuous data and frequency tables for categorical data. The 95% confidence intervals will be presented for rates or means in the recommended dose group of each treatment arm where appropriate. Kaplan-Meier estimates will be used where applicable.