CLINICAL STUDY PROTOCOL
AMENDMENT 11

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 or Refractory Multiple Myeloma

Brief Description of Study	Open-label, multicentre, dose-escalation study to characterize the safety and preliminary efficacy of the human anti-CD38 antibody MOR03087 in adult subjects with relapsed/refractory multiple myeloma as monotherapy and in combination with standard therapy
Study Type:	Phase I/IIa
Sponsor:	MorphoSys AG
Sponsor's Address:	Semmelweisstr. 7 D-82152 Planegg GERMANY
Study Protocol Number:	MOR202C101
EudraCT No.:	2009-015942-50
Original Protocol	Final v1.0, 25 Oct 2010
Protocol Amendment 1	Final v2.0, 21 Mar 2011
Protocol Amendment 2	Final v3.0, 23 Jul 2012
Protocol Amendment 3	Final v4.0, 11 Jan 2013
Protocol Amendment 4	Final v5.0, 27 Sep 2013
Protocol Amendment 5	Final v6.0, 29 Nov 2013
Protocol Amendment 6	Final v7.0, 15 Apr 2014
Protocol Amendment 7	Final v8.0, 30 Jul 2014
Protocol Amendment 8	Final v9.0, 05 Nov 2014
Protocol Amendment 9	Final v10.0, 25 Jun 2015
Protocol Amendment 10	Final v11.0, 20 Feb 2017
Protocol Amendment 11	Final v12.0, 17 Jul 2017

SIGNATURES

Protocol Prepared and Approved/Authorized By:

Signature:	[redacted]
Signature:	
Signature:	
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, Co-Investigator, or Sub-Investigator

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 provisions of the current Helsinki Declaration, copies of both documents have been given to me by the sponsor, I will also ensure that co-investigator(s) and other relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines and the Helsinki Declaration to enable them to work in accordance with the provisions of these documents.

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

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

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

Contact Details of Key Study Personnel

Sponsor's Medical Expert	[redacted]
Sponsor Clinical Project Manager	
Contact for Serious Adverse Events (SAEs):	
Medical Monitor (24/7 Medical Coverage)	
24/7 Medical Coverage	
CRO Project Manager	

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 or Refractory Multiple Myeloma
Investigational Medicinal 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 Semmelweisstr. 7 D-82152 Planegg GERMANY **Clinical Research Organization (CRO):** [redacted]
Study Phase	Phase I/IIa
Background	Despite the approval of the novel therapeutic agents lenalidomide (LEN) and pomalidomide (POM) for relapsed disease, multiple myeloma (MM) 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 MM treatment. MOR03087 is a fully human monoclonal antibody directed to CD38 that has demonstrated *in vitro* and *in vivo* efficacy in preclinical MM 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 an immunomodulatory derivative ("IMiD", LEN) with MOR03087 demonstrated increased cytotoxicity compared with either agent alone in MM cell lines, supporting the combination of these therapies clinically.
Study Purpose/Rationale	The purpose of this study is to characterize the safety profile and preliminary efficacy of MOR03087 and establish the maximum tolerated dose (MTD) or recommended dose of MOR03087 as monotherapy with or without dexamethasone (DEX) as well as in combination with two standard IMiD therapies (POM+DEX and LEN+DEX) in adult subjects with relapsed or refractory MM.

Study Objectives (Key Primary and Secondary)	**PRIMARY OBJECTIVES:** 1. To assess the safety profile and to establish the MTD and/or recommended dose of MOR03087 in subjects with relapsed or refractory MM: a. As monotherapy b. In combination with DEX c. In combination with POM + DEX d. In combination with LEN + DEX 2. To assess the immunogenicity of MOR03087 **SECONDARY OBJECTIVES:** 1. To evaluate the pharmacokinetics and pharmacodynamics of MOR03087 in subjects with relapsed or refractory MM: a. As monotherapy b. In combination with DEX c. In combination with POM + DEX d. In combination with LEN + DEX 2. To evaluate the preliminary efficacy of MOR03087 in subjects with relapsed or refractory MM: a. As monotherapy b. In combination with DEX c. In combination with POM + DEX d. In combination with LEN + DEX
Study Endpoints (Key Primary and Secondary)	**PRIMARY ENDPOINTS:** 1. Determination of the MTD and/or recommended dose of MOR03087 as monotherapy, in combination with DEX, and in combination with POM+DEX and LEN+DEX 2. Determination of the recommended dosing regimen of MOR03087 3. Incidence and severity of adverse events (AEs) 4. 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 of MOR03087 +/- LEN or POM 2. Absolute and percent change from baseline in measurements of B, T, and natural killer (NK) cell populations 3. Overall response rate (stringent complete response [sCR], complete response [CR] + very good partial response [VGPR], partial response [PR]), further tumor response rates (CR, sCR, PR, MR, 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, hematology, 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, standard 3+3 dose-escalation study designed to characterize the safety profile and preliminary efficacy of MOR03087 in adult subjects with relapsed or refractory MM as monotherapy and in combination with DEX or standard IMiD therapy. A 3+3 dose escalation design will be utilized to establish the MTD and/or recommended dose and dosing regimen of MOR03087 as monotherapy, weekly or bi-weekly, with or without DEX, and the MTD and/or recommended dose in combination with POM+DEX and LEN+DEX standard regimens. The MTD and/or recommended dose and dosing regimens will be confirmed in two confirmation cohorts of at least 6 evaluable subjects each. The MOR03087 dose levels proposed for this study range from 0.01 mg/kg to 16.0 mg/kg administered by intravenous (IV) infusion.
Population	Adult subjects with relapsed or refractory MM (after at least two prior regimens).
Key Inclusion / Exclusion Criteria	**INCLUSION CRITERIA FOR ALL SUBJECTS:** 1. Male or female subjects ≥ 18 years of age 2. Presence of serum M-protein ≥ 0.5 g per 100 mL (≥ 5 g/L) and/or urine M-protein ≥ 200 mg per 24-hour period 3. Life expectancy of > 3 months 4. Karnofsky performance status ≥ 60% 5. Absolute neutrophil count (ANC) ≥ 1.0 (1,000/mm^3) 6. Total bilirubin ≤ 2 × ULN 7. Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN 8. Hemoglobin ≥ 8 g/dL 9. If a female of childbearing potential, confirmation of a negative pregnancy test before enrolment and use of double-barrier contraception, oral contraceptive plus barrier contraceptive, for at least 28 days prior to, during therapy and for 28 days after the last dose, or confirmation of having undergone clinically documented total hysterectomy and/or bilateral oophorectomy, tubal ligation 10. If a male, he must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy 11. Ability to comply with all study-related procedures, medication use, and evaluations 12. Ability to understand and give written informed consent, and comply with the protocol **EXCLUSION CRITERIA FOR ALL SUBJECTS:** 1. Primary refractory MM 2. Previous treatment with cytotoxic chemotherapy or large-field radiotherapy or other myeloma-specific therapy within 28 days prior to first study treatment (radiation to a single site as concurrent therapy is allowed)

	3. Treatment with a systemic investigational agent within 28 days prior to first study treatment. 4. Solitary plasmacytoma or plasma cell leukemia 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 targeting the CD38 antigen or prior therapy with other IgG monoclonal antibodies within 3 months prior to first study treatment, or IgM monoclonal antibodies within 1 month prior to first study treatment 9. Clinical or laboratory evidence of active hepatitis B (positive HBsAg with negative HBsAb) or hepatitis C (positive HCV antibody) 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 diarrhea 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. MM with central nervous system (CNS) involvement 19. Prior or concomitant malignancy (other than MM) except adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, prostate cancer not requiring treatment or other cancer for which the subject has been disease-free for at least 3 years. For the combination therapy with LEN or POM, this should be at least 5 years 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 ELGIBILITY CRITERIA FOR TREATMENT WITH MOR03087 WITH/WITHOUT DEXAMETHASONE:** **Inclusion Criteria** 1. Documented diagnosis of MM; specifically, relapsed or refractory MM defined as: • Failure of at least two previous therapies; previous therapies must include an immunomodulatory agent and a proteasome inhibitor (either together or as part of different therapies)

	• All subjects must have documented progression during or after their last prior therapy for MM 2. Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault equation) 3. Platelets: • ≥ 80 × 10^9/L, without previous transfusion within the last 4 weeks before first study drug administration • ≥ 50 × 10^9/L (for dose levels ≥ 4 mg/kg with or without DEX). Subjects are not allowed to have received platelet transfusion within the last 4 weeks before study drug administration. **Exclusion Criteria** 1. For subjects receiving DEX: Known or suspected hypersensitivity to DEX or any of the excipients **ADDITIONAL ELIGIBILITY CRITERIA FOR THE TREATMENT WITH MOR03087, DEXAMETHASONE AND LENALIDOMIDE:** **Inclusion Criteria** 1. Documented diagnosis of MM; specifically, relapsed or refractory MM defined as: • Received at least one previous therapy • All subjects must have documented progression during or after their last prior therapy for MM 2. Ability to understand the reason for and understand the special conditions of the pregnancy prevention risk minimization plan and give written acknowledgement of these 3. Ability and willingness to comply with the special conditions of the pregnancy prevention risk minimization plan 4. Creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault equation) 5. Platelets: • ≥ 75 × 10^9/L for subjects in whom < 50% of bone marrow nucleated cells are plasma cells • ≥ 30 × 10^9/L for subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells. **Exclusion Criteria** 1. Known or suspected hypersensitivity or intolerance to LEN, POM, thalidomide, DEX or to any of the excipients **ADDITIONAL ELIGIBILITY CRITERIA FOR THE TREATMENT WITH MOR03087, DEXAMETHASONE AND POMALIDOMIDE:** **Inclusion Criteria** 1. Documented diagnosis of MM; specifically, relapsed and refractory MM defined as: • Received at least two previous therapies including LEN and a proteasome inhibitor

	• All subjects must have documented progression during or within 60 days after their last prior therapy for MM **2.** Ability to understand the reason for and understand the special conditions of the pregnancy prevention risk minimization plan and give written acknowledgement of these **3.** Ability and willingness to comply with the special conditions of the pregnancy prevention risk minimization plan **4.** Creatinine clearance ≥ 45 mL/min (calculated using the Cockcroft-Gault equation) 5. Platelets • ≥75 × 10^9/L for subjects in whom < 50% of bone marrow nucleated cells are plasma cells • ≥30 × 10^9/L for subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells. **Exclusion Criteria** 1. Known or suspected hypersensitivity to POM, LEN, thalidomide, DEX or to any of the excipients 2. Subjects who are refractory (defined as progression during or within 60 days after their last dose of POM) or intolerant to POM
Sample Size, Planned Total Number of Study Sites and Locations	Up to 126 subjects • Up to 48 subjects for the MOR03087 monotherapy/bi-weekly escalation • Up to 18 for the MOR03087 monotherapy/weekly escalation • Up to 24 for the MOR03087 + DEX part (up to 18 for dose escalation cohorts and at least 6 for confirmatory cohort) • Up to 18 for the MOR03087 + POM + DEX (up to 12 for dose escalation cohorts and at least 6 for confirmatory cohort) • Up to 18 for the MOR03087 + LEN + DEX (up to 12 for dose escalation cohorts and at least 6 for confirmatory cohort) Approximately 10-15 sites in Germany and Austria
Investigational Medicinal Drug(s) (Name, Description)	MOR03087, pomalidomide, lenalidomide, dexamethasone
Dose, Route of Administration, Treatment Regimen	In each cohort, 28-day cycles will be used. An independent Data Monitoring Committee (DMC) will review the relevant safety information before considering dose escalation for the next cohort. **Part A:** ***MOR03087 dose escalation (bi-weekly treatment):*** - 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 - Dose level 8: 16.0 mg/kg*

	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. For Part A, at least 48 hours will pass between the first study drug administration to the subjects within a cohort in order to observe for AEs. **Part B:** ***MOR03087 dose escalation (weekly treatment):*** - Dose level 6b: 4.0 mg/kg* - Dose level 7b: 8.0 mg/kg - Dose level 8b: 16.0 mg/kg Each 28-day cycle will consist of a MOR03087 infusion on Days 1, 8, 15, and 22 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle. **Part C:** ***MOR03087 dose escalation (weekly/biweekly treatment) plus low dose of dexamethasone:*** - Dose level 6c: 4.0 mg/kg* - Dose level 7c: 8.0 mg/kg - Dose level 8c: 16.0 mg/kg Each 28-day cycle will consist of: MOR03087 infusion on Days 1, 8, 15, and 22 of the cycle. In Cycle 1 a loading dose will additionally be administered on Day 4 of the cycle. Only for dose level 8c, for cycles 4 and onwards each 28-day cycle will consist of: MOR03087 infusion on Days 1 and 15 of the cycle. Subjects who have received treatment beyond Cycle 3 will be switched to the biweekly schedule at the next Day 1 or Day 15 visit. In exceptional cases – and after discussion between the investigator and the sponsor – the treating physician may determine that it is in the best interest of the subject to remain on the weekly MOR03087 schedule, in which case the sponsor should be informed accordingly. Oral DEX 40 mg (≤ 75 years old) or 20 mg (> 75 years old) on Days 1, 8, 15, and 22 of the 28-day cycle, irrespective of whether MOR03087 is administered weekly or biweekly. In Cycle 1 on Day 4 (loading dose) oral DEX 40 mg (≤ 75 years old) or 20 mg (> 75 years old) will be added. * *Following the completion of Part B dose level 6b and Part C dose level 6c, and taking into account available safety information from Part A dose level 8, the DMC will provide a recommendation if some or all of the planned weekly MOR03087 monotherapy dose escalation cohorts will be tested.* Following completion of Parts A, B, and C (dose escalation of MOR03087 bi-weekly and weekly schedules), the MTD or recommended dose and dosing regimen will be confirmed in a minimum of 6 subjects.

	Part D: ***MOR03087 (weekly/biweekly treatment) in combination with POM+DEX*** - Dose level 7d: 8.0 mg/kg - Dose level 8d: 16.0 mg/kg Each 28-day cycle will consist of: MOR03087 infusion on Days 1, 8, 15, and 22 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle. Only for dose level 8d, for cycles 4 and onwards each 28-day cycle will consist of: MOR03087 infusion on Days 1 and 15 of the cycle. Subjects who have received treatment beyond Cycle 3 will be switched to the biweekly schedule at the next Day 1 or Day 15 visit. In exceptional cases – and after discussion between the investigator and the sponsor – the treating physician may determine that it is in the best interest of the subject to remain on the weekly MOR03087 schedule, in which case the sponsor should be informed accordingly. Oral POM 4 mg on Days 1-21 of the 28-day cycle. Oral DEX 40 mg (≤ 75 years old) or 20 mg (> 75 years old) on Days 1, 8, 15, and 22 of the 28-day cycle, irrespective of whether MOR03087 is administered weekly or biweekly. In Cycle 1 on Day 4 (loading dose) oral DEX 40 mg (≤ 75 years old) or 20 mg (> 75 years old) will be added. **Part E:** ***MOR03087 (weekly/biweekly treatment) in combination with LEN+DEX*** - Dose level 7e: 8.0 mg/kg - Dose level 8e: 16.0 mg/kg Each 28-day cycle will consist of: MOR03087 infusion on Days 1, 8, 15, and 22 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle. Only for dose level 8e, for cycles 4 and onwards each 28-day cycle will consist of: MOR03087 infusion on Days 1 and 15 of the cycle. Subjects who have received treatment beyond Cycle 3 will be switched to the biweekly schedule at the next Day 1 or Day 15 visit. In exceptional cases – and after discussion between the investigator and the sponsor – the treating physician may determine that it is in the best interest of the subject to remain on the weekly MOR03087 schedule, in which case the sponsor should be informed accordingly. Oral LEN 25 mg on Days 1-21 of the 28-day cycle. Oral DEX 40 mg (≤ 75 years old) or 20 mg (> 75 years old) on Days 1, 8, 15, and 22 of the 28-day cycle, irrespective of whether MOR03087 is administered weekly or biweekly. In Cycle 1 on Day 4 (loading dose) oral DEX 40 mg (≤ 75 years old) or 20 mg (> 75 years old) will be added.

	Following completion of Parts D and E (dose escalation of MOR03087 in combination with POM-DEX and LEN-DEX), the MTD and/or recommended dose in each part will be confirmed in a minimum of 6 subjects. Part A dose levels 1-7 will be tested sequentially and only one dose level will be open for enrolment at any time. Starting with Part A dose level 8, Parts B and C will open in parallel (at dose level 6 [6b and 6c]). Following completion of dose level 7c (8.0 mg/kg MOR03087 + DEX) (and 7b if the DMC recommends to open this cohort), Cohorts 7d and 7e may open in parallel with dose levels 8b (if the DMC recommends to open this cohort) and 8c. New cohorts will not start before the DMC returns a positive recommendation based on safety read-outs from prior cohorts as laid down in the DMC Charter. ***All cohorts:*** 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 for subsequent administrations. Based on the individual risk/benefit ratio, subjects who have an ongoing response of at least SD may continue treatment with the assigned study regimen until disease progression. In case subjects present with progressive disease or with no better status than SD after four treatment cycles starting with Cycle 1 Day 1, the investigator may add a standard weekly dose of dexamethasone to the regimen at his/her discretion, provided dexamethasone is not already part of the treatment regimen. ***Modification or interruption of POM and LEN treatment*** If upon treatment with POM or LEN, subjects present with toxicities, treatment must be modified or interrupted accordingly.
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 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. A stepwise shortening of the infusion duration is specifically laid out in the protocol. POM is supplied by the sponsor as 1 mg, 2 mg, 3 mg and 4 mg capsules for oral administration. The appropriate strength will be supplied to the subject. POM should be stored as directed on the label. LEN is supplied by the sponsor as 5 mg, 10 mg, 15 mg, or 25 mg capsules for oral administration. The appropriate strength will be supplied to the subject. LEN should be stored as directed on the label. DEX is a corticosteroid and will be used in the study as tablets containing 4.0 mg or 8.0 mg DEX and excipients, supplied by the sponsor. Each subject will receive the respective number of tablets. The appropriate

	weekly dose of DEX must be administered as a single oral bolus. DEX should be stored as directed on the label.
Visit Schedule and Assessments	Refer to Schedules of Assessments in Section 7.1
Efficacy Assessments	Efficacy will be evaluated in terms of overall response rate (PR or better), further tumor response rates (sCR, CR, PR, VGPR, MR), SD rate, 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, bone marrow histology.
Special Safety Assessments	Safety will be assessed in terms of physical examination, vital signs, electrocardiograms, hematological and biochemical tests, AEs, cytokines and immunogenicity. Adverse Events will be graded according to NCI CTCAE, version 4.0, with a DLT being defined as an AE assessed as having a suspected or unknown relationship to the study drug (MOR03087, POM, or LEN) and meeting one of the following criteria: • Non-hematologic 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 nausea despite the use of standard antiemetics ≥ Grade 3 diarrhea or constipation despite the use of optimal treatment o All other events ≥ Grade 3 (excluding hypersensitivity reactions and fatigue) • Hematologic DLT: o Grade 4 thrombocytopenia that requires more than one platelet transfusion and does not resolve to grade 2 or less within 14 days o Grade 4 neutropenia that does not resolve to grade 2 or less within 14 days o or any other grade 4 hematologic toxicities that do not resolve to grade 2 or less within 14 days and that are considered clinically relevant by the investigator • Any AE that delays treatment with study drug for more than 14 days In addition, any event will only qualify as a DLT if a worsening of the event from baseline of at least 2 CTCAE Grades occurs. The DLTs for the POM combination cohorts are specified as above except for the hematological DLTs which are as follows: • Hematologic DLT: o Grade 4 neutropenia for > 7 days

	○ Febrile neutropenia (ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥ 38°C for more than 1 hour) ○ Thrombocytopenia - Platelet count < 25,000/µL that requires more than one platelet transfusion or - Platelet count ≥ 25,000/µL to < 50,000/µL with significant bleeding (defined as need for hospitalization and/or platelet transfusion) - Or any other grade 4 hematologic toxicities that do not resolve to grade 2 or less within 14 days and that are considered clinically relevant by the investigator The DLTs for the LEN combination cohorts are specified as above except for the hematological DLTs which are as follows: • Hematologic DLT: ○ Grade 4 neutropenia for > 7 days ○ Febrile neutropenia (ANC <1000/mm^3 with a single temperature of >38.3 °C or a sustained temperature of ≥ 38°C for more than 1 hour) ○ Thrombocytopenia - Platelet count < 30,000/µL that requires more than one platelet transfusion or - Platelet count ≥ 30,000/µL to < 50,000/µL with significant bleeding (defined as need for hospitalization and/or platelet transfusion) - Or any other grade 4 hematologic toxicities that do not resolve to grade 2 or less within 14 days and that are considered clinically relevant by the investigator The DLT period covers Day 1 of cycle 1 (starting with first study drug administration) until Day 29 (before start of the second cycle). Subjects experiencing DLTs should not receive further study drug. A pharmacokinetic interim analysis may be performed at any time during dose escalation if unexpected MOR03087 serum concentration results are observed.
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 MM.
Pharmacokinetics	Concentration-time profiles and pharmacokinetic parameters of MOR03087 +/- LEN or POM will be assessed from samples collected on the following schedules (if not otherwise specified, a deviation of 5 minutes from the planned collection time point will be acceptable): **<u>Parts A, B, C:</u>** ***MOR03087*** • For the first MOR03087 administration, serum samples will be collected predose and then 1, 2, 4, 8, 14 ± 2 (optional), 22 ± 2, and 28 ± 2 hours after start of first infusion. • For all other MOR03087 administrations in Cycles 1 and 2, serum samples will be collected predose for trough level determination and

	then after completion of infusion (subjects in bi-weekly dosing will not have a dose on Day 50, so require only 1 serum sample that day). • From Cycle 3 onwards, samples will be collected once per cycle (predose and after completion of infusion). This means sampling every cycle on D15. • Follow-up: sample will be collected at follow-up visit 1 (or at EOS if no follow-up visit occurs) **Parts D, E:** ***MOR03087 combined with LEN or POM regimens dose escalation*** • For the first MOR03087 administration, MOR03087 serum samples will be collected predose before administration of MOR03087 + LEN or POM and then 1, 2, 4, 8, 14 ± 2 (optional), 22 ± 2, and 28 ± 2 hours after start of first infusion of MOR03087 • For all other MOR03087 administrations in Cycles 1 and 2, MOR03087 serum samples will be collected predose for trough level determination and after completion of infusion • For the first MOR03087 administration, POM or LEN plasma samples will be collected predose before administration of MOR03087 + LEN or POM and then 1, 2, 8 and 22 ± 2 hours after start of first infusion of MOR03087 • For the 3rd, 6th and 8th MOR03087 administration in Cycles 1 and 2, POM or LEN plasma samples will be collected predose for trough level determination and after completion of infusion • From Cycle 3 onwards, samples will be collected once per cycle (predose and after completion of infusion). This means sampling every cycle on D15. • Follow-up: MOR03087 serum sample will be collected at follow-up visit 1 (or at EOS if no follow-up visit occurs)
Biomarker Assessments	CD38 expression on plasma cells in the bone marrow and peripheral blood; CD16 expression on NK cells and FcγRIIIa phenotype
Immunogenicity Assessments	Absolute (number of subjects with anti-MOR03087 antibody development) and semiquantitative (anti-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. The serum chemistry panel at screening will include β2-microglobulin. 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 Del13 and Del17p13 as well as other cytogenetic aberrations with possible prognostic and/or predictive relevance in myeloma (e.g., 1q gain, t(11;14)) will be made at baseline or collected from historical data. Provided sufficient quantities of serum are available, additional measurements of tetanus titer will be performed by central laboratories.

Data Monitoring Committee	An independent DMC will be constituted for dose escalation decisions prior to the enrolment of the first subject. The DMC will review the relevant safety information before considering dose escalation for the next cohort. The DMC membership, full scope of responsibilities, operating procedures, meeting frequency, data availability, reporting and record keeping requirements will be described in detail in the DMC charter.
Statistical Methods and Data Analysis	One of the primary endpoints will be to determine the MTD or recommended dose and dosing regimen for MOR03087 with or without DEX and in combination with two standard IMiD therapies (POM and LEN). This primary endpoint will be determined in the DLT evaluable population. The evaluable population will consist of all enrolled subjects who have received at least 1 cycle of MOR03087 (at least four doses for q1w or two doses for the q2w dosing schedule) (monotherapy or combination therapy) and if applicable per cohort, at least 16 doses of LEN or POM without dose modifications 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). Subjects who withdraw before having received the minimum number of infusions/doses and safety evaluations due to DLT will be included in the DLT evaluable population; subjects who discontinue study treatment or require a dose modification for LEN or POM for reasons unrelated to a DLT within the first cycle will be excluded from the DLT evaluable population. Following completion of Parts A-C (dose escalation of MOR03087 alone, bi-weekly and weekly, and weekly with DEX), the MTD and/or recommended dose will be confirmed in a minimum of 6 subjects. Following completion of Parts D and E (dose escalation of MOR03087 in combination with POM+DEX and in combination with LEN+DEX), the MTD and/or recommended dose in each part will be confirmed in a minimum of 6 subjects. The recommended doses for the confirmation cohorts will be determined after review of all available safety data from the corresponding 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. The other primary and secondary endpoints will be analyzed 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.

2 TABLE OF CONTENTS

2.1 Overall Table of Contents

2.2 List of Tables

2.3 List of Figures

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADR	Adverse drug reaction
AE	Adverse event
AGES	Agentur für Gesundheit und Ernährungssicherheit
ALT	Alanine transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the serum concentration vs. time curve
AUC_{0-t}	Area under the serum concentration vs. time curve from time 0 to the time t of the last quantifiable concentration
$AUC_{0-\infty}$	Area under the serum concentration vs. time curve from time 0 to infinity (extrapolated)
BASG	Bundesamt für Sicherheit im Gesundheitswesen
bpm	Beats per minute (heart rate)
CD38	Cluster of differentiation 38 (antigen expressed on malignant plasma cells)
CL	Total body clearance
C_{max}	Apparent maximum serum concentration
CNS	Central nervous system
CR	Complete response
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DEX	Dexamethasone
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DMC	Data Monitoring Committee
EBMT	European Group for Blood and Marrow Transplantation
ECG	Electrocardiogram
EDC	Electronic data capture
EDTA	Ethylenediamine tetraacetic acid
ELISA	Enzyme-linked immune-sorbent assay
EMA	European Medicines Agency
EOS	End of Study
EORTC	European Organisation for Research and Treatment of Cancer
eCRF	Electronic Case Report Form
FLC	Free light chain
FSH	Follicle stimulating hormone
FCBP	Females of child bearing potential
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyltransferase
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors

ID	Identification
IEC	Independent Ethics Committee
IFN-γ	Interferon-γ
Ig	Immunoglobulin
IL-2	Interleukin-2
IL-6	Interleukin-6
IMiD	Immunomodulatory derivative
IMP	Investigational medicinal product
IRB	Institutional/Independent Review Board
IV	Intravenous
IWRS	Interactive web response system
λ_Z	Apparent terminal rate constant
LEN	Lenalidomide
LLQ	Lower limit of quantification
MABEL	Minimal anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MR	Minimal response
MTD	Maximum tolerated dose
NaCl	Sodium chloride
NCI	National Cancer Institute
NK	Natural killer
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PEI	Paul Ehrlich Institut
PFS	Progression-free survival
PK	Pharmacokinetic
POM	Pomalidomide
PR	Partial response
PR (ECG)	PR interval
PT	Prothrombin time
QLQ	Quality of Life Questionnaire
QRS	QRS interval
QT	QT interval
QTc	QT interval corrected
RBC	Red blood cell
RNA	Ribonucleic acid
rpm	Respirations per minute (respiration rate)
RR	RR interval
SAE	Serious adverse event
SCID	Severe combined immune-deficient mice
sCR	Stringent Complete Response
SD	Stable disease
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Apparent terminal half-life
TEAE	Treatment-emergent adverse event

t_{max}	Time to maximum serum concentration
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
VGPR	Very good partial response
VTE	Venous thrombotic event
Vz	Volume of distribution during the terminal phase
WBC	White blood cell
WHO-DDE	World Health Organization–Drug Dictionary Enhanced

4 BACKGROUND

Despite the approval of the novel therapeutic agents pomalidomide (POM) and lenalidomide (LEN) for relapsed disease, multiple myeloma (MM) remains an incurable malignancy. One of the most strongly and uniformly expressed antigens on malignant plasma cells is CD38 ("cluster of differentiation 38"), a cell-surface antigen which is known to have dual functions, both as a surface antigen and as an enzyme. Because of this expression pattern, an anti-CD38 antibody may have clinical utility as a new therapeutic approach to myeloma treatment.

Relapsed and refractory myeloma, which is associated with median survival rates of less than 30 months in most studies (Chanan-Khan 2010) 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.

4.1 Overview of MOR03087

MOR03087 is a fully human recombinant monoclonal antibody directed to CD38 that has demonstrated *in vitro* and *in vivo* efficacy in preclinical MM models. Antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) are the proposed principal modes of action for MOR03087-induced lysis of MM cells. *In vitro* binding studies showed that the binding affinity of MOR03087 to CD38 is in the nanomolar range. The *in vivo* efficacy of MOR03087 was demonstrated in MM xenograft models in severe combined immune-deficient (SCID) mice. MOR03087 increased survival and reduced bone lysis induced by MM cells inoculated into the tibiae of SCID mice. *In vitro* and *in vivo* combination studies of MOR03087 with the immunomodulatory derivative (IMiD) LEN suggested an at least additive cytotoxicity on myeloma cell lines, providing a preclinical rationale for exploring combination therapy with this drug class in myeloma patients.

Aside from malignant plasma cells, CD38 is known to be expressed on natural killer (NK) cells, hematopoietic progenitor cells, and some T cell subsets. *In vitro* secondary pharmacodynamic studies did not indicate a MOR03087-mediated decrease of CD38+ myeloid progenitor cell colony formation. In human whole blood *ex vivo* assays there was no evidence for a lytic potential of MOR03087 on either human erythrocytes or leukocytes. In an *in vitro* ADCC assay using purified human NK cells, high concentrations of MOR03087 slightly reduced the number of NK cells. No stimulatory or inhibitory effects on aggregation of human platelets were observed in human whole blood *ex vivo*.

On human peripheral blood mononuclear cells (PBMCs) no agonistic effects were observed following antigen binding or antigen crosslinking. MOR03087 caused a weak dose-related release of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) similar to the IgG1 isotype control, which suggests an antigen-independent effect. For interleukin-2 (IL-2) and interferon-γ (IFN-γ), no induction was observed. PBMC proliferation was not affected.

Species differences in CD38 expression on hematologic cells were noted. An approximately 60-fold higher CD38 expression was identified on cynomolgus monkey erythrocytes compared to humans. Anemia was observed *in vivo* in the cynomolgus monkey following single dose administration of MOR03087, which could reflect increased clearance due to high expression levels of CD38 on erythrocytes. In the marmoset monkey, CD38 expression on erythrocytes was 2.5- to 16-fold lower than that on human erythrocytes. No changes in erythrocyte counts were observed in marmoset monkeys in a 12-week toxicity study.

Similarity of CD38 expression on human and marmoset monkey PBMC subpopulations (granulocytes, monocytes, and lymphocytes) was observed. In the cynomolgus monkey, reduced NK cell numbers were noted after single dosing. In the marmoset monkey, no relevant changes in corresponding cell numbers were detected.

Regarding platelets, marmoset monkey platelets had an approximately 3-fold higher CD38 expression than did human platelets. There was no effect upon platelet functionality in either human or marmoset monkey whole blood *ex vivo*.

Based on these comparisons, the high sequence identity between marmoset monkey and human CD38 protein, the comparable binding affinity of MOR03087 to human and marmoset monkey CD38, and a similar activity to induce ADCC in CD38 target cells by human and marmoset monkey PBMCs, the marmoset monkey was selected as the relevant species for the safety assessment of MOR03087.

A pivotal 12-week repeat dose toxicity study was conducted in the marmoset monkey with MOR03087 (once weekly intravenous [IV] administration). Systemic exposure to MOR03087 based upon mean area under the serum concentration vs. time curve from time 0 to the time t of the last quantifiable concentration (AUC_{0-t}) and apparent maximum serum concentration (C_{max}) increased in an approximately dose-proportional manner in both males and females. In both the mid and high dose groups, the unscheduled death of one male animal was observed. However, these were regarded as spontaneous events that were probably not related to the test item administration. Main findings in the treatment groups included soft feces/diarrhea and platelet reduction. A reversibility of these findings at the end of the recovery period was suggested. The increased incidence of subacute inflammation in the cecum and colon of the animals observed in the 12 and 50 mg/kg treatment groups was not fully reversed at the end of the recovery period. A No observed adverse effect level (NOAEL) was set at 3 mg/kg/dose.

There is no human experience with MOR03087, and the planned Phase I/IIa study of MOR03087 will serve as the first study of this agent in humans.

4.2 Rationale for Dose Selection

The selection of the starting dose of 10 µg/kg is based on a minimal anticipated biological effect level (MABEL) approach taking into account the potential binding of MOR03087 to peripheral blood cells. The resulting C_{max} is approximately 0.2 µg/mL at the starting dose of 10 µg/kg. The calculation of serum concentrations of MOR03087 associated with the starting dose is based on a conservative approach excluding the tumor compartment as target tissue. A concentration of 0.2 µg/mL is too low to mediate ADCC of peripheral blood cells, as derived from the *in vitro* whole blood cell assay. In this assay, peripheral blood cells were not affected at concentrations of up to 100 µg/mL. In comparison, ADCC activity towards MM cells was observed at concentrations of 1 µg/mL and above.

Taken together, these data suggest that a starting dose of 10 µg/kg will not result in cytotoxic effects upon peripheral blood cells. Furthermore, the predicted C_{max} in human subjects at a dose of 10 µg/kg is expected to be 200-fold lower than the respective values at NOAEL in marmosets.

The dose escalation scheme and the maximum proposed dose are supported by the 3-month repeated-dose toxicity study in marmoset monkeys. Based on pharmacokinetic (PK) simulations, the predicted human exposure (based on the area under the serum concentration vs. time curve

[AUC]) after weekly administration of 16 mg/kg MOR03087 is comparable to the exposure observed in the highest dose group (50 mg/kg) in the marmoset monkey during the 3-month repeated dose toxicity study.

For simulating the exposure under a weekly dosing of 16 mg/kg MOR03087 in humans (including a loading dose on study Day 4), two different scenarios were set up. For scenario 1, a model based on a standard PK profile of a monoclonal human antibody in humans assuming a terminal elimination half-life of 14 days and a volume of distribution comparable to the blood volume was established. For scenario 2, the exposure was simulated using a clearance rate based on allometric scaling. For both scenarios, no target mediated sink effect in MM patients was taken into account. A broader volume of distribution caused by a sink effect should lead to a significantly lower exposure of free drug in MM patients compared to the simulation. This effect should further increase the distance to the observed exposure of the highest dose group in the toxicological study.

Based on these modelling approaches, the sponsor considers the predicted human exposure for two treatment cycles of weekly MOR03087 at 16 mg/kg (including a loading dose on study Day 4) to be comparable to the highest exposure tested in the 3-month repeated dose toxicity study in the marmoset monkey. Furthermore, in all simulations the modelled C_{max} values of MOR03087 following the administration of 16 mg/kg on a weekly basis were at least 10-fold lower than the C_{max} observed in the marmoset monkey at 50 mg/kg.

According to the International Conference on Harmonisation (ICH) S9 guideline, the highest dose or exposure tested in the nonclinical studies does not limit the highest dose investigated in a clinical study in subjects with cancer. Also, treatment can continue according to the subject's response beyond the duration of the completed toxicology studies. The sponsor therefore considers it appropriate that subjects treated with 16 mg/kg MOR03087 weekly may continue with treatment until disease progression as outlined in the current approved version of the study protocol. Scheduling in the monitoring of relevant safety parameters as (i.e., addition of thyroid stimulating hormone [TSH] and follicle stimulating hormone [FSH] on study Day 29) considered in the clinical study protocol will be adapted to the weekly dosing where required. In the combination parts (POM/dexamethasone [DEX] and LEN/DEX), the starting dose of MOR03087 will be 8 mg/kg, with standard doses of POM, LEN and DEX. Enrolment in these parts will not be initiated until approval has been given by an independent Data Monitoring Committee (DMC), based on safety data obtained during completion of treatment with 8 mg/kg MOR03087 weekly, with and without DEX (cohorts 7b and 7c), thereby ensuring the safety of this dosing regimen before adding additional agents.

5 STUDY PURPOSE/RATIONALE

The purpose of this study is to characterize the safety profile and preliminary efficacy of MOR03087 and establish the maximal tolerated dose (MTD) or recommended dose of MOR03087 as monotherapy and in combination with DEX as well as in combination with standard IMiD therapy (MOR03087 + POM/DEX and MOR03087 + LEN/DEX) in adult subjects with relapsed or refractory myeloma.

Despite recent advances in the field, MM remains incurable and eventually all patients will become refractory to treatment. Further improvements in overall response, duration of clinical benefit, progression-free survival, and overall survival are desirable, and even minor responses

to therapy may be associated with symptomatic benefit in subjects with relapsed or refractory MM.

Novel synergistic combinations of anti-myeloma drugs with different modes of action may be warranted to overcome drug resistance and improve patient outcome (Jagannath 2010). This is especially true for patients with relapsed or refractory MM showing a decreased response rate in comparison to treatment-naïve patients. In contrast to conventional chemotherapeutic agents, monoclonal antibodies as a targeted therapy are ideal for use in combination therapy, with potential for decreased toxicity.

LEN, an immunomodulator, has been described in myeloma to inhibit angiogenesis, induce apoptosis, decrease binding of MM cells to endogenous marrow stromal cells, and modulate cytokines in the bone marrow (Laubach 2009). *In vitro* studies have shown augmentation of both the adaptive and innate immune systems via the costimulation of T-cells and enhanced NK cell ADCC activity in the presence of LEN. MOR03087-induced ADCC has been demonstrated to be enhanced by LEN *in vitro*.

POM is a novel immunomodulatory drug recently approved for the treatment of relapsed and refractory MM. The pleiotropic activities of POM on a range of cell types, including MM cells and immune effector cells, suggest modulation of multiple molecular pathways. POM shares a number of the beneficial pharmacologic properties of thalidomide and LEN.

Corticosteroids such as prednisone and DEX were shown to have significant single-agent activities (Mass 1962; Alexanian 1992). Moreover, responses to immunomodulatory drugs and proteasome inhibitors increase significantly when they are combined with additional agents including glucocorticosteroids and chemotherapeutic agents such as alkylators (Alexanian 1969). For example DEX enhances the anti-myeloma effect of LEN (Minnema 2010), and has been reported to induce apoptotic signalling pathways in MM cells leading to growth arrest and induction of apoptosis (Chauhan 2002).

In light of the need for more effective treatment options for patients with relapsed/refractory myeloma, this study will allow for determination of a MTD or recommended dose, and a recommended dosing regimen, of MOR03087 alone, in combination with DEX, and in combination with DEX and standard IMiD therapies approved for relapsed MM (POM and LEN). To effectively monitor the safety profile of the study subjects, an independent DMC will be utilized for dose escalation decisions.

6 OBJECTIVES

6.1 Primary Objectives

- To assess the safety profile and to establish the MTD and/or recommended dose of MOR03087 in subjects with relapsed or refractory MM:
    a. As monotherapy
    b. In combination with DEX
    c. In combination with POM+DEX
    d. In combination with LEN+DEX
- To assess the immunogenicity of MOR03087

6.2 Secondary Objectives

- To evaluate the pharmacokinetics and pharmacodynamics of MOR03087 in subjects with relapsed or refractory MM:
    a. As monotherapy
    b. In combination with DEX
    c. In combination with POM+DEX
    d. In combination with LEN+DEX
- To evaluate the preliminary efficacy of MOR03087 in subjects with relapsed or refractory MM:
    a. As monotherapy
    b. In combination with DEX
    c. In combination with POM+DEX
    d. In combination with LEN+DEX

7 STUDY DESIGN

7.1 Overall Study Design and Investigational Plan

This is an open-label, multicentre, standard 3+3 dose-escalation study designed to characterize the safety profile and to assess the preliminary efficacy of MOR03087 in adult subjects with relapsed or refractory MM as monotherapy and in combination with DEX or standard IMiD therapy (POM and LEN). Approximately 10-15 sites will participate in this study.

The MTD and/or recommended dose and dosing regimens will be confirmed in a confirmation cohort of at least 6 subjects. A total of up to 126 subjects may participate in the study (including dose escalation and confirmation cohorts).

The overall study design for the latter stages of the study is indicated in Figure 1. A study flow chart for individual subjects is provided in Figure 2.

<table>
<tr><td>Cohort 8
q2w
16 mg/kg
(≥3pts)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Cohort 6b
q1w
4 mg/kg
(≥3pts)</td><td>Cohort 7b
q1w
8 mg/kg
(≥3pts)</td><td>Cohort 8b
q1w
16 mg/kg
(≥3pts)</td><td rowspan="2">Monotherapy
Confirmation Cohort
Recommended dose/schedule
q2w or q1w or q1w/q2w+DEX
(≥6 pts)</td><td></td></tr>
<tr><td>Cohort 6c
q1w
4 mg/kg
+DEX
(≥3pts)</td><td>Cohort 7c
q1w
8 mg/kg
+DEX
(≥3pts)</td><td>Cohort 8c
q1w/q2w
16 mg/kg
+DEX
(≥3pts)</td><td></td></tr>
<tr><td></td><td></td><td>Cohort 7d
8 mg/kg q1w
+POM +DEX
(≥3 pts)</td><td>Cohort 8d
16 mg/kg q1w/q2w
+POM +DEX
(≥3 pts)</td><td>Confirmation Combo
Recommended dose
POM +DEX
(≥ 6 pts)</td></tr>
<tr><td></td><td></td><td>Cohort 7e
8 mg/kg q1w
+LEN +DEX
(≥3 pts)</td><td>Cohort 8e
16 mg/kg q1w/q2w
+LEN +DEX
(≥3 pts)</td><td>Confirmation Combo
Recommended dose
LEN +DEX
(≥ 6 pts)</td></tr>
</table>

q2w: every 2 weeks; q1w: every week; POM: pomalidomide; LEN: lenalidomide; DEX: dexamethasone

Figure 1: Overall Study Design, Dose Levels 6, 7, 8, and Confirmation Cohorts

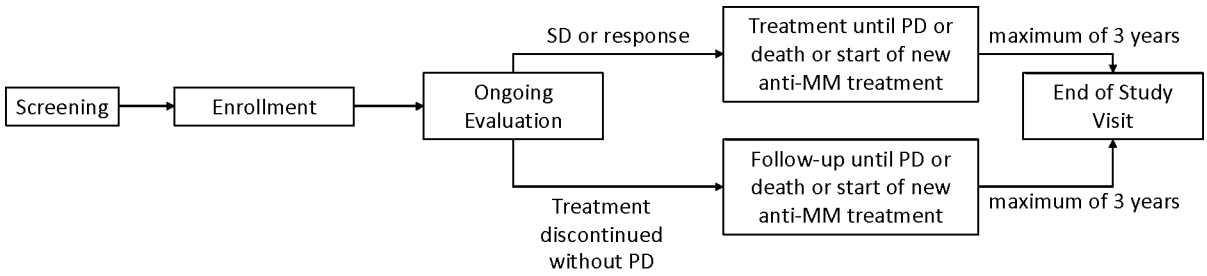

Figure 2: Overall Study Design, Individual Subject Treatment

MM: multiple myeloma; PD: progressive disease; SD: stable disease

Part A: ***MOR03087 dose escalation (bi-weekly treatment):***

Up to 8 dose levels of MOR03087 will be evaluated:

- Cohort 1 - Dose level 1: 0.01 mg/kg
- Cohort 2 - Dose level 2: 0.04 mg/kg
- Cohort 3 - Dose level 3: 0.15 mg/kg
- Cohort 4 - Dose level 4: 0.5 mg/kg
- Cohort 5 - Dose level 5: 1.5 mg/kg
- Cohort 6 - Dose level 6: 4.0 mg/kg
- Cohort 7 - Dose level 7: 8.0 mg/kg
- Cohort 8 - Dose level 8: 16.0 mg/kg

Each 28-day cycle will consist of:

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 adverse events (AEs).

Part B: ***MOR03087 dose escalation (weekly treatment):***

- Dose level 6b: 4.0 mg/kg
- Dose level 7b: 8.0 mg/kg
- Dose level 8b: 16.0 mg/kg

Each 28-day cycle will consist of:

MOR03087 infusion on Days 1, 8, 15, and 22 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle.

Part C: ***MOR03087 dose escalation (weekly/biweekly treatment) plus low dose of DEX:***

- Dose level 6c: 4.0 mg/kg
- Dose level 7c: 8.0 mg/kg
- Dose level 8c: 16.0 mg/kg

Each 28-day cycle will consist of:

MOR03087 infusion on Days 1, 8, 15, and 22 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle.

Only for dose level 8c, for cycles 4 and onwards each 28-day cycle will consist of:

MOR03087 infusion on Days 1 and 15 of the cycle.

Subjects who have received treatment beyond Cycle 3 will be switched to the biweekly schedule at the next Day 1 or Day 15 visit. In exceptional cases – and after discussion between the investigator and the sponsor – the treating physician may determine that it is in the best interest of the subject to remain on the weekly MOR03087 schedule, in which case the sponsor should be informed accordingly.

The low dose of DEX is defined as a single dose of 40 mg once to be orally administered on Days 1, 8, 15, and 22 with the exception of subjects with > 75 years of age, for whom the respective weekly dose should be reduced to 20 mg.

For subjects in Cohort 8c who switch to biweekly MOR03087 treatment from Cycle 4 onwards, the DEX treatment schedule will remain unchanged (Days 1, 8, 15, and 22).

If subjects receive glucocorticosteroids at a dose equivalent of 10 mg prednisone (see exclusion criterion #15), the total weekly dose of glucocorticosteroids must not exceed 20-40 mg of DEX per week. Total dose of DEX should be calculated in accordance with Appendix 18.7.

In Cycle 1 DEX is to be added to the loading dose on Day 4.

Following the completion of Part B dose level 6b and Part C dose level 6c, and taking into account available safety information from Part A dose level 8, the DMC will provide recommendation if some or all of the planned weekly MOR03087 monotherapy dose escalation cohorts will be tested.

Following completion of Parts A, B, and C (dose escalation of MOR03087 bi-weekly and weekly regimen), the MTD or recommended dose and schedule will be confirmed in a minimum of 6 subjects.

Part D: ***MOR03087 (weekly/biweekly treatment) in combination with POM+DEX***

- Dose level 7d: 8.0 mg/kg
- Dose level 8d: 16.0 mg/kg

Each 28-day cycle will consist of:

MOR03087 infusion on Days 1, 8, 15, and 22 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle.

Only for dose level 8d, for cycles 4 and onwards each 28-day cycle will consist of:

MOR03087 infusion on Days 1 and 15 of the cycle.

Subjects who have received treatment beyond Cycle 3 will be switched to the biweekly schedule at the next Day 1 or Day 15 visit. In exceptional cases – and after discussion between the investigator and the sponsor – the treating physician may determine that it is in the best interest of the subject to remain on the weekly MOR03087 schedule, in which case the sponsor should be informed accordingly.

Oral POM 4 mg on Days 1-21 of the 28-day cycle.

Oral DEX 40 mg (≤ 75 years old) or 20 mg (> 75 years old) on Days 1, 8, 15, and 22 of the 28-day cycle.

For subjects in Cohort 8d who switch to biweekly MOR03087 treatment from Cycle 4 onwards, the DEX treatment schedule will remain unchanged (Days 1, 8, 15, and 22).

In Cycle 1 DEX is to be added to the loading dose on Day 4.

Part E: ***MOR03087 (weekly/biweekly treatment) in combination with LEN+DEX***

- Dose level 7e: 8.0 mg/kg
- Dose level 8e: 16.0 mg/kg

Each 28-day cycle will consist of:

MOR03087 infusion on Days 1, 8, 15, and 22 of the cycle. In Cycle 1, a loading dose will additionally be administered on Day 4 of the cycle.

Only for dose level 8e, for cycles 4 and onwards each 28-day cycle will consist of:

MOR03087 infusion on Days 1 and 15 of the cycle.

Subjects who have received treatment beyond Cycle 3 will be switched to the biweekly schedule at the next Day 1 or Day 15 visit. In exceptional cases – and after discussion between the investigator and the sponsor – the treating physician may determine that it is in the best interest of the subject to remain on the weekly MOR03087 schedule, in which case the sponsor should be informed accordingly.

Oral LEN 25 mg on Days 1-21 of the 28-day cycle.

Oral DEX 40 mg (≤ 75 years old) or 20 mg (> 75 years old) on Days 1, 8, 15, and 22 of the 28-day cycle.

For subjects in Cohort 8e who switch to biweekly MOR03087 treatment from Cycle 4 onwards, the DEX treatment schedule will remain unchanged (Days 1, 8, 15, and 22).

In Cycle 1 DEX is to be added to the loading dose on Day 4.

Following completion of Parts D and E (dose escalation of MOR03087 in combination with POM+DEX and LEN+DEX), the MTD and/or recommended dose in each part will be confirmed in a minimum of 6 subjects.

All cohorts:

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 for subsequent administrations.

Based on the individual risk/benefit ratio, subjects who have an ongoing response of at least stable disease (SD) may continue treatment with the assigned study regimen until disease progression or until a maximum of 3 years after first treatment. In case subjects present with progressive disease or with no better status than SD after four treatment cycles starting with Cycle 1 Day 1, the investigator may add a low weekly dose of DEX to the regimen at his/her discretion, provided DEX is not already part of the treatment regimen.

At least 3 subjects meeting all inclusion and none of the exclusion criteria, as determined at the screening visit (see Sections 8.1 and 8.2) will be enrolled into each cohort.

Enrolment into a cohort at the next higher dose level will be based on the data generated from the previous dose level and guided by clinical review until

- the maximum planned dose has been reached, or
- the review of the safety data indicates a need to either expand the current dose level cohort to include 6 subjects or stop the dose escalation or the study, or
- the review of Part B dose level 6b and Part C dose level 6c, including available safety information from Part A dose level 8, indicates that only some of the planned weekly MOR03087 monotherapy dose escalation cohorts should be tested.

The DMC safety review will take place after the third subject enrolled into a cohort has undergone minimum safety evaluations (as defined for the "DLT Evaluable Population" in Section 15.1). The safety assessment will take into account AEs reported from Day 1 after the start of the first infusion through Day 29 before the start of the second cycle. The next cohort will only be started after the positive outcome of the safety assessment.
Cohort expansion up to 6 subjects will be allowed if a dose limiting toxicity (DLT) (as defined in Section 8.5) is observed in 1 of 3 subjects. If 2 or 3 subjects experience a DLT in cohorts 6b or 6c, the study sponsor may decide to test a lower dose. If 2 or 3 subjects of the 3 subjects in any of the other cohorts experience DLT, then the previous cohort should be expanded to 6 subjects.

A pharmacokinetic interim analysis may be performed at any time during dose escalation if unexpected MOR03087 serum concentration results are observed. The rationale for performing the pharmacokinetic interim analysis is to verify whether the derived pharmacokinetic parameters from this interim analysis (e.g., C_{max}, AUC, terminal elimination half-life, etc.) are still within the expected range. If there are major deviations from the expected values, it may be considered necessary to investigate a further dosing regimen or to expand the dose escalation including further cohorts via a substantial amendment to the protocol.

After study drug discontinuation due to reason other than disease progression, all subjects will return for a follow-up visit 1 and follow-up visit 2. Further follow-up visits will be conducted at 4-week intervals until the subject is progressive, begins subsequent anti-myeloma therapy, or dies.

All subjects will be followed up for a maximum of 3 years after first administration of study drug.

Study visits will be conducted according to the Schedules of Assessments provided in Table 1 (for subjects receiving bi-weekly MOR03087 treatment) and Table 2 (for subjects receiving weekly/bi-weekly MOR03087 treatment).

Table 1 Flow Chart and Schedule of Assessments: Part A (Bi-weekly Administration)

		Treatment (Tx) Cycle 1 (Days 1-28)						Tx Cycle 2 (Days 29-56)							
Evaluation or Procedure	**Screening (≤ 4 weeks before Day 1)**	**D1**	**D2**	**D4**	**D8 ± 1 day**	**D15 ± 1 day**	**D22 ± 1 day**	**D29 C2D1 ± 1 day**	**D36 C2D8 ± 1 day**	**D43 C2D15 ± 1 day**	**D50 C2D22 ± 1 day**	**Tx Cycles 3+ Visit: repeated bi-weekly (± 2 days)**	**Follow-up Visit 1 (4 weeks ± 2 days after last dose)**	**Follow-up Visit 2 (4 weeks ± 2 days after Follow-up Visit 1)[1]**	**EOS Visit[2]**
Informed consent	X														
Medical history[3]	X														
Demography	X														
Inclusion/exclusion criteria	X	X[4]													
Karnofsky performance status	X	X[4]								X[4]		X[5]	X	X	X
Premedication		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]			
Study drug administration (2-hour infusion)		X		X		X		X		X		X			
Laboratory															
"Emergency laboratory"[7]		X[8]		X[8]		X[8]		X[8]		X[8]		X			
Hematology	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X	X	X	X
Serum chemistry	X[9]	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X	X	X	X
Coagulation	X							X[4]					X		X
βHCG pregnancy test for women of childbearing potential	X												X	X	X
Urine pregnancy test for women of childbearing potential[4]		X						X				X[5]			
Urinalysis	X	X[4]						X[4]							X
Pharmacokinetics (MOR03087)		X[10]		X[11]		X[11]		X[11]		X[11]	X	X[12]	X		X[13]
Endocrinology (TSH, FSH)	X									X[4]			X		X
Anti-MOR03087 antibodies[14]	X					X[4]				X[4]		X[15]	X	X[16]	X
B, T, and NK cells	X[17]							X[4,17]					X[17]	X	X
Serum and urine M-protein[18], serum free light chains	X[19]	X[4]				X[4]		X[4]		X[4]		X[5, 20]	X	X	X
Response Assessment[20]								X				X[20]	X	X	X
Cytokines		X[21]													
Flow cytometry analysis of peripheral MM cells	X							X							
Serology[22]	X														
Bone/skeletal survey[23]	X														X
Bone marrow (Histology)	X[24]							X[25]							
Biomarker sample (bone marrow)	X[24]														

Table 1 Flow Chart and Schedule of Assessments: Part A (Bi-weekly Administration)

	Treatment (Tx) Cycle 1 (Days 1-28)							Tx Cycle 2 (Days 29-56)				Tx Cycles 3+ Visit: repeated bi-weekly (± 2 days)	Follow-up Visit 1 (4 weeks ± 2 days after last dose)	Follow-up Visit 2 (4 weeks ± 2 days after Follow-up Visit 1)[1]	EOS Visit[2]
Evaluation or Procedure	**Screening (≤ 4 weeks before Day 1)**	**D1**	**D2**	**D4**	**D8 ± 1 day**	**D15 ± 1 day**	**D22 ± 1 day**	**D29 C2D1 ± 1 day**	**D36 C2D8 ± 1 day**	**D43 C2D15 ± 1 day**	**D50 C2D22 ± 1 day**				
Immunophenotyping of MM cells (bone marrow)	X							X[25]							
Cytogenetics of MM cells (bone marrow)	X[24, 26]														
FcγRIIIa polymorphism (mucosal cheek swab)		X[4]													
Examination and other assessments															
Physical examination[27]	X[28]	X[4]			X	X[4]	X	X[4]	X	X[4]	X	X	X	X	X[28]
Body weight and height[29]	X	X[4]		X[4]		X[4]		X[4]		X[4]		X[4]	X	X	X
Quality of life (QLQ-MY20 + QLQ-C30)		X[4]				X[4]				X[4]			X	X	X
Electrocardiogram (ECG)[30]	X		X							X			X[31]	X[31]	X
Vital signs (blood pressure, pulse rate, respiratory rate, body temperature)[32]	X	X[32]	X	X[32]	X	X[32]	X	X[32]	X	X[32]	X	X[32]	X	X	X
Toxicity/AE assessment[33]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X[34]	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X	X	X	X

[1] A follow-up visit will be repeated every fourth week (± 2 days) until progressive disease, or receipt of new anti-myeloma treatment, or until death, but no longer than 3 years from the first study drug administration. Follow-up visits may be delayed for a maximum of 2 weeks after the normal visit window due to other reasons (e.g., logistical).

[2] The EOS visit will occur after at least 28 days after last study drug administration but should be performed before any new MM therapy starts, whichever occurs first. Subjects who complete Cycle 2 but do not receive additional cycles (Cycle 3+) have to perform Follow-up visit 1 and Follow-up visit 2 before EOS visit.

[3] Including disease staging based on Durie-Salmon and International Staging System (ISS) criteria and documentation of immunoglobulin type.

[4] Before study drug administration.

[5] Each cycle, starting with Cycle 3+: pre-dose at Day 1 (CxD1)

[6] During Cycle 1, all subjects should be given premedication including an antipyretic (e.g., paracetamol) and a histamine H1 receptor blocker according to the local standard of care. In medically justified cases, the investigator may use other medications (e.g., steroids as per local standard but not exceeding 10 mg prednisolone equivalent), doses and/or formulations if this is documented thoroughly in the eCRF and the source data. If no infusion reaction occurs during Cycle 1, then premedication can be stopped at discretion of the investigator for subsequent treatment cycles. Otherwise, the premedication should be continued for subsequent administrations of MOR03087 as well.

[7] Emergency Laboratory only to be taken if hematology/serum chemistry is not available prior to study drug administration

[8] Sample to be taken and evaluated before study drug administration. On Day 1, additional sample (except AST and ALT) to be taken 2 hours after end of infusion.

[9] ß2-microglobulin to be measured at Screening only.

[10] Pharmacokinetic sample to be taken predose and then at 1, 2, 4, 8, 14±2 (optional), 22±2, and 28±2 hours after start of first infusion.

[11] Pharmacokinetic sample to be taken predose and 2 hours after start of infusion.

[12] Pharmacokinetic sample during treatment Cycles 3+ to be taken every 2nd study drug administration (CxD15) predose and 2 hours after start of infusion.

[13] Only if subject had no follow-up visit.

[14] Samples for anti-MOR03087 antibodies will also be used to determine tetanus titer if sufficient quantities of serum are available.

[15] Each cycle, starting with Cycle 3+: pre-dose at Day 15 (CxD15)
[16] At second follow-up visit only.
[17] Including CD16 expression on NK cells.
[18] For urine M-protein evaluation, 24-hour urine has to be collected.
[19] For urine M-protein evaluation at Screening, use of pre-collected 24h urine sample which MM subjects bring to the hospital for every routine visit within the scope of usual standard of care procedure is accepted.
[20] Evaluation on Day 1 of every cycle (CxD1). All response categories require two consecutive assessments made at any time prior to the start of any new therapy.
[21] Sample to be taken before study drug administration and 2 hours after end of study drug administration.
[22] Hepatitis B and C.
[23] Where medically indicated, as a regular assessment of standard of care in subjects with relapsed or refractory MM, x-ray, CT, or MRI imaging of the bone will be conducted.
[24] Results from bone marrow examination done within 28 days prior to first dose are acceptable, if the subject has been hematologically stable since then.
[25] Bone marrow on Day 29 (C2D1) is to be assessed only if specific consent for this assessment has been provided.
[26] Only if no historical data are available. First or second bone marrow aspiration sample should be used.
[27] Physical examination will include basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination.
[28] The physical examination should include an ocular examination by an ophthalmologist (including distance visual acuity, optical coherence tomography [if available], and ophthalmoscopy under full mydriasis [if optical coherence tomography is unavailable]).
[29] Height at screening only.
[30] 12-Lead ECG recording with determination of heart rate and RR, PR, QRS, QT, and QT_c intervals.
[31] ECG assessments in Follow-Up Visits are to be conducted only if clinically indicated, per the investigators' discretion.
[32] At Cycles 1 and 2 at study drug administration visits: immediately before infusion; 15 minutes, 30 minutes, and 1 hour after start of infusion; at end of infusion; and 2 and 4 hours after end of infusion. From Cycles 3+ on: only before and at end of infusion.
[33] Infusion reactions, cytokine release syndrome, and allergic reactions to MOR03087 should be reported with respective symptoms (e.g., infusion reaction—hives, chills, fever).
[34] Including history of previous myeloma-specific therapies and prior medications.

Table 2 Flow Chart and Schedule of Assessments: Parts B-E (Weekly/Biweekly Administration)

	Treatment (Tx) Cycle 1 (Days 1-28)							Tx Cycle 2 (Days 29-56)				Tx Cycles 3+ Visit: repeated weekly (biweekly from Cycle 4, CxD1/D15) ± 2 days	Follow-up Visit 1 (4 weeks ± 2 days after last dose)	Follow-up Visit 2 (every 4 weeks ± 2 days after Follow-up Visit 1)[1]	EOS Visit[2]
Evaluation or Procedure	**Screening (≤ 4 weeks before Day 1)**	**D1**	**D2**	**D4**	**D8 ± 1 day**	**D15 ± 1 day**	**D22 ± 1 day**	**D29 C2D1 ± 1 day**	**D36 C2D8 ± 1 day**	**D43 C2D15 ± 1 day**	**D50 C2D22 ± 1 day**				
Informed consent	X														
Medical history[3]	X														
POM or LEN educational leaflet and Pregnancy Counselling	X							X[4]				X[4, 5]			
Demography	X														
Inclusion/exclusion criteria	X	X[4]													
Karnofsky performance status	X	X[4]								X[4]		X[5]	X	X	X
Premedication		X[6]		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]			
Study drug administration MOR03087		X		X	X	X	X	X	X	X	X	X			
Study drug administration DEX tablet[7]		X		X	X	X	X	X	X	X	X	X			
Study drug administration (LEN capsule / POM capsule) and prophylaxis[8]		X	X	X	X	X		X	X	X		X			
Laboratory															
"Emergency laboratory"[9]		X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X			
Hematology	X	X[4]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X
Serum chemistry	X[11]	X[4]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X
Coagulation	X							X[4]					X		X
βHCG pregnancy test for women of childbearing potential	X[12]												X[13]	X	X
Urine pregnancy test for women of childbearing potential[4]		X[12]			X[14]	X[14]	X[14]	X[4]				X[5]			
Urinalysis	X	X[4]						X[4]							X
Pharmacokinetics (MOR03087)		X[15]		X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[17]	X		X[18]
Pharmacokinetics (LEN/POM)		X[19]			X[16]			X[16]		X[16]					
Endocrinology (TSH, FSH)	X							X		X[4]			X		X
Anti-MOR03087 antibodies[20]	X					X[4]				X[4]		X[21]	X	X[22]	X
B, T, and NK cells	X[23]				X[4]			X[4, 23]				X[24]	X[23]	X	X
Serum and urine M-protein[25], serum free light chains	X[26]	X[4]				X[4]		X[4]		X[4]		X[5, 27]	X	X	X
Response assessment[27]								X				X[27]	X	X	X
Cytokines		X[28]													

Table 2 Flow Chart and Schedule of Assessments: Parts B-E (Weekly/Biweekly Administration)

	Treatment (Tx) Cycle 1 (Days 1-28)							Tx Cycle 2 (Days 29-56)				Tx Cycles 3+ Visit: repeated weekly (biweekly from Cycle 4, CxD1/D15) ± 2 days	Follow-up Visit 1 (4 weeks ± 2 days after last dose)	Follow-up Visit 2 (every 4 weeks ± 2 days after Follow-up Visit 1)[1]	EOS Visit[2]
Evaluation or Procedure	**Screening (≤ 4 weeks before Day 1)**	**D1**	**D2**	**D4**	**D8 ± 1 day**	**D15 ± 1 day**	**D22 ± 1 day**	**D29 C2D1 ± 1 day**	**D36 C2D8 ± 1 day**	**D43 C2D15 ± 1 day**	**D50 C2D22 ± 1 day**				
Flow cytometry analysis of peripheral MM cells	X							X							
Serology[29]	X														
Bone/skeletal survey[30]	X														X
Bone marrow (Histology)	X[31]							X[32]							
Biomarker sample (bone marrow)	X[31]														
Immunophenotyping of MM cells (bone marrow)	X[31]							X[32]							
Cytogenetics of MM cells (bone marrow)	X[33]														
FcγRIIIa polymorphism (mucosal cheek swab)		X[4]													
Examinations and other assessments															
Physical examination[34]	X[35]	X[4]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X	X[35]
Body weight and height[36]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	X	X
Quality of life (QLQ-MY20 + QLQ-C30)		X[4]				X[4]				X[4]			X	X	X
Electrocardiogram (ECG)[37]	X	X[37]	X	X[37]	X[37]	X[37]	X	X[37]	X[37]	X[37]	X	X[37]	X[38]	X[38]	X
Venous thrombotic event monitoring[39]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (blood pressure, pulse rate, respiratory rate, body temperature)	X	X[40]	X	X[40]	X[40]	X[40]	X[40]	X[40]	X[40]	X[40]	X[40]	X[40]	X	X	X
Toxicity/AE assessment[41]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X[42]	X[4]	X	X[4]	X[4]	X[4]	X	X[4]	X	X[4]	X	X	X	X	X
Subsequent anti-myeloma treatment															X[43]

[1] A Follow-up visit will be repeated every fourth week (± 2 days) until progressive disease, or receipt of new anti-myeloma treatment, or until death, but no longer than 3 years from the first study drug administration. Follow-up visits may be delayed for a maximum of 2 weeks after the normal visit window due to other reasons (e.g., logistical).

[2] The EOS visit will occur after at least 28 days after last study drug administration but should be performed before any new MM therapy starts, whichever occurs first. Subjects who complete Cycle 2 but do not receive additional cycles (Cycle 3+), have to perform Follow-up visit 1 and Follow-up visit 2 before EOS visit.

[3] Including disease staging based on Durie-Salmon and International Staging System (ISS) criteria and documentation of immunoglobulin type.

[4] Before study drug administration.

[5] Each cycle, starting with Cycle 3+: pre-dose at Day 1 (CxD1)

[6] During Cycle 1, all subjects should be given premedication including an antipyretic (e.g., paracetamol) and a histamine H1 receptor blocker according to the local standard of care. In medically justified cases, the investigator may use other medications (e.g., steroids for the non-DEX cohorts) as per local standard but not exceeding 10 mg prednisolone equivalent), doses

and/or formulations if this is documented thoroughly in the eCRF and the source data. If no infusion reaction occurs during Cycle 1, then premedication can be stopped at investigator's discretion of the investigator for subsequent treatment cycles. Otherwise, the premedication should be continued for subsequent administrations of MOR03087 as well.

[7] DEX should be given up to 3 hours prior to MOR03087 infusion start.

[8] Subjects in Parts D and E are to take POM or LEN capsules, respectively, on Days 1-21 of each treatment 28-day cycle. Thromboembolism prophylaxis during the study treatment is required for subjects; low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given to all subjects taking POM or LEN; Oral application of POM or LEN must be performed at start of MOR03087 infusion (+/- 5min)

[9] Emergency Laboratory only to be taken if hematology/serum chemistry is not available prior to study drug administration

[10] Sample to be taken and evaluated before study drug administration. On Day 1, additional sample (except AST and ALT) to be taken 2 hours after end of infusion.

[11] ß2-microglobulin to be measured at Screening only.

[12] For subjects treated with POM or LEN (Parts D or E), the first pregnancy test must be performed within 10-14 days prior to the start of study treatment, and a second pregnancy test must be performed within 24 hours prior to the start of study treatment.

[13] For female subjects with irregular cycles treated in Parts D and E (POM and LEN), an additional pregnancy test is required 14 days after treatment discontinuation.

[14] Subjects treated in Parts D and E only (POM and LEN): Serum or urine pregnancy test must be performed.

[15] Pharmacokinetic sample (MOR03087) to be taken predose and then at 1, 2, 4, 8, 14±2 (optional), 22±2, and 28±2 hours after start of first MOR03087 infusion.

[16] Pharmacokinetic sample (MOR03087, LEN or POM) to be taken predose and after completion of MOR03087 infusion.

[17] Pharmacokinetic sample during treatment cycles 3+ to be taken every CxD15 predose and after completion of infusion.

[18] Only if subject had no follow-up visit.

[19] Pharmacokinetic sample (POM or LEN) to be taken predose before administration of MOR03087 + LEN or POM and then at 1, 2, 8, 22±2 hours after start of first MOR03087 infusion.

[20] Samples for anti-MOR03087 antibodies will also be used to determine tetanus titer if sufficient quantities of serum available.

[21] Anti-MOR03087 antibody sample during treatment Cycles 3+ to be taken every CxD15 predose.

[22] At second follow-up visit only.

[23] Including CD16 expression on NK cells.

[24] Each cycle, starting with Cycle 3+: pre-dose at Day 15 (CxD15)

[25] For urine M-protein evaluation, 24-hour urine has to be collected. During the first two cycles more Serum and urine M-protein, serum free light chains will be collected.

[26] For urine M-protein evaluation at Screening, use of pre-collected 24h urine sample which MM subjects bring to the hospital for every routine visit within the scope of usual standard of care procedure is accepted.

[27] Evaluation on Day 1 of every cycle (CxD1). All response categories require two consecutive assessments made at any time prior to the start of any new therapy.

[28] Sample to be taken before study drug administration and 2 hours after end of study drug administration.

[29] Hepatitis B and C.

[30] Where medically indicated, as a regular assessment of standard of care in subjects with relapsed or refractory MM, x-ray, CT, or MRI imaging of the bone will be conducted.

[31] Results from bone marrow examination done within 28 days prior to first dose are acceptable, if the subject has been hematologically stable since then.

[32] Bone marrow on Day 29 (C2D1) is to be assessed only if specific consent for this assessment has been provided.

[33] Only if no historical data are available. First or second bone marrow aspiration sample should be used.

[34] Physical examination will include basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination.

[35] The physical examination should include an ocular examination by an ophthalmologist (including distance visual acuity, optical coherence tomography [if available], and ophthalmoscopy under full mydriasis [if optical coherence tomography is unavailable]).

[36] Height at screening only.

[37] 12-Lead ECG recording with determination of heart rate and RR, PR, QRS, QT, and QT_c intervals. Subjects in Part D (POM) only: ECG monitoring will be performed on Cycle 3 Day 1, and on Day 1 of every third cycle thereafter (Cycles 3, 6, 9 etc.) and at treatment discontinuation. Subjects with QT prolongation (or borderline QT prolongation) but otherwise non-

clinically significant will require more frequent ECG monitoring at the discretion of the investigator. Subjects in Part E (LEN) only: ECG monitoring will be performed at each visit at the discretion of the investigator.

[38] ECG assessments in Follow-Up Visits are to be conducted only if clinically indicated, per the investigators' discretion.

[39] Clinical review of signs/symptoms for possible venous thrombotic events in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms.

[40] At Cycles 1 and 2 at study drug administration visits: immediately before infusion; 15 minutes, 30 minutes, and 1 hour after start of infusion; at end of infusion; and 2 and 4 hours after end of infusion. From Cycles 3+ on: before and at end of infusion

[41] Infusion reactions, cytokine release syndrome, and allergic reactions to MOR03087 should be reported with respective symptoms (e.g., infusion reaction—hives, chills, fever).

[42] Including history of previous myeloma-specific therapies and prior medications.

[43] Investigators are to record details of the subjects' subsequent anti-myeloma therapy.

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7.2 Study Timeframe

The anticipated overall time frame for the study will be approximately 8 years.

7.3 Risks and Benefits to Subjects

MOR03087 provides a novel mechanism of action that may add to the care of MM patients and complement standard-of-care treatment. Based on the available data from nonclinical studies and experiments as well as literature data on CD38, the sponsor is of the opinion that the potential benefit of MOR03087 outweighs the potential risk.

The most likely expected effects—thrombocytopenia, anemia, and diarrhea—are frequently encountered events in malignant hematologic practice. The identified potential toxicities can be readily monitored and managed, e.g., by platelet and red blood cell transfusion or respective treatment of gastrointestinal symptoms. It is expected that the potential risks will be adequately controlled by the design of this first-in-human study (e.g., by the inclusion and exclusion criteria) and by frequent monitoring of potential side effects throughout the entire study.

Based on the results of the 12-week repeated dose toxicity study in marmoset monkeys, the earliest biological effect of MOR03087 expected on non-tumor cells is thrombocytopenia and – at higher doses – diarrhea. Diarrhea was almost reversible at the end of the recovery period. A dose-dependent, reversible thrombocytopenia occurred with the first dose and remained stable thereafter.

The most common serious adverse reactions in subjects treated with a combination of LEN or POM and DEX are venous thromboembolism and grade 4 neutropenia, grade 3 or 4 thrombocytopenia, and venous thromboembolism (see Summaries of Product Characteristics [SmPCs]). It is considered unlikely that neutropenia would be potentiated in combination with MOR03087, as neutrophils only express low levels of CD38.

Generally, it cannot be excluded that treatment with LEN and POM may have an additive effect on thrombocytopenia when used in combination with MOR03087.

Although the mechanism for thrombocytopenia induced by MOR03087 is unknown, there is no preclinical evidence of thrombosis associated with MOR03087 in the marmoset monkey. In addition, *ex vivo* analysis of human and marmoset thrombocytes did not show any signs of thrombocyte activation and aggregation by MOR03087.

Close and frequent monitoring of hematological parameters, i.e., complete blood cell count including white blood cell count with differential count, platelet count, hemoglobin and hematocrit, is implemented in the clinical trial protocol.

White blood cell (WBC) counts will be frequently monitored and anticoagulation treatment is mandatory during combination treatment with LEN and DEX, per guidelines.

Other adverse events observed with immunomodulatory agents (i.e., IMiDs) include infection, fatigue, renal failure, neuropathy, venous thromboembolic events, and constipation. With POM and LEN, there are also risks associated with fetal exposure (see Section 7.3.1).

Adverse reactions of long-term treatment with high doses of glucocorticosteroids may include among others: elevation of blood pressure, sodium and water retention, hypothalamic-pituitary

adrenal axis suppression, infections, cataracts, glaucomas, peptic ulcers and myopathies. In the current study, stringent criteria have been established to exclude subjects with pre-existing clinically significant cardiovascular disease, systemic diseases, coexistent infections or antibiotic administration. Study participants will be subjected to close medical scrutiny involving medical history collection and frequent physical and laboratory examinations aimed at the early detection of adverse events.

More extensive information on the risks and benefits associated with the study drugs is provided in the Investigator's Brochure (IB) for MOR03087, and SmPCs for LEN and POM, which will be supplied to the sites. For the information on DEX, please refer to the SmPC of the provided brand.

7.3.1 Pregnancy Prevention Risk Minimization Plans

POM and LEN are structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that LEN produced malformations in the offspring of female monkeys who received the drug during pregnancy; POM was found to be teratogenic in a developmental study in rats and rabbits. A teratogenic effect of POM and LEN in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed. Pregnancy prevention risk minimization plans are provided in Appendix 18.8 and are summarized below.

Appendix 18.8.1 applies to all subjects receiving LEN therapy; Appendix 18.8.2 applies to all subjects receiving POM therapy. The following Pregnancy risk minimization plan documents are included in these appendices:

1) Lenalidomide/Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods;
2) Lenalidomide/Pomalidomide Education and Counseling Guidance Document;
3) Lenalidomide/Pomalidomide Information Sheet.

1. The Lenalidomide/Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document provides the following information:
    - Potential risks to the fetus associated with LEN/POM exposure
    - Definition of Female of Childbearing Potential
    - Pregnancy testing requirements for subjects receiving LEN/POM who are females of childbearing potential
    - Acceptable birth control methods for both female of childbearing potential and male subjects receiving LEN/POM in the study
    - Requirements for counseling of all study subjects receiving LEN/POM about pregnancy precautions and the potential risks of fetal exposure to LEN/POM

2. The Lenalidomide/Pomalidomide Education and Counseling Guidance Document must be completed and signed by either a trained counselor or the Investigator at the participating clinical site prior to each dispensing of LEN/POM study treatment. A copy of this document must be maintained in the subject records.
3. The Lenalidomide/Pomalidomide Information Sheet will be given to each subject receiving LEN/POM study therapy. The subject must read this document prior to starting LEN/POM study treatment and each time they receive a new supply of study drug.

8 POPULATION

This study will be conducted in adult subjects with refractory or relapsed MM. The planned sample size will be up to 126 subjects.

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

8.1 Inclusion Criteria For All Subjects

1. Male or female subjects ≥ 18 years of age
2. Presence of serum M-protein ≥ 0.5 g per 100 mL (≥ 5 g/L) and/or urine M-protein ≥ 200 mg per 24-hour period
3. Life expectancy of > 3 months
4. Karnofsky performance status ≥ 60%
5. Absolute neutrophil count (ANC) ≥ 1.0 (1,000/mm^3)
6. Total bilirubin ≤ 2 × the upper limit of normal (ULN)
7. Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN
8. Hemoglobin ≥ 8 g/dL
9. If a female of childbearing potential, confirmation of a negative pregnancy test before enrolment and use of double-barrier contraception, oral contraceptive plus barrier contraceptive, for at least 28 days prior to, during therapy and for 28 days after the last dose, or confirmation of having undergone clinically documented total hysterectomy and/or bilateral oophorectomy, tubal ligation
10. If a male, he must practise complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy
11. Ability to comply with all study-related procedures, medication use, and evaluations
12. Ability to understand and give written informed consent, and comply with the protocol

Subjects for whom at least one inclusion criterion is not fulfilled are considered screening failures.

8.2 Exclusion Criteria For All Subjects

1. Primary refractory MM
2. Previous treatment with cytotoxic chemotherapy or large-field radiotherapy or other myeloma-specific therapy within 28 days prior to first study treatment (radiation to a single site as concurrent therapy is allowed)
3. Treatment with a systemic investigational agent within 28 days prior to first study treatment.
4. Solitary plasmacytoma or plasma cell leukemia
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 targeting the CD38 antigen or prior therapy with other IgG monoclonal antibodies months within 3 months prior to first study treatment, or IgM monoclonal antibodies within 1 month prior to first study treatment.
9. Clinical or laboratory evidence of active hepatitis B (positive hepatitis B surface antigen [HBsAg] with negative hepatitis B surface antibody [HBsAb]) or hepatitis C (positive hepatitis C virus [HCV] antibody)
10. History of positive human immunodeficiency virus (HIV) test result (enzyme-linked immune-sorbent assay [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 diarrhea 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. MM with central nervous system (CNS) involvement
19. Prior or concomitant malignancy (other than MM) except adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, prostate cancer not requiring treatment or other cancer for which the subject has been disease-free for at least 3 years. For the combination therapy with lenalidomide or pomalidomide, this should be at least 5 years

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

Subjects for whom at least one exclusion criterion is fulfilled are considered screening failures.

8.2.1 Additional Eligibility Criteria for Treatment With MOR03087 With/Without Dexamethasone

Inclusion Criteria

1. Documented diagnosis of MM; specifically, relapsed or refractory MM defined as:
   - Failure of at least two previous therapies; previous therapies must include an immunomodulatory agent and a proteasome inhibitor (either together or as part of different therapies)
   - All subjects must have documented progression during or after their last prior therapy for MM
2. Creatinine clearance $\geq$ 30 mL/min (calculated using the Cockcroft-Gault equation)
3. Platelets:
   - $\geq 80 \times 10^9$/L, without previous transfusion within the last 4 weeks before first study drug administration
   - $\geq 50 \times 10^9$/L (for dose levels $\geq$4 mg/kg with or without DEX). Subjects are not allowed to have received platelet transfusion within the last 4 weeks before study drug administration.

Exclusion Criteria

1. For subjects receiving DEX: Known or suspected hypersensitivity to DEX or any of the excipients

8.2.2 Additional Eligibility Criteria for the Treatment With MOR03087, Dexamethasone and Lenalidomide

Inclusion Criteria

1. Documented diagnosis of MM; specifically, relapsed or refractory MM defined as:
   - Received at least one previous therapy
   - All subjects must have documented progression during or after their last prior therapy for MM
2. Ability to understand the reason for and understand the special conditions of the pregnancy prevention risk minimization plan and give written acknowledgement of these

3. Ability and willingness to comply with the special conditions of the pregnancy prevention risk minimization plan
4. Creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault equation)
5. Platelets:
   - ≥ 75 × 10^9/L for subjects in whom < 50% of bone marrow nucleated cells are plasma cells
   - ≥ 30 × 10^9/L for subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells.

Exclusion Criteria

1. Known or suspected hypersensitivity or intolerance to LEN, POM, thalidomide, DEX or to any of the excipients

During the treatment with LEN, the investigators need to follow the corresponding Pregnancy prevention risk minimization plans (see Appendix 18.8.1).

8.2.3 Additional Eligibility Criteria for the Treatment With MOR03087, Dexamethasone and Pomalidomide

Inclusion Criteria

1. Documented diagnosis of MM; specifically, relapsed and refractory MM defined as:
   - Received at least two previous therapies including LEN and a proteasome inhibitor
   - All subjects must have documented progression during or within 60 days after their last prior therapy for MM
2. Ability to understand the reason for and understand the special conditions of the pregnancy prevention risk minimization plan and give written acknowledgement of these
3. Ability and willingness to comply with the special conditions of the pregnancy prevention risk minimization plan
4. Creatinine clearance ≥ 45 mL/min (calculated using the Cockcroft-Gault equation)
5. Platelets:
   - ≥ 75 × 10^9/L for subjects in whom < 50% of bone marrow nucleated cells are plasma cells
   - ≥ 30 × 10^9/L for subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells

Exclusion Criteria

1. Known or suspected hypersensitivity to POM, LEN, thalidomide, DEX or to any of the excipients

2. Subject who are refractory (defined as progression during or within 60 days after their last dose of POM) or intolerant to POM

During the treatment with POM, the investigators need to follow the corresponding Pregnancy prevention risk minimization plans (see Appendix 18.8.2).

8.3 Definition of Woman of Childbearing Potential

This protocol defines a female of childbearing potential as a sexually mature woman who:

- has not undergone a hysterectomy or bilateral oophorectomy or
- has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

8.4 Procedures for Enrollment

A full written informed consent must be available before the start of screening activities. In addition, for subjects who could potentially be assigned to the MOR03087 + LEN + DEX or MOR03087 + POM + DEX combination therapy parts, a pregnancy prevention information leaflet must also be available before assignment to these parts (see Appendix 18.8).

Enrolment will be performed at baseline after all inclusion and exclusion criteria have been checked and the subject is found to be eligible. Enrolment will be performed by means of an interactive web response system (IWRS) connected to the electronic data capture (EDC) system. The investigator will be informed about the enrolment via an e-mail or FAX.

Part A dose levels 1-7 will be tested sequentially, and only one dose level will be open for enrolment at any time. Starting with Part A dose level 8, Parts B and C will open in parallel (at dose level 6 [6b and 6c]). Following completion of dose level 7c (8.0 mg/kg MOR03087 + DEX) (and dose level 7b if the DMC recommends to open this cohort), Cohorts 7d and 7e may open in parallel with dose levels 8b (if the DMC recommends to open this cohort) and 8c. New cohorts will not start before the DMC returns a positive recommendation based on safety read-outs from prior cohorts as laid down in the DMC Charter.

8.5 Dose Limiting Toxicities

Adverse events will be graded according to NCI CTCAE, version 4.0, with a DLT being defined as an AE assessed as having a suspected or unknown relationship to the study drug (MOR03087, POM, or LEN) and meeting one of the following criteria:

- Non-hematologic DLT:
  - 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)
  - Gastrointestinal
    ≥ Grade 3 vomiting or nausea despite the use of standard antiemetics

≥ Grade 3 diarrhea or constipation despite the use of optimal treatment
- All other events
  ≥ Grade 3 (excluding hypersensitivity reactions and fatigue)

- Hematologic DLT:
  - Grade 4 thrombocytopenia that requires more than one platelet transfusion and does not resolve to grade 2 or less within 14 days
  - Grade 4 neutropenia that does not resolve to grade 2 or less within 14 days
  - Or any other grade 4 hematologic toxicities that do not resolve to grade 2 or less within 14 days and that are considered clinically relevant by the investigator
- Any AE that delays treatment with study drug for more than 14 days

In addition, any event will only qualify as a DLT if a worsening of the event from baseline of at least 2 CTCAE Grades occurs.

The DLTs for the POM combination cohorts are specified as above except for the hematological DLTs which are as follows:

- Hematologic DLT:
  - Grade 4 neutropenia for > 7 days
  - Febrile neutropenia (ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥ 38°C for more than 1 hour)
  - Thrombocytopenia
    - Platelet count < 25,000/µL that requires more than one platelet transfusion or
    - Platelet count ≥ 25,000/µL to < 50,000/µL with significant bleeding (defined as need for hospitalization and/or platelet transfusion)
  - Or any other grade 4 hematologic toxicities that do not resolve to grade 2 or less within 14 days and that are considered clinically relevant by the investigator

The DLTs for the LEN combination cohorts are specified as above except for the hematological DLTs which are as follows:

- Hematologic DLT:
  - Grade 4 neutropenia for > 7 days
  - Febrile neutropenia (ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥ 38°C for more than 1 hour)
  - Thrombocytopenia
    - Platelet count < 30,000/µL that requires more than one platelet transfusion or
    - Platelet count ≥ 30,000/µL to < 50,000/µL with significant bleeding (defined as need for hospitalization and/or platelet transfusion)
  - Or any other grade 4 hematologic toxicities that do not resolve to grade 2 or less within 14 days and that are considered clinically relevant by the investigator

The DLT period covers Day 1 of cycle 1 (starting with first study drug administration) until Day 29 (before start of the second cycle). Granulocyte-colony stimulating factor (GCSF) therapy is prohibited during this time.

Laboratory DLTs will be reported as AEs.

Subjects experiencing DLTs in the study should not receive further study drug.

If upon treatment with POM or LEN, subjects present with protocol-defined DLTs or toxicities or conditions described in the corresponding Section 9.1.4, treatment must be modified or interrupted accordingly.

If upon treatment with DEX, subjects present with protocol-defined toxicities or conditions described in the corresponding SmPC, treatment must be modified or interrupted accordingly.

8.6 Other Reasons for Treatment Postponement

Study drug administration may be delayed for medical or other reasons (e.g., social reasons, weather circumstances). In case of a delay in study drug administration, the treatment should be restarted as early as possible. Should treatment be delayed for more than 14 days after the missed dose, then the treatment should be permanently discontinued. The subject should continue with the first follow-up visit in the study.

8.7 Withdrawal and Termination Criteria

8.7.1 Subject Withdrawal

In accordance with the current version of the Declaration of Helsinki and the European Parliament and Council Directive 2001/20/EC in its current version, each subject is free to withdraw from the study at any time without giving any reason for his or her decision. Investigators also have the right to withdraw subjects from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation and/or protocol non-compliance.

Should the investigator decide to discontinue Investigational Medicinal Product (IMP) administration for a specific subject during the treatment period in the event of illness, AEs, or other reasons concerning the health or well-being of the subject, then the subject will be allowed to complete the follow-up visits in accordance with the protocol.

Should a subject decide to withdraw after administration of the IMP, or should the investigators decide to withdraw the subject, all efforts should be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal (End of Study visit) should be made.

During the conduct of the study, the sponsor will also review the safety data for trends and signals that would indicate the need for withdrawal of a subject or subjects.

If available, the reason for withdrawal should be noted in the electronic Case Report Form (eCRF). If the reason for withdrawal is an AE, monitoring will continue until the outcome is evident (provided that the reason for withdrawal is not "withdraw consent"). The specific event or test result(s) must be recorded in the eCRF.

Subjects may withdraw or may be withdrawn from the study for the following reasons:

- A subject is significantly non-compliant with the requirements of the protocol (e.g., a subject who takes prohibited concomitant medications for a consistent period that, in the investigator's opinion, would interfere with the interpretation of the study data).
- A subject becomes pregnant.
- A subject has an AE that would, in the investigator's judgment, make continued participation in the study an unacceptable risk.
- The sponsor decides to discontinue the study.
- A subject withdraws at his or her own request (withdrawal of consent).
- A subject has major protocol violations.
- A subject is withdrawn at the specific request of the sponsor in case of serious safety concerns.
- A subject is treated with another monoclonal antibody.
- A subject requires different myeloma-specific treatment due to progressive disease.

Subjects who receive specific anti-myeloma treatment other than those specified in the protocol should be withdrawn from the study.

Subjects who withdraw whilst their safety assessment period is not evaluable will only be replaced during the dose-escalation phase until the applicable cohort consists of a sufficient number of evaluable subjects. However, withdrawals due to DLTs will not be replaced.

8.7.2 Study or Site Termination

There are no formal termination criteria for this study. The sponsor reserves the right to terminate the study at any time. The investigator reserves the right to terminate conduct of the study at his/her site at any time. Also, the DMC can recommend termination of the study at any time for reasonable safety reasons. Should this be necessary, 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 subjects' interests. Independent Ethics Committees (IECs) and Competent Authorities will be notified of premature termination in accordance with applicable regulatory requirements.

9 TREATMENT OF SUBJECTS

Each investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor 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.

All IMP containers (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 have been completed by the sponsor or representative. A list of IMP 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 MOR03087, SmPCs for DEX (sample), LEN, and POM, will be supplied to the sites.

9.1 Investigational Medicinal Products

9.1.1 MOR03087

Laboratory Evaluations prior to each Administration of MOR03087

For all administrations of MOR03087, the following parameters should be taken pre-dose on the day of study drug administration and, if outside the limits described below, administration of MOR03087 should be postponed (see Section 8.6):

Value	Subject should not be dosed with MOR03087 if the value is:
Creatinine	> 3 × ULN
Hemoglobin	< 8.0 g/dL (subject should be transfused before dosing)
Platelets	< 25.0 × 10^9/L (< 30.0 × 10^9/L in the LEN and POM parts)
WBC	< 1.0 × 10^9/L
Potassium	> 6.0 mmol/L
Sodium	> 155 mmol/L
AST/ALT	> 3 × ULN

POM, LEN or DEX might have to be interrupted and/or dose reduced as well according to Section 9.1.4.

MOR03087 is a fully human monoclonal antibody targeting the CD38 membrane protein. It is presented as a clear to slightly opalescent, slightly yellowish sterile solution for injection formulated in a histidine buffer at pH 6.8, with sodium chloride (NaCl) and Tween20. MOR03087 will be provided in a labelled 10R glass vial at a concentration of 8-12 mg/mL with an extractable volume of 5 mL (40 mg/vial-60 mg/vial). The appropriate number of vials will be supplied to each respective site. Four vials will be packed in 1 drug box. MOR03087 must be stored at -20°C ± 5°C. The drug has to be obtained from the freezer between 3 days to 16 hours before the planned start of the infusion to allow for the preparation of the infusion. The drug has to be thawed as well as stored at 2-8°C until the preparation for infusion. MOR03087 will be diluted in 100 mL or 250 mL as appropriate with commercially available 0.9% NaCl saline (Ecoflac® plus from B. Braun) for injection and will be provided by the sponsor.

The individual MOR03087 infusion will be prepared at the site, according to directions of the sponsor, which will be laid down in a drug preparation manual. It will be administered by slow intravenous (IV) infusion over approximately 2 hours. If any given infusion is well tolerated and could be administered without any infusion reaction, the subsequent infusion should be administered with the next shortest infusion duration according to the following steps: 90 min.,

60 min., 45 min., 30 min. (scheme in Table 3). Infusion duration should not be shorter than 30 minutes.

Should infusion reactions appear at infusion durations shorter than 2 hours, the subsequent infusion duration should be at least one step higher, i.e., the next longest infusion duration. Only one further series of reductions to shorter infusion durations will then be allowed when at least two consecutive infusions have been well tolerated without infusion reactions (Figure 3).

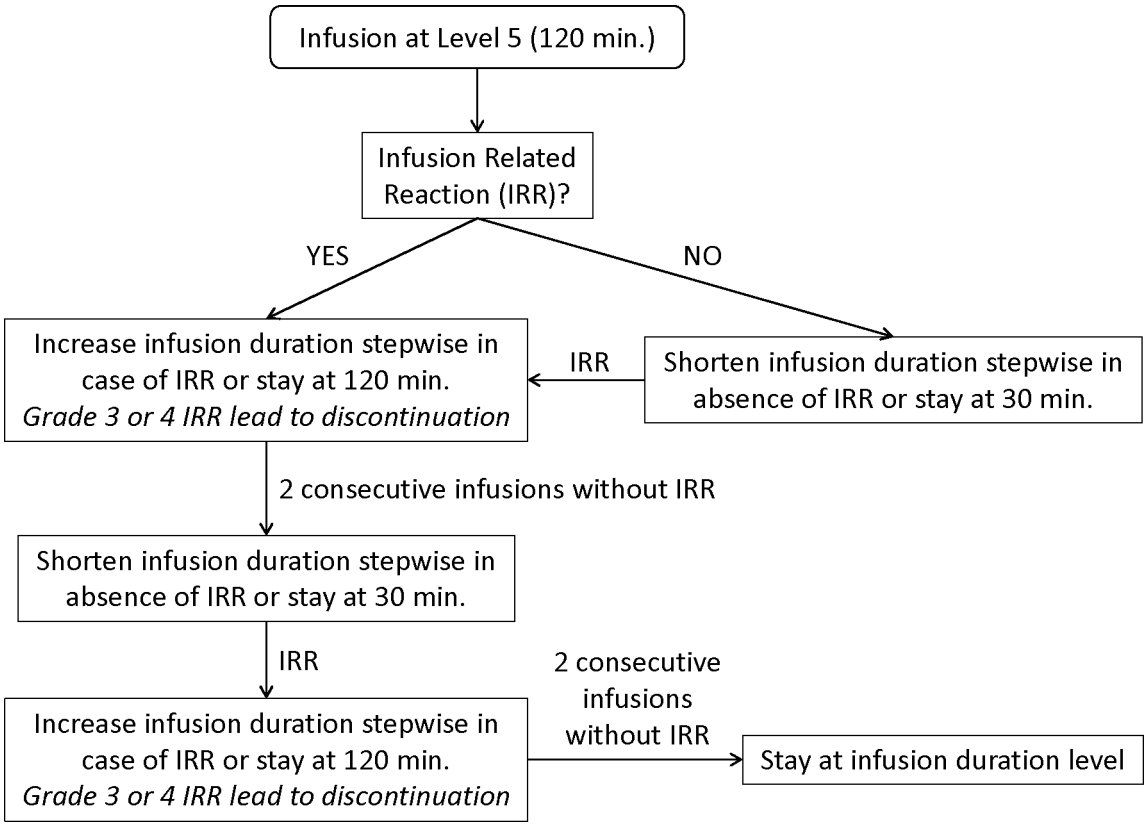
Any grade 3 or 4 infusion-related reactions should lead to discontinuation of the subject, and infusion-related reactions should be managed as outlined in Section 9.1.3.

In exceptional cases – and after discussion between the investigator and the sponsor – the investigator may determine that it is in the best interest of the subject not to change the duration of the infusion following this scheme but to continue to use a 2 hour infusion duration, in which case the sponsor should be informed accordingly.

Table 3 Scheme for Shortening of Infusion Duration

Level	Infusion Duration
5	120 min.
4	90 min.
3	60 min.
2	45 min.
1	30 min.

Figure 3 Flow-chart for the Shortening of Infusion Duration



In the first cohort only, the infusion of MOR03087 will be preceded by a 1-hour infusion of 50 mL 5% human albumin (Alburex®; CSL Behringer), to saturate the infusion line with protein in order to block binding of the antibody to the plastic infusion line. This aims to optimize the amount of antibody delivered at such a low dose as that given in Part A/ escalation dose 1.

9.1.2 Drugs Used in Combination with MOR03087

9.1.2.1 Lenalidomide

Lenalidomide (Revlimid®) will be supplied by the sponsor. LEN capsules for oral administration are commercially available in multiple dosage strengths containing LEN (5 mg, 10 mg, 15 mg, and 25 mg) and conventional solid oral dosage excipients. The appropriate strength will be supplied to the subject. LEN should be stored as directed on the label.

Lenalidomide must be handled per special warnings and precautions for use as specified in the SmPC for Revlimid®.

9.1.2.2 Pomalidomide

Pomalidomide (Imnovid®) will be supplied by the sponsor. POM (Imnovid®) capsules for oral administration are commercially available in multiple dosage strengths containing POM (1 mg,

2 mg, 3 mg and 4 mg) and conventional solid oral dosage excipients. The appropriate strength will be supplied to the subject. POM should be stored as directed on the label.

Pomalidomide must be handled per special warnings and precautions for use as specified in the SmPC for Imnovid®.

9.1.2.3 Dexamethasone

DEX tablets containing 8.0 mg dexamethasone for oral administration will be provided by the sponsor from a commercial source. DEX should be stored as directed on the label.

9.1.3 Premedication and Management of Infusion Reactions

During Cycle 1, all subjects should be given premedication, including an antipyretic (e.g., paracetamol), and a histamine H1 receptor blocker according to the local standard of care. In medically justified cases, the investigator may use other medications (e.g., steroids for the non-DEX-cohorts as per local standard but not exceeding 10 mg prednisolone equivalent), doses and/or formulations if this is documented thoroughly in the eCRF and the source data. If the subject did not have any infusion reaction during Cycle 1, then premedication can be stopped at the discretion of the investigator for subsequent treatment cycles. Otherwise, the premedication should be continued for subsequent administrations of MOR03087 as well.

Grade 1 or 2 infusion reactions

If a subject presents with grade 1 or grade 2 infusion reactions:

- Infusion should be stopped.
- Subject should receive appropriate treatment with an H1 antihistamine and/or paracetamol or prednisolone.
- Once symptoms are resolved, the infusion can be continued at an infusion rate of 50% of the initial rate until the complete dose is administered.

Grade 3 or 4 infusion reactions

If a subject presents with grade 3 or grade 4 infusion reactions:

- Infusion should be discontinued immediately.
- Subject should receive appropriate treatment with an H1 antihistamine and/or paracetamol or prednisolone as clinically indicated and, if necessary, further medications (i.e., epinephrine, bronchodilator).
- Subject should not receive further study drug.

9.1.4 Dose Reductions and Modifications for POM, LEN and DEX

If the treatment has been interrupted and the next cycle is delayed beyond 29 days after Day 1 of the prior cycle, then Day 1 of the next cycle will be defined as the first day that the treatment is resumed.

9.1.4.1 LEN Dose Modification

Subjects will be evaluated for AEs at each visit with the NCI CTCAE version 4.0 as a guide for the grading. Interruptions and reductions are permitted throughout the study.

Table 4 outlines the dose reduction steps for LEN. Instructions for dose interruptions and reductions for LEN are outlined in Table 5.

Table 4 Lenalidomide Dose Reduction Steps by Dose Level

Dose Levels	LEN Dose Reduction (Days 1 – 21 of Every 28-Day Cycle)
Starting Dose	25 mg
Dose Level -1	15 mg
Dose Level -2	10 mg
Dose Level -3	5 mg

LEN: lenalidomide

Table 5 LEN Dose Modification Instructions for Toxicities

Toxicity	LEN Dose Modification
Neutropenia (ANC < 0.5 x 10^9/L)	Stop LEN dosing and follow hematology weekly. If the subject was not receiving GCSF therapy, GCSF therapy may be started at the discretion of the treating physician. When ANC returns to ≥ 0.5 x10^9/L, LEN dosing may be restarted at same dose level if neutropenia was the only DLT and GCSF treatments are continued, or decreased by one dose level. Note: GCSF is prohibited during Cycle 1
Thrombocytopenia (Platelets <30 x10^9/L)	Stop LEN dosing and follow hematology weekly. When platelets return to ≥ 30 x10^9/L, resume LEN dosing at one dose level lower

Toxicity	LEN Dose Modification
Rash	Grade 2-3 skin rash: LEN interruption or discontinuation should be considered at the discretion of the treating physician. Angioedema, Grade 4 rash, exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis is suspected, LEN must be discontinued permanently
Other ≥ Grade 3 LEN-related adverse events	Stop LEN dosing and restart at one dose level lower when toxicity has resolved to ≤ Grade 2 at physician's discretion.

ANC: absolute neutrophil count; DLT: dose limiting toxicity; GCSF: granulocyte colony-stimulating factor; LEN: lenalidomide

LEN should be discontinued if the subject is unable to tolerate the lowest dose level. At the discretion of the investigator, the treatment with MOR03087 and dexamethasone may be continued.

9.1.4.2 POM Dose Modification

Subjects will be evaluated for AEs at each visit with the NCI CTCAE version 4.0 as a guide for the grading. Interruptions and reductions are permitted throughout the study.

Table 6 outlines the dose reduction steps for POM. Instructions for dose interruptions and reductions for POM are outlined in Table 7 (hematologic and non-hematologic toxicities).

Table 6 Pomalidomide Dose Reduction Steps by Dose Level

Dose Level (Days 1-21 of 28 days)	POM Dose Reduction (Days 1-21 of Every 28-Day Cycle)
Starting dose	4 mg
Dose Level -1	3 mg
Dose Level -2	2 mg
Dose Level -3	1 mg[1]

POM: pomalidomide
[1] The POM treatment regimen should be discontinued if the subject cannot tolerate the 1 mg dose.

Table 7 Pomalidomide Dose Modification Instructions for Toxicities

Toxicity	POM Dose Modification
Neutropenia ANC < 0.5 x 10^9/L) or Febrile neutropenia (fever ≥ 38.5 °C and ANC < 1.0 x 10^9/L)	Hold POM dosing and follow hematology weekly. If the subject was not receiving GCSF therapy, GCSF therapy may be started at the discretion of the treating physician. When ANC returns to ≥ 0.5 x 10^9/L, restart POM dosing at one dose level lower. Note: GCSF is prohibited during Cycle 1
Thrombocytopenia (Platelets < 25 x 10^9/L)	Hold POM dosing and follow hematology weekly. POM dosing may resume at one dose level lower once the platelet count has recovered to ≥ 50,000/µL.
Other ≥ Grade 3 POM-related toxicities	Interrupt POM dosing and restart at one dose level lower when toxicity has resolved to ≤ Grade 2 at the physician's discretion

ANC: absolute neutrophil count; GCSF: granulocyte colony-stimulating factor; POM: pomalidomide

To initiate a new cycle of POM, the neutrophil count must be ≥ 0.5 x 10^9/L with or without GCSF, the platelet count must be ≥ 50 x 10^9/L.

POM should be discontinued if subject is unable to tolerate the lowest dose level. At the discretion of the investigator, the treatment with MOR03087 and dexamethasone may be continued.

9.1.4.3 DEX Dose Modifications

Table 8 and Table 9 outline the dose reduction steps for DEX, and instructions for dose interruptions and reductions can be found in Table 10.

Table 8 DEX Dose Reduction Steps (Less Than or Equal to 75 Years Old)

Dose Level	DEX Dose (Days 1, 8, 15, 22 of 28 days)
Starting Dose	40 mg
Dose Level -1	20 mg
Dose Level -2	10 mg[1]

1 DEX should be discontinued if subject is unable to tolerate 10 mg dose. Subjects may continue on single agent POM or LEN until disease progression.

Table 9 DEX Dose Reduction Steps (More Than 75 years Old)

Dose Level	DEX Dose (Days 1, 8, 15, 22 of 28 days)
Starting Dose	20 mg
Dose Level -1	12 mg
Dose Level -2	8 mg[1]

[1] DEX should be discontinued if subject is unable to tolerate 8 mg dose. Subjects may continue on single agent POM or LEN until disease progression.

Table 10 Dose Reductions for Dexamethasone Related Toxicities

Toxicity	DEX Dose Modification
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Hold dose until symptoms are controlled. Add histamine (H2) blocker or equivalent and decrease one dose level when dose is restarted.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Hold dose until symptoms resolve. When dose is restarted decrease dose by one dose level.
Muscle weakness (steroid myopathy) ≥ Grade 2	Hold dose until muscle weakness ≤ Grade 1. When dose is restarted decrease dose by one dose level.
Hyperglycemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue subject from DEX treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop DEX dosing until the adverse event resolves to ≤ Grade 2. Decrease by one dose level when DEX dosing is resumed.

DEX: dexamethasone
If recovery from toxicities is prolonged beyond 14 days, then the dose of DEX will be decreased by one dose level.

9.2 Method of Numbering Subjects and Assigning Subjects to Treatment Groups

Part A dose levels 1-7 will be tested sequentially and only one dose level will be open for enrolment at any time. Starting with Part A dose level 8, Parts B and C will open in parallel (at dose level 6 [6b and 6c]). Following completion of dose level 7c (8.0 mg/kg MOR03087 + DEX) (and dose level 7b if the DMC recommends to open this cohort), Cohorts 7d and 7e may open in parallel with dose levels 8b (if the DMC recommends to open this cohort) and 8c (see Section 7.1, Figure 1). New cohorts will not start before the DMC returns a positive recommendation based on safety read-outs from prior cohorts as laid down in the DMC Charter.

The allocation to a cohort will be technically managed by the IWRS system based on an external algorithm starting from cohorts 7c and 8.

For each subject screened, the investigator or designee will log into the IWRS system and will enter the month and year of birth and the gender. The IWRS will allocate the next available screening identification (ID) number, ensuring that screening ID numbers are assigned sequentially per site. The screening ID number will be a 5-digit number with the first 2 digits identifying the site (10, 11, …) and the last 3 digits identifying the sequence number assigned

by the IWRS (001, 002, ...) for each site continuously. For sites located in Germany, the site number will start with 1 or 2, and for sites located in Austria with 3. Leading zeros will be used for the second part of the ID number to ensure a consistent length of 5 digits. The third subject screened at site 14 in Germany would, for example, be identified as 14003. The fourth subject screened at site 14 in Germany would, for example, be identified as 14004.

The investigator will enter the information (i.e., gender, month and year of birth and the associated screening ID number) into the confidential subject identification list.

If the subject qualifies, enrolment will be done centrally at baseline, again employing the IWRS. The part and dose level assignment has to be triggered via IWRS between 3 days and at least 16 hours before the planned administration of MOR03087. The fact that a subject has been enrolled will be reported immediately and automatically by the system to the dedicated pharmacist (if applicable), the investigator, the Clinical Research Organization (CRO), and the sponsor. The IWRS report will contain the information on the respective part/dose level the subject is enrolled to.

The IWRS will only allow enrolment to the next cohort with a higher dosing regimen in the respective study arm after that cohort has been actively opened in the IWRS system for enrolment following DMC review.

The subject will be identified by the previously assigned screening ID number throughout the study. No additional subject or randomization number will be used.

A subject enrolled in the study is not permitted to re-enroll for a second course of study participation.

Subjects who are considered screening failures may be re-screened again only once. In this case, the subjects will receive a new subject number. The period between both screening visits needs to be at least 6 weeks.

9.3 Blinding

Blinding at the level of study treatment does not apply since the study will be open label.

9.4 Prior and Concomitant Therapy

Any prior, concomitant, or procedural medications or therapy given to or taken by the subject within 1 month before and up to the end of the study will be recorded in the eCRF along with the indication and dosage. However, information should be provided on any previous myeloma-specific therapies since the time point of the first diagnosis of MM. This information should include start and end of administration, best response achieved using respective medication(s) with corresponding date and diagnosis of disease progression (date and type) using respective medication(s). The generic or the trade name may be recorded. Other than the IMP, subjects should not receive any other myeloma-specific therapy during the study.

Non-investigational medications needed to treat concomitant medical conditions may be continued during the study. Any other medication for treatment of symptoms of MM 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 myeloma-related therapies before those therapies are started.

Subjects will continue to receive packed red blood cell (RBC) as clinically indicated. Information regarding transfusions during the study will be recorded in the eCRF.

Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM parts of the study is mandatory. Low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given during the study to all subjects assigned to receive POM or LEN. As of Day 29 (Cycle 2), GCSF therapy can be given at the discretion of the investigator, if clinically indicated.

However, treatments that might potentially interfere with the IMPs should be avoided and, with the exception of treatments required in emergency situations, these should be approved by the medical monitor prior to administration.

The investigator should instruct the subject 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 subject has signed the informed consent must be listed on the concomitant medications form in the eCRF.

All respective treatments, including for example transfusions, should be recorded in the eCRF as concomitant medication.

9.5 Treatment Compliance

LEN, POM and DEX will be taken orally either under the supervision of the investigator or at home.

Subjects will be provided with the appropriate number of POM or LEN capsules and DEX tablets.

Drug accountability will be noted by the field monitor during site visits and at the completion of the study. On all other occasions, the subject will take LEN or POM capsules and DEX tablets as directed by the investigator at home. Compliance will be confirmed by the accounting of used and unused medication, which will be recorded in the eCRF.

10 STUDY PROCEDURES

All efficacy and safety measurements obtained during the course of the study are summarized in the study flow charts and schedule of assessments (see Section 7.1).

All subjects must satisfy all of the inclusion criteria and none of the exclusion criteria listed in Sections 8.1 and 8.2. Signed and dated informed consent must be obtained from all subjects prior to their entering the study.

10.1 Dose Escalation Parts A - E (Bi-Weekly or Weekly MOR03087 With or Without DEX, Weekly with POM+DEX, Weekly with LEN+DEX) and Confirmation Cohorts

10.1.1 Screening (≤ 4 Weeks before Day 1)

The following will be obtained or performed at screening:

- Informed consent
- Obtain screening ID from IWRS
- Medical history, including disease staging based on Durie-Salmon and International Staging System (ISS) criteria (Durie 1975; Greipp 2005) and documentation of immunoglobulin type; in addition, in subjects assigned to receive POM or LEN, all prior venous thrombotic events (VTE) and pulmonary embolisms that occurred will be collected
- Demography
- Inclusion/exclusion criteria
- Karnofsky performance status
- Blood samples for evaluation of hematology, serum chemistry (including ß2-microglobulin), coagulation, beta human chorionic gonadotropin (βHCG) pregnancy test for women of childbearing potential (**to be performed within 10-14 days prior to the start of treatment in study cohorts that include LEN or POM**), endocrinology, anti-MOR03087 antibodies, B, T, and NK cells including CD16 expression, serum M-protein, serum free light chains (FLCs), serology (hepatitis B and C), and flow cytometry of peripheral MM cells
- Urine sample for urinalysis
- Sample from 24-hour urine for evaluation of urine M-protein. It is accepted that the pre-collected 24-hour urine sample which MM subjects bring to the hospital for every routine visit within the scope of usual standard of care procedure is used for the screening analysis.
- Bone marrow biopsy sample for histology, immunophenotyping (CD38 expression on MM cells), cytogenetics of MM cells (if no historical data are available), and biomarker storage sample (results from bone marrow examination done within 28 days prior to first dose are acceptable, if the subject has been hematologically stable since then)
- Bone skeletal survey by x-ray, CT, or MRI imaging (where medically indicated, as a regular assessment of standard of care in subjects with relapsed or refractory MM)
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Ocular examination by an ophthalmologist (including distance visual acuity, optical coherence tomography [if available], and ophthalmoscopy under full mydriasis [if optical coherence tomography is unavailable])

- Body weight and height
- 12-Lead electrocardiogram (ECG)
- Vital signs (blood pressure, pulse rate, respiratory rate, body temperature)
- Prior and concomitant medications, including history of previous myeloma-specific therapies and best response and type of disease progression for each previous MM treatment line

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed:

- All subjects (females as well as males) enrolled in the LEN and POM parts will receive an educational leaflet appropriate to their treatment, and will receive Pregnancy Counselling (see Section 12.2 and Appendix 18.8.1.3 / 18.8.2.3).
- Clinical review of sign/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms.

10.1.2 Cycle 1: Day 1

The inclusion/exclusion criteria should be reviewed prior to study drug administration on Day 1. Eligibility is based on screening and pre-dose day 1 laboratory values. If the subject is eligible, drug release via IWRS has to be triggered between 3 days to 16 hours before the planned start of MOR03087 infusion. The MOR03087 vial(s) have to be obtained from the freezer 3 days to 16 hours, thawed at 2-8°C, and stored at 2-8°C before the planned start of study drug administration.

For women of childbearing potential in study cohorts that include LEN or POM, a pregnancy test (serum or urine) is to be performed within 24 hours prior to the start of treatment (see Section 12.2 and Appendix 18.8.1.3 / 18.8.2.3).

On Day 1, the following will be obtained, performed, or assessed prior to study drug administration:

- Inclusion/exclusion criteria
- Toxicity/AE assessment since last visit
- Concomitant medications
- Karnofsky performance status
- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration), hematology, serum chemistry, predose pharmacokinetics (MOR03087 +/- LEN or POM), cytokines, serum M-Protein and serum FLC assessments.

- Sample from 24-hour urine for M-Protein
- Urine sample for urinalysis, and urine pregnancy test for women of childbearing potential
- Mucosal cheek swab for DNA analysis of FcγRIIIa polymorphism
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Body weight
- Quality of life questionnaires (QLQ-MY20 and QLQ-C30)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature immediately before infusion)
- Premedication

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed:

- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- For subjects treated with LEN, 12-lead ECG may be performed at the investigator's discretion

Study drug administration:

- MOR03087 Study drug administration (2-hour infusion)
- DEX, POM, LEN administration according to cohort assignment; time point for oral application of POM or LEN at start of MOR03087 infusion (+/- 5min). DEX should be given up to 3 hours prior to MOR03087 infusion start.

The following will be obtained, performed, or assessed after start of study drug administration:

- Blood samples for MOR03087 pharmacokinetics at 1, 2, 4, 8, and optional at 14 ± 2 (if on Day 1) hours after start of first infusion
- According to cohort assignment blood samples for POM or LEN pharmacokinetics at 1, 2 and 8 hours after start of first infusion
- Blood sample for "emergency laboratory" (except AST and ALT) for immediate evaluation and cytokines both 2 hours after end of infusion
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion

- Ongoing toxicity/AE assessment during the visit

10.1.3 Cycle 1: Day 2

On Day 2, the following will be obtained, performed, or assessed:

- Blood sample for hematology and serum chemistry
- Blood samples for MOR03087 pharmacokinetics at 14 ± 2 (if not taken on day 1) (optional), 22 ± 2, and 28 ± 2 hours after start of first infusion
- According to cohort assignment blood samples for POM or LEN pharmacokinetics at 22 ± 2 hours after start of first infusion
- 12-Lead ECG
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature)
- Toxicity/AE assessment
- Concomitant medication

For subjects receiving weekly treatment, study drug administration:

- POM, LEN administration according to cohort assignment; POM and LEN will be administered daily on Days 1-21 of each 28-day cycle.

At least 48 hours will pass between the first study drug administrations to the subjects of a cohort in order to observe for AEs. This provision will be waived for subjects in cohorts 6b/6c - 8b/8c as well as 7d/7e and 8d/8e.

After the first administration of study drug, the subjects will remain at the site until the end of Day 2 for safety monitoring.

10.1.4 Cycle 1: Day 4

The MOR03087 vial(s) have to be obtained from the freezer 3 days to 16 hours before planned start of study drug administration. The vials have to be thawed and stored at 2-8°C until preparation for administration.

On Day 4, the following will be obtained, performed, or assessed prior to study drug administration:

- Toxicity/AE assessment since the last visit
- Concomitant medications

- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration), hematology, serum chemistry, and predose pharmacokinetics (MOR03087)
- Body weight
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)
- Premedication

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed:

- For subjects treated with LEN, 12-lead ECG may be performed at the investigator's discretion
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts

Study drug administration

- MOR03087 Study drug administration.
- POM, LEN administration according to cohort assignment; POM and LEN will be administered daily on Days 1-21 of each 28-day cycle; time point for oral application of POM or LEN at start of MOR03087 infusion (+/- 5min)

The following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion
- Blood sample for MOR03087 pharmacokinetics (after completion of infusion)
- Ongoing toxicity/AE assessment during the visit

10.1.5 Cycle 1: Day 8

On Day 8, the following will be obtained, performed, or assessed (for weekly treatment prior to study drug administration):

- Toxicity/AE assessment since last visit
- Concomitant medications
- Blood sample for hematology and serum chemistry

- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed prior to study drug administration:

- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- For women of childbearing potential in study cohorts that include LEN or POM, a pregnancy test (serum or urine) is to be performed.
- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration), for predose pharmacokinetics (MOR03087, +/-DEX, +/- POM / LEN) and for B, T, and NK cells
- Body weight
- 12-Lead ECG (for subjects treated with LEN this assessment is at the investigator's discretion)
- Premedication

For subjects receiving weekly treatment, study drug administration:

- MOR03087 Study drug administration
- DEX, POM, LEN administration according to cohort assignment; POM and LEN will be administered daily on Days 1-21 of each 28-day cycle; time point for oral application of POM or LEN at start of MOR03087 infusion (+/- 5min). DEX should be given up to 3 hours prior to MOR03087 infusion start.

The following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion
- Ongoing toxicity/AE assessment during the visit
- Blood sample for MOR03087 pharmacokinetics (after completion of infusion)
- According to cohort assignment, blood samples for POM or LEN pharmacokinetics (after completion of infusion)

10.1.6 Cycle 1: Day 15

The MOR03087 vial(s) have to be obtained from the freezer 3 days to 16 hours before planned start of study drug administration. The vials have to be thawed and stored at 2-8°C until preparation for administration.

On Day 15, the following will be obtained, performed, or assessed prior to study drug administration:

- Toxicity/AE assessment since the last visit
- Concomitant medications
- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration), hematology, serum chemistry, anti-MOR03087 antibodies, and predose pharmacokinetics (MOR03087), serum M-Protein and serum FLC assessments.
- Sample from 24-hour urine for M-Protein
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Body weight
- Quality of life questionnaires (QLQ-MY20 and QLQ-C30)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)
- Premedication

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed prior to study drug administration:

- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- For subjects treated with LEN, 12-lead ECG may be performed at the investigator's discretion
- For women of childbearing potential in study cohorts that include LEN or POM, a pregnancy test (serum or urine) is to be performed

Study drug administration:

- MOR03087 Study drug administration
- DEX, POM, LEN administration according to cohort assignment; POM and LEN will be administered daily on Days 1-21 of each 28-day cycle; time point for oral application of

POM or LEN at start of MOR03087 infusion (+/- 5min). DEX should be given up to 3 hours prior to MOR03087 infusion start.

The following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion
- Blood sample for MOR03087 pharmacokinetics (after completion of infusion)
- Ongoing toxicity/AE assessment during the visit

10.1.7 Cycle 1: Day 22

On Day 22, the following will be obtained, performed, or assessed (for weekly treatment prior to study drug administration):

- Toxicity/AE assessment since last visit
- Concomitant medications
- Blood sample for hematology and serum chemistry
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed prior to study drug administration:

- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration) and for predose pharmacokinetics (MOR03087)
- 12-Lead ECG (for subjects treated with LEN this assessment is at the investigator's discretion)
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- For women of childbearing potential in study cohorts that include LEN or POM, a pregnancy test (serum or urine) is to be performed within 24 hours prior to the start of treatment
- Body weight
- Premedication

For subjects receiving weekly treatment, study drug administration:

- MOR03087 Study drug administration
- DEX administration according to cohort assignment. DEX should be given up to 3 hours prior to MOR03087 infusion start.

For subjects receiving weekly treatment, the following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion
- Blood sample for MOR03087 pharmacokinetics (after completion of infusion)
- Ongoing toxicity/AE assessment during the visit

10.1.8 Day 29 Visit (C2D1)

The MOR03087 vial(s) have to be obtained from the freezer 3 days to 16 hours before planned start of study drug administration. The vials have to be thawed and stored at 2-8°C until preparation for administration.

The following will be obtained, performed, or assessed prior to study drug administration:

- Toxicity/AE assessment since the last visit
- Concomitant medication
- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration), hematology, serum chemistry, coagulation, B, T, and NK cells including CD16 expression, flow cytometry of peripheral MM cells, and predose pharmacokinetics (MOR03087), serum M-Protein and serum FLC assessments.
- Sample from 24-hour urine for M-Protein
- Urine sample for urinalysis and urine pregnancy test for women of childbearing potential
- Body weight
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Premedication (at the investigator's discretion if no infusion reaction during Cycle 1)

For subjects who signed specific consent for additional bone marrow aspiration

- Bone marrow aspirate and biopsy: histology, immunophenotyping of MM cells (CD38 expression on MM cells)

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed prior to study drug administration:

- All subjects (females as well as males) enrolled in the LEN and POM parts will receive an educational leaflet appropriate to their treatment, and will receive Pregnancy Counselling (see Section 12.2 and Appendix 18.8.1.3 / 18.8.2.3)
- Blood sample for endocrinology and predose pharmacokinetics (LEN / POM)
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- For subjects treated with LEN, 12-lead ECG may be performed at the investigator's discretion

Study drug administration:

- MOR03087 Study drug administration
- DEX, POM, LEN administration according to cohort assignment; POM and LEN will be administered daily on Days 1-21 of each 28-day cycle; time point for oral application of POM or LEN at start of MOR03087 infusion (+/- 5min). DEX should be given up to 3 hours prior to MOR03087 infusion start.

The following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion
- Blood sample for MOR03087 pharmacokinetics (after completion of infusion)
- According to cohort assignment, blood samples for POM or LEN pharmacokinetics (after completion of infusion)
- Response assessment. Note: all responses require two consecutive assessments, and should ideally be confirmed at Day 1 of the following cycle.
- Ongoing toxicity/AE assessment during the visit

10.1.9 Day 36 Visit (C2D8)

On Day 36, the following will be obtained, performed, or assessed (for weekly treatment prior to study drug administration):

- Toxicity/AE assessment since last visit
- Concomitant medications

- Blood sample for hematology and serum chemistry
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed prior to study drug administration:

- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration) and for predose pharmacokinetics (MOR03087)
- Body weight
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- For subjects treated with LEN, 12-lead ECG may be performed at the investigator's discretion
- Premedication

For subjects receiving weekly treatment, study drug administration:

- MOR03087 Study drug administration
- DEX, POM, LEN administration according to cohort assignment; POM and LEN will be administered daily on Days 1-21 of each 28-day cycle; time point for oral application of POM or LEN at start of MOR03087 infusion (+/- 5min). DEX should be given up to 3 hours prior to MOR03087 infusion start.

For all cohorts the following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion
- Blood sample for MOR03087 pharmacokinetics (after completion of infusion)
- Ongoing toxicity/AE assessment during the visit

10.1.10 Day 43 Visit (C2D15)

The MOR03087 vial(s) have to be obtained from the freezer 3 days to 16 hours before planned start of study drug administration. The vials have to be thawed and stored at 2-8°C until preparation for administration.

The following will be obtained, performed, or assessed prior to study drug administration:

- Toxicity/AE assessment since the last visit
- Concomitant medication
- Karnofsky performance status
- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration), hematology, serum chemistry, endocrinology, anti-MOR03087 antibodies, serum M-protein, serum FLCs, and predose pharmacokinetics (MOR03087)
- Sample from 24-hour urine for urine M-protein
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Body weight
- Quality of life questionnaires (QLQ-MY20 and QLQ-C30)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)
- Premedication (at the investigator's discretion if no infusion reaction during Cycle 1)

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed prior to study drug administration:

- Blood sample for predose pharmacokinetics (LEN / POM)
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- For subjects treated with LEN, 12-lead ECG may be performed at the investigator's discretion

Study drug administration:

- MOR03087 Study drug administration
- DEX, POM, LEN administration according to cohort assignment; POM and LEN will be administered daily on Days 1-21 of each 28-day cycle; time point for oral application of POM or LEN at start of MOR03087 infusion (+/- 5min). DEX should be given up to 3 hours prior to MOR03087 infusion start.

The following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion
- Blood sample for MOR03087 pharmacokinetics (after completion of infusion)
- Ongoing toxicity/AE assessment during the visit

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed after study drug administration:

- According to cohort assignment blood samples for POM or LEN pharmacokinetics (after completion of infusion)

10.1.11 Day 50 Visit (C2D22)

On Day 50, the following will be obtained, performed, or assessed:

- Toxicity/AE assessment since last visit
- Concomitant medications
- Blood sample for hematology, serum chemistry, and pharmacokinetics (MOR03087)
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)

For subjects receiving weekly treatment, the additional following will be obtained, performed, or assessed prior to study drug administration:

- Blood sample for "emergency laboratory" for immediate evaluation before study drug administration (only to be taken if hematology/serum chemistry is not available prior to study drug administration)
- Body weight
- 12-Lead ECG (for subjects treated with LEN this assessment is at the investigator's discretion)
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts
- Premedication (at the investigator's discretion if no infusion reaction during Cycle 1)

For subjects receiving weekly treatment, study drug administration:

- MOR03087 Study drug administration
- DEX administration according to cohort assignment. DEX should be given up to 3 hours prior to MOR03087 infusion start.

For all cohorts the following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at 15 minutes, 30 minutes, and 1 hour after start of infusion; end of infusion; and 2 and 4 hours after end of infusion
- Blood sample for MOR03087 pharmacokinetics (after completion of infusion)
- Ongoing toxicity/AE assessment during the visit

10.1.12 Follow-Up Visits

Follow-Up Visit 1:

After treatment discontinuation without disease progression a follow-up visit will occur 4 weeks (± 2 days) after the last dose of study drug.

At this visit, the following will be obtained, performed, or assessed:

- Toxicity/AE assessment since the last visit
- Concomitant medications
- Karnofsky performance status
- Blood sample for hematology, serum chemistry, coagulation, βHCG pregnancy test for women of childbearing potential, endocrinology, anti-MOR03087 antibodies, serum M-protein, serum FLCs, pharmacokinetics (MOR03087), and B, T, and NK cells
- Sample from 24-hour urine for urine M-protein
- Response assessment. Note: all responses require two consecutive assessments, and should ideally be confirmed.
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Body weight
- Quality of life questionnaires (QLQ-MY20 and QLQ-C30)
- 12-Lead ECG, if clinically indicated at the discretion of the investigator
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)

For subjects receiving POM or LEN, the additional following will be obtained, performed, or assessed:

- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms

For women of childbearing potential with irregular cycles in study cohorts that include LEN or POM, a pregnancy test (serum or urine) is to be performed 14 days after treatment discontinuation.

Follow-Up Visit 2 and Subsequent Follow-Up Visits:

Four weeks (± 2 days) after Follow-up Visit 1, a second follow-up visit will occur. If there is still a response to therapy at this visit, then a follow-up visit will be repeated every fourth week (± 2 days) until there is a disease progression (but no longer than 3 years), death, or the subject starts a new anti-myeloma therapy. Follow-up visits may be delayed for a maximum of 2 weeks after the normal visit window due to other reasons (e.g., logistical).

At each of these visits, the following will be obtained, performed, or assessed:

- Toxicity/AE assessment since the last visit
- Concomitant medication
- Karnofsky performance status
- Blood sample for hematology, serum chemistry, βHCG pregnancy test for women of childbearing potential, anti-MOR03087 antibodies (at Follow-up Visit 2 only), B, T, and NK cells, serum M-protein, and serum FLCs
- Sample from 24-hour urine for urine M-protein
- Response assessment, to be continued until disease progression or death or subsequent anti MM therapy start whatever occurs first. Note: all responses require two consecutive assessments, and should ideally be confirmed at the next follow-up visit.
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Body weight
- Quality of life questionnaires (QLQ-MY20 and QLQ-C30)
- 12-Lead ECG, if clinically indicated at the discretion of the investigator
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms

10.1.13 Treatment Cycles 3+ Visits

Subjects with an ongoing response of at least SD subsequent to the end of cycle 2 will be offered continued treatment with MOR03087 until disease progression or death or start of new anti-myeloma treatment.

At the discretion of the investigator, subjects with disease progression or a status no better than stable disease after four cycles may be treated with up to 40 mg DEX (elderly subjects aged > 75 years should receive 20 mg) per week if not otherwise receiving DEX via assigned cohort. Only subjects who do not present with known or suspected hypersensitivity to DEX or any of the excipients could qualify for the treatment with DEX (see exclusion criterion for the concomitant treatment of MOR03087 and DEX, Section 8.2). DEX must be administered as a single oral dose.

In case subjects are treated with DEX in the course of the study, the investigator may decide to decrease the dose of DEX when medically justified in the light of signs and symptoms resulting from the excess of glucocorticosteroids. The investigator must then adhere to the rules of local medical practice and their clinical judgment in the process, ensuring that subject treatment is stable (down-titration completed) prior to the End of Study (EOS) visit.

In case a subject discontinues treatment for reasons other than disease progression, they should proceed to the Follow-up Visit.

All subjects (females as well as males) continuing in the LEN and POM parts will receive an educational leaflet appropriate to their treatment, and will receive Pregnancy Counselling (see Section 12.2 and Appendix 18.8.1.3 / 18.8.2.3) at Day 1 of each cycle, starting with Cycle 3+.

At each ongoing treatment visit, the following will be obtained, performed, or assessed prior to study drug administration:

- Toxicity/AE assessment since the last visit
- Concomitant medication
- Karnofsky performance status only at Day 1 (CxD1) of each cycle, starting with Cycle 3+
- Laboratory assessments according to local guidelines/practice for the administration of monoclonal antibodies at the local laboratory should be performed. The assessment at the local laboratory should contain at the minimum serum chemistry including the "emergency laboratory parameters" and calcium concentration, and hematology
- Urine pregnancy test for women of child-bearing potential only at Day 1 (CxD1) of each cycle, starting with Cycle 3+
- Serum M-protein and serum free light chains only at Day 1 (CxD1) of each cycle, starting with Cycle 3+
- Sample from 24-hour urine for urine M-protein only at Day 1 (CxD1) of each cycle, starting with Cycle 3+
- B, T and NK cells at Day 15 (CxD15) of each cycle, starting with Cycle 3+
- Blood sample for predose pharmacokinetics (MOR03087) and anti-MOR03087 antibodies every CxD15
- Response assessment on Day 1 of every cycle (CxD1), to be continued until disease progression or death or subsequent anti MM therapy start whatever occurs first. Note: all responses require two consecutive assessments, and should ideally be confirmed at Day 1 of the next cycle

- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Body weight
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature immediately before infusion)
- Premedication (at the investigator's discretion if no infusion reaction during Cycle 1)

For subjects receiving POM or LEN, the additional following will be obtained, performed, or assessed prior to study drug administration:

- 12-lead ECG
    - For subjects treated in Part D (POM), 12-lead ECG monitoring will be performed on Cycle 3 Day 1, and on Day 1 of every third cycle thereafter (Cycles 3, 6, 9, etc.), and at treatment discontinuation. Subjects with QT prolongation (or borderline QT prolongation) but otherwise non-clinically significant will require more frequent ECG monitoring at the discretion of the investigator.
    - For subjects treated in Part E (LEN), 12-lead ECG will be performed at each visit during treatment if clinically indicated per investigator's judgment, and at treatment discontinuation if clinically indicated per investigator's judgment
- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms
- Prophylactic treatment of thromboembolism for subjects enrolled into the LEN or POM cohorts

Study drug administration:

- MOR03087 study drug administration
- DEX, POM, LEN administration according to cohort assignment; POM and LEN will be administered daily on Days 1-21 of each 28-day cycle; time point for oral application of POM or LEN at start of MOR03087 infusion (+/- 5min). DEX should be given up to 3 hours prior to MOR03087 infusion start.

The following will be obtained, performed, or assessed after start of study drug administration:

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) at end of infusion
- Blood sample for pharmacokinetics (MOR03087; after completion of infusion but only every CxD15
- Ongoing toxicity/AE assessment during the visit

10.1.14 End of Study (EOS) Visit

The EOS visit will occur after confirmed disease progression, or after withdrawal from the study for other reasons, or at a maximum of 3 years from the first study drug administration. The EOS visit will occur at least 28 days after last study drug administration but should be performed before any new MM therapy starts, whichever occurs first.

At the EOS visit, the following will be obtained, performed, or assessed:

- Toxicity/AE assessment since the last visit
- Concomitant medications
- Karnofsky performance status
- Blood sample for hematology, serum chemistry, coagulation, βHCG pregnancy test for women of childbearing potential, MOR03087 pharmacokinetics (only if subject had no follow-up visit), endocrinology, anti-MOR03087 antibodies, B, T, and NK cells, serum M-protein, and serum FLCs
- Urine sample for urinalysis
- Sample from 24-hour urine for urine M-protein
- Bone skeletal survey by x-ray, CT, or MRI imaging (where medically indicated, as a regular assessment of standard of care in subjects with relapsed or refractory MM)
- Response assessment
- Physical examination (including basic neurological examination of general motor and sensory systems, mental status, cranial nerves, and coordination)
- Ocular examination by an ophthalmologist (including distance visual acuity, optical coherence tomography [if available], and ophthalmoscopy under full mydriasis [if optical coherence tomography is unavailable])
- Body weight
- Quality of life questionnaires (QLQ-MY20 and QLQ-C30)
- 12-Lead ECG
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)
- Documentation of subject's subsequent anti-myeloma therapy, as appropriate

For subjects receiving POM or LEN, the additional following will be obtained, performed, or assessed:

- Clinical review of signs/symptoms for possible VTEs in subjects treated with POM or LEN. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms

11 EFFICACY, PHARMACOKINETIC, SAFETY, AND OTHER VARIABLES

The endpoints to be assessed for this study are as follows:

Primary Endpoints

1. Determination of the MTD and/or recommended dose of MOR03087 as monotherapy, in combination with DEX, and in combination with POM+DEX and LEN+DEX
2. Determination of the recommended dosing regimen of MOR03087
3. Incidence and severity of adverse events (AEs)
4. 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 of MOR03087 +/- LEN or POM
2. Absolute and percent change from baseline in measurements of B, T, and NK cell populations
3. Overall response rate (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], partial response [PR]), further tumor response rates (CR, stringent complete response [sCR], PR, minimal response [MR], VGPR), and SD rate
4. Duration of response, time to progression (TTP), and PFS
5. Absolute and percentage change from baseline in serum and urine M-protein levels
6. Absolute and percent change from baseline in serum FLC levels and serum FLC ratio
7. Absolute changes from baseline in laboratory parameters (serum chemistry, hematology, urinalysis) and clinically relevant abnormal values
8. Absolute change from baseline in overall quality of life scores
9. Change in cytokines from baseline

11.1 Efficacy and Pharmacodynamic Assessments

11.1.1 Efficacy Assessment

Efficacy will be evaluated in terms of overall response rate (ORR) (sCR + CR + VGPR + PR) (Kyle 2009), further tumor response rates (CR, sCR PR, MR, VGPR), SD rate, duration of response, TTP, and PFS, using the modified European Group for Blood and Marrow Transplantation (EBMT) criteria (Blade 1998) plus the International Myeloma Working Group Uniform Response Criteria (2006), taking the supplement by Kyle (Kyle 2009) into consideration.

All of these tumor response criteria for MM are defined in Appendix 18.3. All of them are based on the International Myeloma Working Group Uniform Response Criteria (Durie 2006 and

Erratum 2007), except for MR, which is based on the EBMT criteria (Blade 1998). Disease progression is defined as progressive disease according to the IMWG, 2006 (see Appendix 18.3, Table 14), death or start of new anti-MM treatment.

All responses need two consecutive assessments, ideally being confirmed at Day 1 of the next cycle.

The response evaluation will be based on serum and urine M-protein levels, serum FLC level, and FLC ratio.

11.1.2 Immune Cells

For evaluation of the status of the immune system, B, T, and NK cells will be measured frequently throughout the study. The absolute and percent changes from baseline will be evaluated.

Flow cytometry of peripheral MM cells and CD16 expression on NK cells will be evaluated at baseline and at Day 29 (Cycle 2 Day 1) (exploratory assay).

Pending sample availability, endogenous antibody titers (e.g., tetanus titers) will be measured from remaining anti-MOR03087 antibody back-up samples in order to gain information about the influence of MOR03087 treatment on normal plasma cells and immunity, especially when MOR03087 is administered over extended periods of time.

11.1.3 Bone Marrow

Pharmacodynamics will also be assessed in terms of changes in bone marrow for subjects with negative immunofixation on the serum and urine. For subjects with positive immunofixation of the serum and urine, bone marrow is to be assessed only if specific consent for this assessment has been provided. Changes from baseline in histology and immunophenotyping (CD38 expression) will be assessed depending on sample availability, at Day 29 (Cycle 2 Day 1).

11.2 Pharmacokinetic Assessments

Concentration-time profiles and pharmacokinetic parameters will be assessed for MOR03087 and, as applicable, for POM and LEN, from serum or plasma samples collected on the following schedules (if not otherwise specified, a deviation of 5 minutes from the planned collection time point is acceptable, but time of collection should be documented accurately.):

Parts A, B, C:
MOR03087

- For the first MOR03087 administration, serum samples will be collected predose and then 1, 2, 4, 8, 14 ± 2 (optional), 22 ± 2, and 28 ± 2 hours after start of first infusion.
- For all other MOR03087 administrations in Cycles 1 and 2, serum samples will be collected predose for trough level determination and then after completion of infusion (subjects in bi-weekly dosing will not have a dose on Day 50, so require only one serum sample that day).

- From Cycle 3 onwards, samples will be collected once per cycle (predose and after completion of infusion). This means sampling every cycle on D15.

- Follow-up: sample will be collected at follow-up visit 1 (or at EOS if no follow-up visit occurrs)

Parts D, E:

MOR03087 combined with LEN or POM regimens dose escalation

- For the first MOR03087 administration, MOR03087 serum samples will be collected predose before administration of MOR03087 + LEN or POM and then 1, 2, 4, 8, 14 ± 2 (optional), 22 ± 2, and 28 ± 2 hours after start of first infusion of MOR03087
- For all other MOR03087 administrations in Cycles 1 and 2, MOR03087 serum samples will be collected predose for trough level determination and after completion of infusion
- For the first MOR03087 administration, POM or LEN plasma samples will be collected predose before administration of MOR03087 + LEN or POM and then 1, 2, 8 and 22 ± 2 hours after start of first infusion of MOR03087
- For the 3rd, 6th and 8th MOR03087 administration in Cycles 1 and 2, POM or LEN plasma samples will be collected predose for trough level determination and after completion of infusion
- From Cycle 3 onwards, samples will be collected once per cycle (predose and after completion of infusion). This means sampling every cycle on D15.
- Follow-up: MOR03087 serum sample will be collected at follow-up visit 1 (or at EOS if no follow-up visit occurred)

Serum samples for MOR03087 pharmacokinetic analysis will be handled and stored at -20°C or below at the site until shipment on dry ice to an external analytical laboratory. Samples for LEN or POM pharmacokinetic analysis will be handled and stored at -70°C at the site until shipment on dry ice to an external analytical laboratory. At the analytical laboratories, the samples will also be stored at or below -20°C or -70°C, respectively, until analysis.

Detailed instructions for handling of serum samples will be provided in the laboratory-specific documentation.

11.3 Safety Assessments

Safety monitoring for all subjects enrolled in the study will include laboratory safety assessments (hematology, blood and urine chemistry) and clinical evaluations (physical examinations, vital signs, 12-lead ECG) as detailed in the schedules of assessments (Section 7.1) and Section 11.3.4. All AEs and serious AEs (SAEs) will be recorded.

All AEs and SAEs will be graded according to NCI CTCAE, version 4.0. For definition of DLTs, please refer to Section 8.5.

11.3.1 Adverse Events

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 reactions, anaphylaxis, and other emergencies and who have access to appropriate clinical supplies must be immediately available for no less than 30 minutes after dosing.

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s). Please refer to Sections 9 and 10 for the protocol-specific definitions of study drug and study treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP, whether or not considered related to that IMP. AEs include any clinically significant deterioration of a subject's medical status after signing of the informed consent form.

Any abnormal laboratory value judged to be clinically significant is defined as AE.

The subjects 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 non-leading questioning (e.g., "How do you feel?"). AEs also may be detected when they are volunteered by the subject during or between study visits or through physical examination, laboratory tests, or other assessments. 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
- Toxicity grade
- Outcome
- Action taken (no action taken; dose reduction; study drug temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- Whether it is serious, where a serious adverse event (SAE) is defined as one which:
    - Results in death.
    - Is life-threatening.
    - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for
        - Routine treatment or monitoring of the studied indication, not associated with deterioration of symptoms related to MM
        - Elective or preplanned treatment for a preexisting condition that is unrelated to MM and has not worsened since signing of the informed consent
        - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given in this section and not resulting in hospital admission

- Social reason and respite care in the absence of any deterioration in the subject's general condition

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" refers to an event in which the subject 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/reaction is serious in other situations: Important AEs/adverse drug reactions (ADRs) that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 12.1).

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 until resolution or until the EOS visit, 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.

Information about common side effects already known about the investigational study drugs can be found in the IB or SmPCs, as applicable, or will be communicated between IB or SmPC updates in the form of Investigator Notifications. This information will be included in the subject informed consent form and should be discussed with the subject during the study as needed.

11.3.2 Physical Examination

A qualified physician 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, cardiovascular system, back and spine, abdomen, extremities, infusion site, lymph nodes, and basic neurological examination (general motor and sensory systems, mental status, cranial nerves, and coordination).

At Screening and End of Study, an ocular examination should be conducted by an ophthalmologist (including distance visual acuity, optical coherence tomography [if available], and ophthalmoscopy under full mydriasis [if optical coherence tomography is unavailable]).

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 subject'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 subject's abnormal baseline physical examination becomes worse post baseline, also based on clinical grounds. Any new and/or worsening findings should be recorded as AEs.

11.3.3 Vital Signs

Vital signs will be measured at the various pre- and post-treatment time points described in the flow charts in Section 7.1. Vital sign parameters include measurements of pulse rate, systolic and diastolic blood pressures, respiratory rate, and body temperature. Before vital signs are measured, the subject 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 subject, and blood pressure will be measured from the arm contralateral to the site of IMP administration whenever possible. Body temperature should be measured with a digital thermometer.

The actual time for measurement of vital signs should not deviate more than 5 minutes from the planned time.

11.3.4 Laboratory Evaluations

Clinical laboratory parameters to be assessed in this study are displayed in Table 11.

Table 11 Laboratory Evaluations

Evaluation	Analysis	Sample Collection (approximate amount per collection)
"Emergency laboratory" (EDTA blood and serum sample)	Serum creatinine, hemoglobin, white blood cells (WBC), platelets, sodium, potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT)	Same sample as for chemistry and hematology
Hematology (EDTA blood)	WBC with differential, hematocrit, hemoglobin, mean corpuscular volume, platelet count, red blood cell (RBC) count	5 mL blood
Serum chemistry (Serum sample)	ALT, albumin, alkaline phosphatase, amylase, AST, bicarbonate (optional), bilirubin (total), blood urea nitrogen, calcium, chloride, creatinine, creatine kinase, gamma-glutamyltransferase (GGT), glucose, lactate dehydrogenase, lipase, phosphorus, potassium, protein (total), sodium, uric acid, β2-microglobulin[b]	10 mL blood
Coagulation parameters (Sodium citrate blood)	Activated partial thromboplastin time (aPTT), prothrombin time (PT)	3 mL of blood
Endocrinology (Serum sample)	Follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH)	Same sample as for chemistry
Serology parameters (Serum sample)	Hepatitis B: HBsAg and anti-HBs; Hepatitis C: Anti-HCV, (HCV RNA quantification if anti-HCV-positive)	Same sample as for chemistry
Pregnancy test (Serum sample)	β human chorionic gonadotropin (βHCG) serum, females of childbearing potential only	Same sample as for chemistry
Pregnancy test (Urine)	βHCG urine, females of childbearing potential only	30 mL (midstream urine)
Urinalysis	Specific gravity, pH, semiquantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leucocytes, RBCs, and microscopic evaluation if abnormal findings	30 mL (midstream urine)
Serum M-Protein, FLC	M-protein, serum free light chains	10 mL of blood
M-protein (urine)	M-protein quantification	2x 10 mL out of 24h-urine sampling
Immune cells (blood)	B, T, NK cell population CD16 expression on NK cells	2 mL of blood (for CD16 expression, same sample as for flow cytometry)
Flow cytometry (blood)	Peripheral blood plasma (MM) cells (CD38 expression)	2 mL of blood
Immunophenotyping (bone marrow)	Bone marrow plasma (MM) cells (CD38 expression)	6 mL bone marrow aspirate
Histology (bone marrow)	Microscopic examination	6 mL bone marrow aspirate (same aspirate as for Immunophenotyping)
Biomarkers (bone marrow)	Potential identification of biomarkers	6 mL bone marrow aspirate (same aspirate as for Immunophenotyping)
Cytogenetics (bone marrow)	Cytogenetics of MM cells	6 mL bone marrow aspirate (same aspirate as for Immunophenotyping)

Table 11 Laboratory Evaluations

Immunogenicity [a] (serum sample)	Anti-MOR03087 antibodies	4 mL of blood
Cytokines (serum sample)	Tumor necrosis factor alpha (TNF-α), interleukin-1b (IL-1b), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10) interferon-γ (IFN-γ)	4 mL of blood
Pharmacokinetics MOR03087[a] (Serum sample)	MOR03087	4 mL of blood
Pharmacokinetics POM or LEN[a] (Plasma sample)	POM or LEN	3 mL of blood
Genotyping	FcγRIIIa polymorphism	Mucosal cheek swab

[a] Provided sufficient quantities of serum are available, additional measurements of tetanus titer will be performed by central laboratories
[b] β2-microglobulin measured at screening only

The signed and interpreted laboratory results will be kept as supplemental pages to the subject's eCRF.

With the exception of pharmacokinetic parameters, anti-MOR03087 antibodies, cytokines, CD16 expression, and flow cytometry, all clinical laboratory parameters (see Table 11) will be analyzed at the local hospital laboratories. Samples for M-Protein and FLC will be analyzed centrally in order to be able to evaluate potential variances and to assess additional time points. Tetanus titers will be analyzed by a central laboratory. All blood samples will be processed and handled according to standard laboratory procedures.

Serum samples will be collected for pharmacokinetic parameters (MOR03087), anti-MOR03087 antibodies and cytokines and stored at -20°C or below at the study site until shipment on dry ice to the external analytical laboratory. At the analytical laboratory, the samples will also be stored at -20°C or below until analysis.

Plasma samples will be collected for pharmacokinetic parameters (LEN or POM) and stored at -70°C at the study site until shipment on dry ice to the external analytical laboratory. At the analytical laboratory, the samples will also be stored at -70°C or below until analysis.

Detailed instructions for sample handling will be provided in the laboratory manual.

Before the initial administration of study drug (MOR03087, POM, or LEN), the respective inclusion and exclusion criteria defined in Sections 8.1 and 8.2 should be followed. For all administrations of MOR03087, the following parameters should be taken predose on the day of study drug administration and, if outside the limits described below, administration of MOR03087 should be postponed (see Section 8.6):

Value	Subject should not be dosed if the value is:
Creatinine	> 3 × ULN
Hemoglobin	< 8.0 g/dL (subject should be transfused before dosing)
Platelets	< 25.0 × 10^9/L (< 30.0 × 10^9/L in the LEN and POM parts)
WBC	< 1.0 × 10^9/L
Potassium	> 6.0 mmol/L
Sodium	> 155 mmol/L
AST/ALT	> 3 × ULN

POM, LEN or DEX may have to be interrupted and/or dose reduced as well, according to Section 9.1.4.

Urine will be collected at the various pre- and post-treatment time points described in the flow charts in Section 7.1. The time of void will be documented on the eCRF. In the case of any abnormal result, a microscopic urine examination should be conducted. For the evaluation of urine M-protein 24-hour urine is required and has to be sent to the central laboratory. If urine was collected as standard of care, it is acceptable to use 24-hour urine samples for which collection started up to 48 hours before the respective visit.

A pregnancy test will be performed for women of childbearing potential at various pre- and post-treatment time points either by urine pregnancy test or βHCG test of a serum sample. The pregnancy test assay should have a minimum sensitivity of 25 IU/mL. On dosing days, the result must be available prior to IMP administration.

Laboratory results should be reviewed in a timely manner (i.e., hematology and chemistry prior to dosing). Emergency laboratory samples should only be taken if hematology and serum chemistry results are not available prior to study drug administration. Judgment of clinical significance should be added on the printout for out of range laboratory values, and the printout should be dated and signed.

Emergency Laboratory instruments for measuring parameters relevant for treatment decisions and for documentation of laboratory AEs have to be adequately qualified. In case of discrepancies between the emergency laboratory and principal local laboratory values, the emergency laboratory value should be the relevant value if the emergency laboratory value was used to decide on treatment (administration, continuation or interruption). Further, laboratory AEs should be followed up by the instrument with which the laboratory AE was first reported.

If an abnormal laboratory value of grade 4 or an abnormal laboratory value judged to be clinically significant 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 subject's condition (e.g., ordering a WBC differential count to help characterize a high or low WBC count, or ordering a determination of RBC indices to help characterize a low hematocrit).

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 laboratory manuals.

Blood samples will be obtained for assessment of serum chemistry, hematology, and coagulation parameters at the various pre- and post-treatment time points described in the flow charts in Section 7.1. The time of blood collection should be documented in the eCRF.

11.3.5 Electrocardiogram

A standard 12-lead ECG will be obtained at the various time points described in the flow charts in Section 7.1. A 12-lead ECG will be recorded after 5 minutes in a supine position. Heart rate and RR, PR, QS, and QT intervals will be determined. All ECG recordings will be reviewed on an ongoing basis at the site. The investigator will evaluate the clinical significance of each value outside the reference ranges, based upon the nature and degree of the observed abnormality. Any new abnormal values considered to be clinically significant should be reported as AEs.

11.4 Other Variables

11.4.1 Demographic Data

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

11.4.2 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 MM should be documented in detail. This should include the date of first diagnosis, previous treatments, best response under respective drug treatment with corresponding date, duration of response to these treatments and date(s) and type(s) of disease progression. Any previous therapy (e.g., chemotherapy, immunotherapy, or radiation therapy) for the myeloma-specific therapy should be recorded in the eCRF. Disease staging will be determined based on Durie-Salmon and ISS criteria (see Appendix 18.6) and immunoglobulin type will be documented.

Examinations leading to the diagnosis of the latest progression of MM should be documented in the eCRF as well. This may include, for example, results of laboratory examinations (e.g., M-protein), imaging results (e.g., x-ray, computed tomography, magnetic resonance imaging), or clinical symptoms related to the MM (e.g., bone pain).

All prior VTEs and pulmonary embolisms will be documented.

11.4.3 Prior and Concomitant Medication and Examinations

All prior medications in use at the time of study enrolment and all concomitant medications used during the study period will be recorded in the source document and on the eCRF.

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 eCRF as well.

11.4.4 Bone Marrow Aspiration/Biopsy

At the Screening visit (Baseline), a bone marrow aspirate and a biopsy should be obtained if no bone marrow aspiration or biopsy was obtained within 28 days prior to first dose, provided the subject was hematologically stable in the meantime. If data from a bone marrow sample taken before the screening are used, then data should be limited to the available information.

Bone marrow is to be assessed on Day 29 (C2D1) only if specific consent for this assessment has been provided.

The following examinations are planned:

- Histology: Percentage of infiltration by plasma cells
- Immunophenotyping of MM cells: CD38 expression (exploratory assay)
- Cytogenetics of MM cells: Determination of translocations t(4;14) and t(14;16) and deletions Del13 and Del17p13 as well as other cytogenetic aberrations with possible prognostic and/or predictive relevance in myeloma (e.g., 1q gain, t(11;14)) at screening if no historical data are available

11.4.5 Pharmacogenetics and Genotyping

For subjects who agree to it by signing an additional informed consent, an extra bone marrow sample for analysis of biomarkers (e.g., DNA, RNA) will be collected at screening. The primary purpose of this analysis would be to understand possible pharmacokinetic and pharmacodynamic variability as a result of genetic heterogeneity in the study population.

Additionally, a mucosal cheek swab will be used for DNA analysis of the FcγRIIIa polymorphism.

Further hypothesis-driven genotyping may be performed on specific genes of special interest. In addition, to better understand underlying disease mechanisms, discovery-driven genotyping with open-platform methodologies may be performed for the definition of endophenotypes, i.e., substratification of disease groups according to genetic patterns.

11.4.6 Subject-reported Outcomes

Subject-reported outcomes and quality of life will be assessed using the QLQ-C30 (version 3) and QLQ-MY20 questionnaires developed by the European Organisation for Research and Treatment of Cancer (EORTC) (Sprangers 1998, Stead 1999). The QLQ-C30 instrument is a reliable and validated 30-item questionnaire composed of five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain) and a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The QLQ-MY20 instrument is a 20-item

disease-specific modular questionnaire regarding subject-reported symptoms or problems. Both quality of life instruments will be completed by the subject.

12 SAFETY MONITORING

12.1 Adverse Event and Serious Adverse Event Recording and Reporting

All AEs/SAEs (except non-serious AEs for screening failures) that occur after the signing of informed consent and up to the End of Study visit (or up to 28 days after the last administration of study medication, whichever is earlier), will be recorded in the eCRF and in the subject's medical records, whether or not considered by the investigator to be related to the study drug. The SAEs should thereafter be recorded in the SAE Report Form and reported to the sponsor. All AEs/SAEs should be recorded using acceptable diagnoses, if possible. For screening failure subjects the non-serious AEs will not be recorded in the eCRF but only in the subject's medical records. The SAEs for screening failures will only be recorded until (including) the day when a subject is officially declared as screening failure.

Infusion reactions of grade 3 and higher, cytokine release syndrome, or allergic reaction to MOR03087, which are AEs of special interest in this study, should be reported along with their respective symptoms (e.g., urticaria, chills, and pyrexia for infusion reaction). 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.

Second primary malignancies will be monitored as events of special interest regardless of the treatment arm the subject is in. This includes any second primary malignancy, regardless of causal relationship to IP occurring at any time for the duration of the study. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting (e.g., any confirmatory histology or cytology results, x-rays, CT scans, etc.).

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)

The toxicity grade of AEs will be graded according to the NCI 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 non-invasive 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.

The causal relationship of all AEs to IMP intake will be judged as either suspected or not suspected. If no relationship has been provided by the investigator, the event will be considered as related to study drug and notified to authorities according to regulatory reporting requirements.

In addition to the investigator's own description of the AEs, each AE will be encoded by the sponsor (or its delegate) according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

All non-serious AEs must be followed up for a final outcome until resolution or until the EOS visit. 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 non-serious AEs at the end of a subject's participation in a study. SAEs must be followed up for a final outcome until resolution or, if resolution becomes unlikely, until stabilization or death. This includes obtaining information on recovery and any sequelae and, in case of a fatal outcome, the cause of death. For SAEs which are due to progression of MM, follow-up only until the end of subject's participation in the study is acceptable.

[redacted] will report all reportable events to all competent authorities (including the European Medicines Agency [EMA]), IECs or Institutional/Independent Review Boards (IRBs), and investigators as required by local regulations and Premier Research standard operating procedures (SOPs).

Sites are instructed to report all SAEs and AEs of special interest (i.e., infusion reactions of grade 3 and higher, cytokine release syndrome, allergic reaction to MOR03087, second primary malignancies and DLTs) to [redacted] within 24 hours using the study-specific SAE report form.

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

Email: [redacted]

Fax: [redacted]

For any safety-related questions, please contact [redacted] Global Pharmacovigilance by telephone, fax or email:

[redacted]

[redacted]

For any protocol-related questions, please contact the [redacted] medical monitor:

[redacted]

If the [redacted] medical monitor cannot be reached, then please contact the following 24/7 emergency medical cover phone line:

Telephone: [redacted]

If the [redacted] medical monitor cannot be reached, then the following person should be contacted:

[redacted]

As detailed in the schedules of assessments (Section 7.1) and Section 11.3.4, serum or urine pregnancy testing will be carried out at the Screening visit, during treatment, during follow-up visits, and at the EOS visit. 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 Study Pregnancy Form. To ensure subject safety, each pregnancy of a study subject or a female partner of a study subject must also be reported within 24 hours of learning of its occurrence to [redacted] Global Pharmacovigilance by fax at the following number:

Fax: [redacted]

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

A newly diagnosed pregnancy in a subject or female partner of a study subject who has received study medication is not considered an SAE unless it meets any criteria of seriousness or it is suspected that the study medication interacted with a contraceptive method and led to pregnancy.

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.

Cohorts with POM or LEN administration:

Pregnancy Counseling (males and females): Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for all subjects at screening, at Cycle 1 Day 1 prior to dosing, every 28 days during treatment, and at treatment discontinuation. Refer to Appendix 18.8 (pregnancy prevention risk minimization plan).

Pregnancy Testing for Females of Childbearing Potential (FCBP): All FCBP must have two medically supervised negative serum or urine pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting the study. The first pregnancy test must be performed within 10-14 days prior to the start of study treatment and the second pregnancy test must be performed within 24 hours prior to the start of study treatment. FCBP with regular or no menstrual cycles must agree to have pregnancy tests every 7 days (weekly) for the first 4 weeks of study treatment and then every 4 weeks while on study, at treatment discontinuation, and 4 weeks following treatment discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 4 weeks and then every 2 weeks while on study, at treatment discontinuation, and at 2 weeks and 4 weeks following treatment discontinuation. Study drug may not be dispensed for FCBP until the investigator has verified that the result of the pregnancy test is negative.

12.3 Venous Thrombotic Event Monitoring

In subjects randomized to receive either POM or LEN, all prior VTEs and pulmonary embolisms that occurred will be collected with complete medical history during the screening period. Clinical review of signs/symptoms for possible VTEs will be performed at every scheduled visit during study treatment, and at treatment discontinuation. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institution's standard of care. See Appendix 18.9 for deep vein thrombosis and pulmonary embolism diagnostic algorithms.

12.4 Independent Data Monitoring Committee

An independent DMC will be constituted prior to the enrolment of the first subject into a new cohort.

The DMC membership, full scope of responsibilities, operating procedures, meeting frequency, data availability, reporting and record keeping requirements will be described in the DMC charter. Recommendations for dose escalation, additional review of the current cohort, or termination of the study will be presented in the DMC Charter.

No DMC members will be participating as investigators in the study. The DMC will review the safety data as per the charter.

13 PROTOCOL AMENDMENTS AND OTHER CHANGES IN STUDY CONDUCT

13.1 Protocol Amendments

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

13.2 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.

14 DATA HANDLING AND ARCHIVING

14.1 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 printout of the eCRF after database lock for archiving.

14.2 Clinical Data Management

The 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 the 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 World Health Organization-Drug Dictionary Enhanced (WHO-DDE) for medication.

14.3 Archiving and Filing

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

15 STATISTICAL METHODS AND PLANNED ANALYSIS

15.1 General Statistical Considerations

The following analysis populations will be defined:

Total Population (All Subjects)

The Total Population will consist of all subjects including screening failures.

Safety Population

The Safety Population will consist of all enrolled subjects who received the IMP at least once.

DLT Evaluable Population

- The DLT Evaluable Population will consist of all enrolled subjects who have received at least 1 cycle of MOR03087 (at least four doses for q1w or two doses for the q2w dosing schedule) (monotherapy or combination therapy) and if applicable per cohort, at least 16 doses of LEN or POM without dose modifications 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).
  - Subjects who withdraw before having received the minimum number of infusions/doses and safety evaluations due to DLT will be included in the DLT evaluable population.
  - Subjects who discontinue study treatment or require a dose modification for LEN or POM for reasons unrelated to a DLT within the first cycle will be excluded from the DLT evaluable population.

Efficacy Evaluable Population

The Efficacy Evaluable Population will consist of all subjects who take at least one dose of IMP and who have a baseline and at least one post-baseline efficacy assessment.

Pharmacokinetic Population

The Pharmacokinetic Population will consist of all subjects who have sufficient pharmacokinetic data to characterize the time course of MOR03087 or LEN or POM in serum or plasma for the first IMP administration at a minimum.

The Safety Population will be used for safety analysis and to analyze immunogenicity and the pharmacodynamic endpoints. The DLT Evaluable Population will be used to determine the maximum tolerated dose. Summaries for the analysis of tumor response will be provided for the Efficacy Evaluable Population and the Safety 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 subjects (N) (with non-missing values), mean, standard deviation, median, minimum, maximum, and first and third quartiles.

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

In general, data will be summarized by treatment arm (A-E) and dose level.

Furthermore, there will be specific summaries for the recommended dose groups of each treatment arm. Summaries for recommended dose data will combine data from the confirmation

cohort with the data from the cohort of the dose-escalation scheme that received the same dose and regimen and combination treatment (if applicable).

The last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline. All data obtained on the eCRF and entered into the database will be provided in separate data listings showing individual subject values. The planning and reporting of statistical analyses will be carried out as described in the CRO's SOPs.

15.2 Subject Characteristics

A table will be provided with the following information:

- Number of subjects including screening failures (total population).
- Number of subjects included in each analysis population.
- Number of subjects withdrawn from the study and the reason for withdrawal.

Subject baseline characteristics will be summarized based on the Safety Population by treatment arm and dose level. Demographic information (age, height, weight, and body mass index) will be summarized using descriptive statistics. Gender, race, and disease stage will be summarized by counts and percentages.

Medical history data (coded using MedDRA) will be summarized by system organ class and preferred term. Concurrent medications will be recorded and coded using WHO-DDE and grouped by different classes, if applicable.

The MM-specific medical history will be summarized for the duration of disease, number of previous therapies, type of previous therapy, best response under respective drug treatment with corresponding date(s), and date(s) and type(s) of disease progression following any previous instances of previous myeloma-specific therapy.

15.3 ImmunogenicityAnalysis

One of the primary objectives will be to evaluate the immunogenicity of MOR03087 in the Evaluable Population and the Safety Population. This analysis will be 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.

The number and percentage of subjects who develop confirmed anti-MOR03087 antibodies will be summarized descriptively by treatment arm and dose level. Exact 95% confidence intervals will be provided for the rate of subjects who developed anti-MOR03087 antibodies in the recommended dose group of each treatment arm.

Time to development of anti-MOR0387 antibodies will be summarized descriptively by treatment arm and dose level using Kaplan-Meier estimates for the median, 25% quartile, and 75% quartile. If only a few subjects develop anti-MOR03087 antibodies, quantitative assessments will only be presented in listings. Otherwise, summary tables will also be provided.

15.4 Efficacy Analysis

Overall response rate (PR or better), further tumor response rates (CR, sCR, PR, MR, VGPR), and SD rate will be summarized descriptively by visit (including Cycles 3+ and follow-up period) and by treatment arm and dose level.

The denominator for calculating the rates will be the total number of subjects within the corresponding population and treatment arm or dose level.

Exact 95% confidence intervals will be provided for the overall response rate in the recommended dose group of each treatment arm.

In addition, the best overall response will be determined for each subject.

Duration of response, time to progression, and progression-free survival will be summarized descriptively by treatment arm and dose level using Kaplan-Meier estimates for the median, 25% quartile, and 75% quartile. Kaplan-Meier plots will be provided for the recommended dose group of each treatment arm.

All efficacy analyses will be provided for the Efficacy Evaluable Population and the Safety Population.

15.5 Pharmacodynamic and Biomarker Analysis

Baseline values and absolute and percent changes from baseline by visit will be summarized descriptively by visit and by treatment arm and dose level for the following:

- Measurements of B, T, and NK cell populations
- CD16 expression on NK cells
- Result of flow cytometry of peripheral MM cells
- Serum and urine M-protein levels
- Serum FLC level and FLC ratio

The 95% confidence intervals will be provided for absolute and percent mean changes from baseline in the recommended dose group of each treatment arm.

Pharmacodynamics will also be assessed by evaluating bone marrow data for subjects with complete remission and subjects who provided an additional informed consent. Baseline values and absolute and percentage changes from baseline in histology, and immunophenotyping will be assessed. If there is a sufficient number of subjects who have bone marrow data after start of treatment, the bone marrow data will be summarized descriptively; otherwise the bone marrow data will only be included in listings.

15.6 Pharmacokinetic Analysis

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

Based on the data available, the following pharmacokinetic parameters will be computed:

C_{max}	Maximum serum concentration observed
t_{max}	Time to maximum serum concentration observed
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)

More detailed information on the methodology of pharmacokinetic analysis will be supplied in the Statistical Analysis Plan.

15.7 Safety Analysis

15.7.1 Dose Limiting Toxicities and Maximum Tolerated Dose

One of the primary endpoints will be to determine the MTD or recommended dose and dosing regimen for MOR03087 with or without DEX and in combination with two standard IMiD therapies. This primary endpoint will be determined in the DLT Evaluable Population and will be based on a 4-week safety assessment period (one 28-day cycle).

Following completion of Parts A-C (dose escalation of MOR03087 alone and in combination with DEX using two dosing schedules), the MTD and/or recommended dose will be confirmed in a minimum of 6 subjects. Following completion of Parts D and E (dose escalation of MOR03087 in combination with POM+DEX and in combination with LEN+DEX), the MTD and/or recommended dose in each treatment arm will be confirmed in a minimum of 6 subjects.

The recommended doses for the confirmation cohorts will be determined after review of all available safety data from the corresponding 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. Additionally, the number and percentage of DLTs will be summarized descriptively for all subjects including subjects from the confirmation cohorts receiving the recommended dose and including further cycles of MOR03087 or cycles of combination therapy. For definition of DLT see Section 8.5.

15.7.2 Adverse Events

One of the primary endpoints will be to determine the incidence and severity of AEs. This primary endpoint will be determined based on the Safety Population.

An AE summary table will be presented showing the incidence and frequency of treatment-emergent AEs (TEAEs), SAEs, MOR03087-related TEAEs, MOR03087-related TEAEs by severity/toxicity (according to NCI CTCAE criteria), and infusion reactions. The incidence refers to the number and percentage of subjects and the frequency to the number and percentage of AEs. Exact 95% confidence intervals for the incidence rates will be included for the recommended dose group of each treatment arm.

The number and percent of subjects with one or more TEAEs will be summarized by treatment arm and dose level 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 IMP.

The sponsor will describe other AEs of special interest (i.e., infusion reactions, cytokine release, allergic reaction to MOR03087, second primary malignancies and DLTs), in addition to those reported as SAEs.

The number and percent of subjects with one or more pre-treatment AEs will be summarized by treatment arm and dose level and by system organ class and preferred term.

15.7.3 Clinical Laboratory Evaluations

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

For hematology and serum chemistry, the laboratory values will be transformed to SI values based on SI units to make laboratory parameters comparable between different local laboratories. The relevant reference ranges supplied by each laboratory will also be transformed to SI reference ranges for each laboratory.

Descriptive summaries of actual (absolute) values and changes from baseline values will be presented for hematology and serum chemistry by treatment arm and dose level 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, five categories will be used that determine 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 by treatment arm and dose level (frequency tables). Additionally, for each laboratory parameter, shifts in assessments from baseline to all

post-administration time points will be presented for the recommended dose groups of each treatment arm (shift tables).

Grades for a clinical laboratory analyte will be derived according to NCI CTCAE, version 4.0 and used to present additional frequency and shift tables based on NCI CTCAE grades.

The assessment of categorical urinalysis variables will be tabulated by time point for each urine parameter for the Safety Population by part and dose level (frequency tables). Additionally, for each of these urine parameters, shifts in assessments from baseline to all post-administration time points will be presented for the recommended dose groups of each treatment arm (shift tables).

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

15.7.4 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs. These summaries will be presented by part and dose level for the Safety Population and 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 Appendix 18.2).

15.7.5 Electrocardiograms

The summary ECG assessment (categories: <normal; abnormal clinically significant; abnormal not clinically significant>) will be tabulated by time point for the Safety Population by treatment arm and dose level.

Each abnormal PR, QRS, and RR interval value will be flagged to show whether it is a value below or above the normal limit. The normal limits are detailed in Appendix 18.2).

Summary statistics for all time points will be displayed for QT and QTc correction methods, side-by-side, and by treatment arm and dose level. 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 / heart rate (HR)

Also, the number and percent of subjects in each treatment arm and dose level with QTc values above the normal limit (441-480 ms, 481-500 ms, or > 500 ms) and the number and percent of subjects in each treatment arm and dose level who experienced a change > 30 ms or a change > 60 ms will be presented by time point.

15.7.6 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.

15.8 Other Variables

15.8.1 Pharmacogenetics and Genotyping

The frequency of genetic mutations will be summarized for different genetic markers by part and dose level. Subgroups based on different genetic patterns may be defined. The definition of subgroups will be dependent on the frequency of mutations and the genetic markers analyzed. Exploratory subgroup analysis may be used to understand possible pharmacokinetic and pharmacodynamic variability as a result of genetic heterogeneity in the study population.

15.8.2 Analysis of Quality of Life

Overall quality of life scores will be calculated for both quality of life questionnaires, the QLQ-C30 (version 3) and QLQ-MY20 questionnaire, by applying the commonly used scoring system.

The change from baseline in overall quality of life scores will be summarized descriptively by part and dose level.

15.9 Sample Size Determination

A 3 + 3 design will be used for the dose-escalation part of the study with confirmation cohorts of 6 subjects. At least 9 subjects will be analyzed in the recommended dose groups of each part: 6 subjects from the confirmation cohort and at least 3 subjects from the dose-escalation cohort who receive the same dose and regimen and combination treatment (if applicable). This ensures that AEs that occur in a subject with a probability of 17% will be observed at least once within this group with a probability of 81%. If the AEs occur with a probability of 23%, then the probability of observing the AEs will increase to 90%.

15.10 Significance Level

Confidence intervals, both individual and simultaneous, will be at the 95% confidence level unless stated otherwise.

15.11 Procedures for Missing, Unused, and Spurious Data

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

15.12 Rules for Excluding Subjects from Analysis

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

15.13 Procedures for Reporting Deviations from Original Statistical Plan

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.

16 SPECIAL REQUIREMENTS AND PROCEDURES

16.1 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. The study will not start in the concerned Member State before the respective IEC/IRB gives written approval or a favorable opinion in accordance with ICH E6 GCP and all applicable regulatory bodies/local health authorities give approval or a favorable 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 favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The sponsor will authorize and the principal investigator(s) will sign the protocol amendment prior to 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 violation, and will be addressed as such during the reporting of the study.

16.2 Ethical Considerations

16.2.1 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 (including the national implementation of European Directive 2001/20/EC), and with the ethical principles laid down in the current version of the Declaration of Helsinki.

16.2.2 Responsibilities of the Investigator and IRB/IEC

The protocol and the proposed subject 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 subjects 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 subjects. A final report of study outcome, if required, should also be submitted to the IRB/IEC.

16.3 Investigator's Responsibilities

16.3.1 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 sites participating in this study that do not comply with these standards will be documented, and non-compliant sites should be excluded.

The investigator is accountable for the performance of the study (treatment of the subject 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, site staff (e.g., 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 randomization, 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.

An independent DMC will be installed to review the data from each cohort of the study (dose escalation) and to make the decision whether to proceed to combination therapy arms, as well as review the data from each dose-escalation cohort in the combination therapy arms. The detailed composition, obligations, and procedures of the DMC will be presented in a separate charter

provided by the sponsor. The investigator should not enroll any subject to the next cohort or next study part if the positive DMC decision is not available.

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.

16.3.2 Subject Informed Consent

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

The investigator will explain that the subjects 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 will complete the informed consent section of the eCRF for each subject enrolled.

Each subject will be informed that his or her source records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector (e.g., Paul-Ehrlich-Institut [PEI], Bundesamt für Sicherheit im Gesundheitswesen (BASG)/Agentur für Gesundheit und Ernährungssicherheit [AGES]) 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.

Three separate informed consents will be set up: one for subjects entering dose-escalation in Parts A, B and C, one for the confirmation cohorts (Parts A, B and C), and one for the POM/LEN combination therapy arms (Parts D and E). The subjects must sign the correct version of the informed consent before being enrolled to the specific treatment arms.

In addition, for subjects who could potentially be enrolled to the LEN/MOR03087 combination therapy arm or POM/MOR03087 combination therapy arm, a signed LEN/POM information leaflet must also be available before enrollment to the combination treatment arm.

In addition, bone marrow samples on Day 29 (C2D1) may be taken from subjects only if specific consent for this assessment has been provided.

In addition to the standard study procedures, pharmacogenetic samples (e.g., for analysis of RNA, DNA) will be taken from subjects who agree to this procedure. A separate informed consent form will be signed for this. The procedure for obtaining this informed consent will be the same as for obtaining the study informed consent. Consent to donate these pharmacogenetic samples is completely voluntary and denying consent will have no effect on the subjects' study participation.

16.3.3 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 (e.g., medical charts/records, laboratory results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

16.3.4 Confidentiality Regarding Study Subjects

The investigators must assure that the privacy of the subjects, 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, subjects will not be identified by their names, but by an identification code (e.g., initials and study subject 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.

16.3.5 Relevant Protocol Deviations

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

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

- Subjects who enter the study even though they did not satisfy the entry criteria
- Subjects who develop withdrawal criteria during the study
- Subjects who receive the wrong treatment or incorrect dose
- Subjects who receive an excluded concomitant treatment (e.g., another monoclonal antibody).
- Non-compliance with protocol setting that puts the safety of the subject or the scientific validity of the study at risk

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

A list of all included subjects with all deviations from the intended study procedures and other criteria that may affect the subject'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 subject in the subject populations for statistical analysis.

16.4 Study Monitoring

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

16.5 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 the 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.

16.6 Insurance

This study is covered under the sponsor's Liability Insurance Policy covering damage to subjects according to the legal requirements of each country. 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.

The investigator must inform the subjects accordingly and must also point out that the subjects 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.

16.7 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 site personnel and appropriate sponsor personnel. Authorship will follow the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals and will be defined prior to the first publication. All other investigators, co-investigators, and study coordinators will be listed in an acknowledgement.

For multicentre studies, it is mandatory that the first publication be based on data from all sites, 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, subject to the provisions of this section. The 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, and the authors shall consider all comments and reviews of the sponsor and may not unduly disregard such comments and reviews of the sponsor. With respect to the review process, the authors shall send the relevant manuscript to the sponsor at least 60 days before submission or presentation of the data. This is not intended to restrict or hinder publication or presentation, but to allow the sponsor to protect the confidentiality of information and to provide comments that may not yet be available to the investigator. The sponsor has the right to have removed any confidential information from the manuscripts. 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, and the authors shall grant, 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.

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18 APPENDICES

18.1 Information on Investigational and Registered Products

The Investigator's Brochure for MOR03087, and SmPCs for dexamethasone (sample), lenalidomide, and pomalidomide will be supplied to the sites.

18.2 Normal Limits for Vital Signs, Weight, Height, and ECG Intervals

Criteria for normal limits are provided for vital signs, weight (Table 12) and for ECG parameters (Table 13).

Table 12 Criteria for Normal Limits for Vital Signs and Weight

Weight and Vital Signs Parameter	Normal Limits	
	Low	High
Systolic blood pressure (mmHg)	85	139
Diastolic blood pressure (mmHg)	60	89
Pulse rate (bpm)	60	100
Respiration rate (rpm)	12	22
Body temperature (°C)	36.4	37.7
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) since BMI is not collected on the eCRF.
[b] BMI is calculated and analyzed retrospectively by the sponsor, at which time height is taken into account.

Table 13 Criteria for Normal Limits for ECGs

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

[a] No lower boundary set for QTc.

18.3 Response Criteria for Multiple Myeloma

The tumor response criteria for multiple myeloma in this study are those defined in Table 14 below. All of them are based on the International Myeloma Working Group Uniform Response Criteria (Durie 2006), except for MR, which is based on the adopted EBMT criteria (Blade 1998).

Table 14 Response Criteria for Multiple Myeloma

Response subcategory	Criteria[a]
sCR	• CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b]
VGPR	• Serum and urine M-protein detectable by immunofixation but not electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hours
PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between levels of involved and uninvolved free-light-chains instead of the M-protein criteria • In addition to the above-listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR[d,e]	• 25–49% reduction in level of serum M-protein • 50–89% reduction in 24-hour urinary M-protein, which still exceeds 200 mg/24 hours If present at baseline, 25–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination) • No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response)
SD[f]	• Not meeting criteria for CR, VGPR, PR, MR, or PD
PD	NOTE: Requires any one or more of the following: Increase of ≥ 25% from nadir in • Serum M-component and/or (absolute increase must be ≥ 0.5 g/dL)[g] • Urine M-component and/or (absolute increase must be ≥ 200 mg/24 hours) • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. Absolute increase must be > 10 mg/dL. • Bone marrow plasma cell percentage: absolute % must be ≥ 10%[h] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Abbreviations: CR = complete response; FLC = free light chain; MR = minimal response; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

[d] MR also includes subjects in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

[e] The response criterion MR will not apply to subjects who present with serum FLCs only.

[f] Per the International Myeloma Working Group Uniform Response Criteria (Durie 2006), stable disease is not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates.

[g] For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

[h] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

18.4 New York Heart Association Functional Classification

The NYHA criteria for classifying the extent of cardiac failure are presented in Table 15.

Table 15 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 (e.g., walking short distances, approximately > 20 – 100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest, mostly bedbound patients.

Abbreviation: NYHA = New York Heart Association

18.5 Karnofsky Performance Status

The Karnofsky criteria for assessing performance status are presented in Table 16.

Table 16 Criteria for Karnofsky Performance Status

Score (Percent)	Criteria
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated; death not imminent
20	Very sick, hospitalization indicated; death not imminent
10	Moribund, fatal processes progressing rapidly
0	Dead

18.6 International Staging System (ISS) Criteria and Durie-Salmon Staging Criteria

Details of multiple myeloma staging are provided according to the International Staging System (Table 17) and the Durie-Salmon criteria (Table 18). Staging should be performed at the time of screening.

Table 17 Criteria for International Staging System (ISS)

Stage I	β2-microglobulin (β2M) < 3.5 mg/L, albumin ≥ 3.5 g/dL
Stage II	β2M < 3.5 mg/L and albumin < 3.5 g/dL; or β2M 3.5–5.5 mg/L irrespective of the serum albumin
Stage III	β2M ≥ 5.5 mg/L

Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, Boccadoro M, Child JA, Avet-Loiseau H, Kyle RA, Lahuerta JJ, Ludwig H, Morgan G, Powles R, Shimizu K, Shustik C, Sonneveld P, Tosi P, Turesson I, Westin J. International staging system for multiple myeloma. J Clin Oncol 2005 23:3412-20.

Table 18 Criteria for Durie-Salmon Staging

Stage	**Criteria**	**Measured Myeloma Cell Mass[a]**
Stage I (low cell mass)	All of the following: • Hemoglobin value >10 g/dL • Serum calcium value normal or <10.5 mg/dL • Bone x-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only • Low M-component production rates IgG value <5 g/dL; IgA value <3 g/dL • Urine light chain M-component on electrophoresis <4 g/24h	600 billion
Stage II (intermediate cell mass)	Fitting neither Stage I nor Stage III	600 to 1,200 billion
Stage III (high cell mass)	One or more of the following: • Hemoglobin value <8.5 g/dL • Serum calcium value >12 mg/dL • Advanced lytic bone lesions (scale 3) • High M-component production rates IgG value >7 g/dL IgA value >5 g/dL • Bence Jones protein >12 g/24h	>1,200 billion
Subclassification (either A or B)	• A: relatively normal renal function (serum creatinine value) <2.0 mg/dL • B: abnormal renal function (serum creatinine value) >2.0 mg/dL Examples: Stage IA (low cell mass with normal renal function) Stage IIIB (high cell mass with abnormal renal function	

[a] Myeloma cells in whole body, in billions/m^2

Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975; 36: 842-854.

18.7 Equivalent Doses for Corticosteroids

Table 19 presents a summary of corticosteroid doses that are equivalent to standard methylprednisolone doses.

Table 19 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

18.8 Pregnancy Prevention Risk Minimization Plans

18.8.1 Lenalidomide Pregnancy Prevention Risk Minimization Plan

18.8.1.1 Lenalidomide Pregnancy Risk Minimization Plan for Clinical Trials

Appendix 18.8.1 applies to all subjects receiving LEN therapy. The following Pregnancy risk minimization plan documents are included in this appendix:

1) Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Appendix 18.8.1.2);
2) Lenalidomide Education and Counseling Guidance Document (Appendix 18.8.1.3);
3) Lenalidomide Information Sheet (Appendix 18.8.1.4).

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Appendix 18.8.1.2) provides the following information:
    - Potential risks to the fetus associated with LEN exposure
    - Definition of Female of Childbearing Potential
    - Pregnancy testing requirements for subjects receiving LEN who are females of childbearing potential
    - Acceptable birth control methods for both female of childbearing potential and male subjects receiving LEN in the study
    - Requirements for counseling of all study subjects receiving LEN about pregnancy precautions and the potential risks of fetal exposure to LEN
2. The Lenalidomide Education and Counseling Guidance Document (Appendix 18.8.1.3) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of LEN study treatment. A copy of this document must be maintained in the subject records.
3. The Lenalidomide Information Sheet (Appendix 18.8.1.4) will be given to each subject receiving LEN study therapy. The subject must read this document prior to starting LEN study treatment and each time they receive a new supply of study drug.

18.8.1.2 Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

LEN is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that LEN produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of LEN in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who:

1) has not undergone a hysterectomy or bilateral oophorectomy or

2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, LEN is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of LEN study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Appendix 18.8.1.2)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of LEN

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk management, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, LEN is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of LEN study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of LEN

Traces of LEN have been found in semen. Male subjects taking LEN must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of LEN study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study:

1) for at least 28 days before starting study drug;

2) while participating in the study;

3) dose interruptions; and

4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking LEN and DEX, combined oral contraceptive pills are not recommended. If a subject is

currently using combined oral contraception the subject should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with DEX.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Subjects:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Subjects:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study subject, study drug must be immediately discontinued.

- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Subjects:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to LEN must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the investigator must be notified immediately.

Additional precautions

- Subjects should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female subjects should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male subjects should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

18.8.1.3 Lenalidomide Education and Counselling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

□ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

□ NOT FCBP

Male: □

Do Not Dispense study drug if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].**

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
   - That even if she has amenorrhea she must comply with advice on contraception

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the subject agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the subject's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the subject missed a period or has unusual menstrual bleeding.
  - When the subject is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Lenalidomide Information Sheet to the subject.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counseled the female NOT of child bearing potential regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the subject.

MALE:

1. I counseled the Male subject regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
   - NEVER share study drug with anyone else.
   - Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the subject.

Investigator/Counselor Name (Print): _____

(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____

(circle applicable)

Maintain a copy of the Education and Counseling Guidance Document in the subject records.

18.8.1.4 Lenalidomide Information Sheet

FOR SUBJECTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy.

   If you are a female who is able to become pregnant:

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting study drug
     - while taking study drug
     - during dose interruptions of study drug
     - for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days and again 24 hours prior to the first dose of study drug
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking study drug if you become pregnant during treatment**
     - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation
   - **Do not breastfeed while taking study drug**
   - The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

Lenalidomide is detected in trace quantities in human semen. The risk to the foetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking study drug
  - During dose interruptions of study drug
  - For 28 days after you stop taking study drug
- **Male subjects should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**
   - **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
   - **Do not break, chew, or open study drug capsules.**
   - You will get no more than a 28-day supply of study drug at one time.
   - Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

18.8.2 Pomalidomide (CC-4047) Pregnancy Prevention Risk Minimization Plan

18.8.2.1 Pomalidomide Pregnancy Risk Minimization Plan for Clinical Trials

Appendix 18.8.2.1 applies to all subjects receiving POM therapy. The following Pregnancy risk minimization plan documents are included in this Appendix:

1) Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Appendix 18.8.2.2);
2) Pomalidomide Education and Counselling Guidance Document (Appendix 18.8.2.3);
3) Pomalidomide Information Sheet (Appendix 18.8.2.4).

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Appendix 18.8.2.2) provides the following information:
    - Potential risks to the fetus associated with POM exposure
    - Definition of Female of Childbearing Potential (FCBP)
    - Pregnancy testing requirements for subjects receiving POM who are females of childbearing potential
    - Acceptable birth control methods for both female of childbearing potential and male subjects receiving POM in the study
    - Requirements for counselling of all study subjects receiving POM about pregnancy precautions and the potential risks of fetal exposure to POM
2. The Pomalidomide Education and Counselling Guidance Document (Appendix 18.8.2.3) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of POM study treatment. A copy of this document must be maintained in the subject records.
3. The Pomalidomide Information Sheet (Appendix 18.8.2.4) will be given to each subject receiving POM study therapy. The subject must read this document prior to starting POM study treatment and each time they receive a new supply of study drug.

18.8.2.2 Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

POM was found to be teratogenic in a developmental study in rabbits. POM is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If POM is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who:

1) has not undergone a hysterectomy or bilateral oophorectomy or

2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counselling

For a female of childbearing potential, POM is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counselled concerning the following risks and requirements prior to the start of POM study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Appendix 18.8.2.2)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of POM

The investigator must ensure that females of childbearing potential:

- Comply with the conditions for pregnancy risk management, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, POM is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counselled concerning the following risks and requirements prior to the start of POM study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of POM

The effect of POM on spermatogenesis is not known and has not been studied. Therefore, male subjects taking POM must meet the following conditions (i.e., all males must be counselled concerning the following risks and requirements prior to the start of POM study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study:

1) for at least 28 days before starting study drug;

2) while participating in the study;

3) dose interruptions; and

4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking POM and DEX, combined oral contraceptive pills are not recommended. If a subject is

currently using combined oral contraception, the subject should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with DEX.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Subjects:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Subjects:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counselling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study subject, study drug must be immediately discontinued.

- Pregnancy testing and counselling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Subjects:

- Counselling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to POM must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the investigator must be notified immediately.

Additional precautions

- Subjects should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Subjects should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male subjects should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

18.8.2.3 Pomalidomide Education and Counselling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female:

If female, check one:

FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

NOT FCBP

Male:

Do Not Dispense study drug if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].**

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counselled FCBP regarding the following:
    - Potential risk of fetal exposure to pomalidomide: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.
    - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
    - That even if she has amenorrhea she must comply with advice on contraception

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the subject agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the subject's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the subject missed a period or has unusual menstrual bleeding.
  - When the subject is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the subject.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counselled the female NOT of childbearing potential regarding the following:
    - Potential risk of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
    - NEVER share study drug with anyone else.
    - Do not donate blood while taking study drug and for 28 days after stopping study drug.
    - Do not break, chew, or open study drug capsules
    - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the subject.

MALE:

1. I counselled the Male subject regarding the following:
    - Potential study drug fetal exposure to pomalidomide (Refer to item #2 in FCBP).
    - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
    - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant
    - NEVER share study drug with anyone else.
    - Do not donate blood while taking study drug and for 28 days after stopping study drug.
    - Do not donate semen or sperm while taking study drug and for 28 days after stopping study drug.
    - Do not break, chew, or open study drug capsules.
    - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the subject.

Investigator/Counselor Name (Print): _____
(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____
(circle applicable)

Maintain a copy of the Education and Counselling Guidance Document in the subject records.

18.8.2.4 Pomalidomide Information Sheet

FOR SUBJECTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits.
   If you are a female who is able to become pregnant:
   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting study drug
     - while taking study drug
     - during dose interruptions of study drug
     - for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**
     - within 10 – 14 days and again 24 hours prior to the first dose of study drug
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking study drug if you become pregnant during treatment**
     - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking study drug**
   - The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

1. Male subjects (including those who have had a vasectomy) must either **not have any sexual relations with a pregnant female or a female who can become pregnant,** or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
    - While you are taking study drug
    - During dose interruptions of study drug
    - For 28 days after you stop taking study drug
2. **Male subjects should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
3. **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**
    1. **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
    2. **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
    3. **Do not break, chew, or open study drug capsules.**
    4. You will be supplied with no more than one cycle of study drug
    5. Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

18.9 Venous Thrombotic Event Algorithms

Venous Thrombotic Event (VTE) Diagnostic Procedure

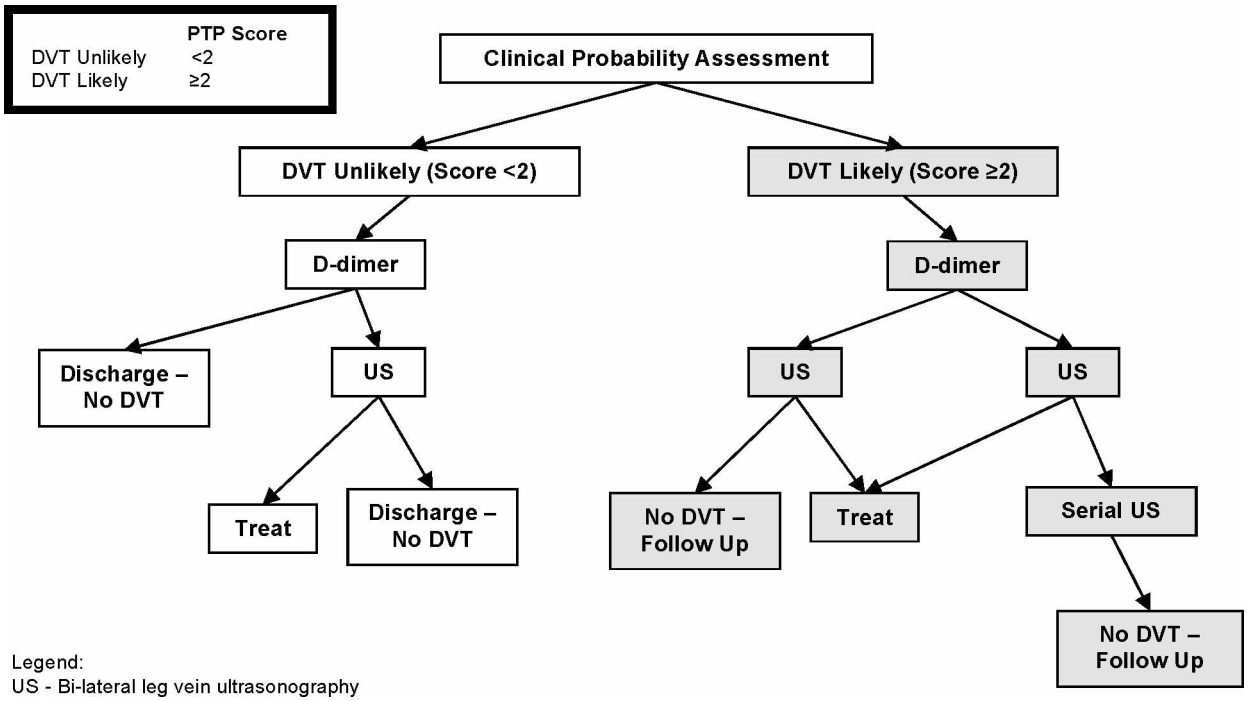
1. Refer to the DVT Pre-Test Probability Score Table (Table 20). Add up the score and determine the subject's pre-test probability for DVT.

2. Refer to the DVT Diagnostic Algorithm (Figure 4). According to the pre-test probability follow the relevant diagnostic algorithm.

Table 20 Wells[1] Deep Vein Thrombosis Pre-Test Probability (PTP) Score

Clinical Characteristic	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis as likely or greater than that of DVT	-2

1 Wells PS, Anderson D et al. Evaluation of D-dimer in the Diagnosis of Suspected Deep Vein Thrombosis. N Engl J Med Sept 25, 2003 349(13): 1227-35



Adapted from 6B6 D-Dimer[tm] The Essential Element Wall Chart

Figure 4: Deep Vein Thrombosis Diagnostic Algorithm

Pulmonary Embolism (PE) Diagnostic Procedure

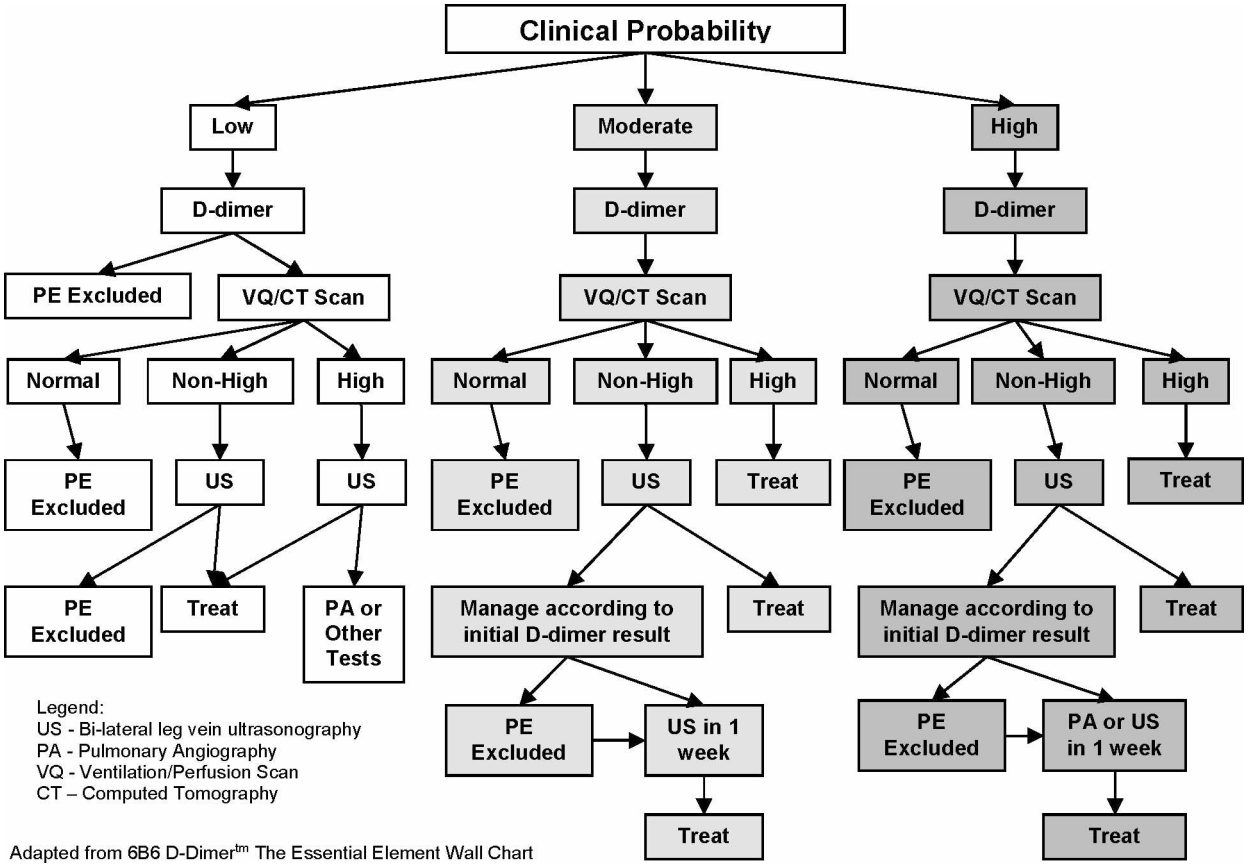
1. Refer to the PE Pre-Test Probability Score Table (Table 21). Add up the score and determine the subject's pre-test probability for PE.

2. Refer to the PE Diagnostic Algorithm (Figure 5). According to the pre-test probability follow the relevant diagnostic algorithm.

Table 21 Wells[1] Pulmonary Embolism Pre-Test Probability (PTP) Score

Clinical Characteristic	Score
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate greater than 100 beats/min	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (at treatment, treated in the last 6 months or palliative)	1.0

1 Wells P.S., Anderson D. et al. Derivation of a simple Clinical Model to Categorize Patients Probability of Pulmonary Embolism: Increasing the Models Utility with SimpliRED D-dimer. Thromb Haemost 2000;83:416-20



	PTP Score
Low Probability	<2.0
Moderate Probability	2.0 – 6.0
High Probability	>6.0

Figure 5: Pulmonary Embolism Diagnostic Algorithm