Title Page

Clinical Study Protocol Title:	A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma
Study Number:	MS201814-0010
Amendment Number	3.0
Merck Compound Number:	M3258
Short Title:	First in Human Dose Escalation of M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	For all countries, except the US: Merck Healthcare KGaA Frankfurter Str. 250 Darmstadt, Germany In the US: EMD Serono Research & Development Institute, Inc. An affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA Medical Responsible: Name: PPD Phone: PPD Fax: PPD
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Protocol Version:	11 May 2020/Version 4.0
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Approval Date:	11 May 2020

Medical Monitor Name and Contact Information:	PPD PPD Tel: PPD

Protocol Amendment Summary of Changes

Type	Scope	Version Number	Notes
Original Protocol	Global	1.0	Initial version approved by first IRB
Global Amendment to the Original Protocol	Global	2.0	Revised according to Health Authority Request (United States Food & Drug Administration [US FDA])
Global Amendment	Global	3.0	Revised according to Health Authority Request (ANSM [France])
Global Amendment	Global	4.0	Added doses and regimen options for more flexibility.

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	15 April 2019
2.0	Global Amendment	01-Jul-2019
3.0	Global Amendment	12-Sep-2019
4.0	Global Amendment	11-May-2020

Protocol Version 4.0 (11-May-2020)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Major changes to the protocol and the rationale for these changes are listed in the table below. Minor revisions, including minor editorial revisions and clarifications, are not listed.

Section Number and Name	Description of Change	Brief Rationale
Multiple sections	Introduction of additional treatment regimens, including 21-day treatment regimens, which may be used if required. Includes the addition of Schedule of Activities for the 21-day treatment regimens for Part A (Table 2) and Part B (Table 4) in Section 1.3. Alignment of dexamethasone treatment in Part B to the newly introduced treatment regimens. PK sampling times altered in order to align sampling across the treatment regimens. Tables 1, 3 (formerly Table 2), 5 (formerly Table 3), and 6 (formerly Table 4) reflect these changes.	Adding regimen change for more flexibility.
Multiple sections	DLT period is defined as the first cycle of treatment	DLT definition reflects one treatment cycle for either the 21-day or 28-day treatment regimen.
Multiple sections	Allowance for a drug holiday if a consistent decease in platelet counts is observed in the 28-day dosing regimen.	Adding a drug holiday to allow for treatment if a consistent decrease in platelets, which may be a transient effect on megakaryocyte function, possibly related to platelet budding similar to pan-proteasome inhibitors, is observed.
Multiple sections	Addition that participants who did not experience a DLT and who either did not receive at least 80% of the planned cumulative dose of treatment during the DLT period, *or at least 80% of the planned administrations* [added] or did not complete the DLT observation period will not be considered for DLT evaluation.	Addition that in order to be evaluable in DLT analysis set, it is not only necessary to have received a certain amount of the planned cumulative dose, but also to have received a minimum number of administrations.
Multiple sections	For Part B, text modified to state: " If data obtained during the safety run-in of Part B indicate that a higher dose than the RDE may be tolerated when M3258 is administered in combination with dexamethasone, then a careful escalation beyond the monotherapy RDE in combination with dexamethasone can be recommended in dosing steps of maximum 25% dose increase in Part B. SMC will review all available data to provide recommendations on the next dose level."	Data obtained during the safety run-in of Part B may indicate that a higher dose than the RDE for M3258 may be tolerated when M3258 is combined with dexamethasone. If so, SMC will review all available data to provide recommendations on the next dose level as now indicated in text.
Multiple sections	Revisions and updates to required protocol template language were incorporated within the protocol.	Prior to this amendment, the protocol template was revised. With this amendment, required protocol template language has been incorporated to align with the current template.
1.3 Schedule of Activities, Tables 1 and 3 (Table 3 was formerly Table 2)	Addition of safety 12-lead ECG testing on Days 8 and 22 Cycle 1 and Day 1 Cycle 2.	To align sampling times/visits for the 21- and 28-day regimens.
	Sampling timepoints for L-citrulline reduced.	As an exploratory biomarker, to determine if citrulline can be used to predict small intestine injury. Based upon preclinical studies this is expected to occur early during treatment.
	Skeletal Survey moved from Day 1 Cycle 1 to within the 28-day screening period	Site and participant convenience.

1.3 Schedule of Activities, Tables 1, 3, 5, and 6 (Table 3 was formerly Table 2, Table 5 was formerly Table 3, and Table 6 was formerly Table 4)	Moved assessments from Day 15 to Day 8 for 12-Lead QTc Assessment and LMP7 activity & β5c.	To align sampling times/visits for the 21- and 28-day regimens.
1.3 Schedule of Activities, Tables 3 and 6 (Table 3 was formerly Table 2 and Table 6 was formerly Table 4)	Added 3 PK sampling times on Day 8 Cycle 1 (Part B). Added 1 LMP7 activity & β5c sampling on Day 2 Cycle 1.	Increased the number of PK samples in order to enhance the PK data on this day. Added 1 LMP7 activity & β5c sampling on Day 2 Cycle 1 to correspond with PK sampling. .
5.1 Inclusion Criterion #5	Addition that platelet transfusions are permitted until 5 days before the first dose of study intervention and that at Day 1 Cycle 1 the Hb should meet inclusion criterion without transfusion > 7 days wash-out window.	Clarification
5.1 Inclusion Criterion #6	Aspartate aminotransferase level redefined as ≤ 3.0 × ULN (was ≤ 2.5 × ULN) and alanine aminotransferase level redefined as ≤ 3.0 × ULN (was ≤ 2.5 × ULN).	Aligned with NCI-CTC v5.
6.1 Study Intervention(s) Administration table	Addition of the 1mg unit to the Unit Dose Strength(s)/Dosage Level(s)	Available formulation which may be used in this study.
6.6 Dose Selection and Modification	Adjustment and clarification to the definition of DLT and to the DLT period.	Adjustment and clarification to align for all treatment regimens.
	Adjustment to assessing a DLT if a participant misses days or doses.	Adjustment to align for all treatment regimens.
	Duration of exceptions of Grade ≥ 3 nonhematologic AE considered DLTs were lengthened to <1 week (from ≤72 h) for Grade 3 fatigue, local reactions, and flu-like symptoms that resolve to Grade ≤ 1 with adequate treatment. Addition of Grade 4 thrombocytopenia lasting >7 days, or platelets <10,000/mm^3 at any time as a DLT	Adjustment to AEs judged as DLTs
	Addition of permission of transfusions if clearly related to multiple myeloma	Allowance for transfusions if required for multiple myeloma
	For Parts A and B, instruction on administration of missed doses or if a participant vomits after taking a M3258 dose.	Additional guidance on missed or vomited M3258 doses.
	Table 11 Recommended Dose Modification for New Onset or Worsening Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy (outside of DLT Period): adjustments to the recommendations for dose and regimen modification for Grade 1 with pain or Grade 2 and for Grade 2 with pain or Grade 3.	Clarification
	Table 12 Dose Modifications and Temporary/Permanent Treatment Discontinuation for Hematologic Toxicity (outside of DLT Period): adjustment to the dose medication recommendation for Grade 3 neutropenia associated with fever or neutropenia Grade 4 and for platelet count <25000/μL or Grade 3 thrombocytopenia with bleeding.	Clarification

	Table 15 Adverse Events of Special Interest (formerly Table 13): • severe anemia removed from myelosuppression (Grade > 3) with complications; • COVID-19 included in opportunistic infections; • skin rash added to allergic /hypersensitivity reaction; • guidance on limiting dexamethasone added to allergic /hypersensitivity reaction guidance	Adjustments to adverse events of special interest for M3258 and addition of consideration of COVID-19.
8.1 Efficacy Assessments and Procedures	Replaced "skeletal surveys" with "assessment of bone lesions", removed that skeletal surveys could be omitted at Day 1 Cycle 1 if other imaging is conducted, indicated that aspirates are preferred for the bone marrow examinations and clarified that all responses require 2 consecutive assessments with the same, worse, or better outcome in the list of disease evaluations for efficacy assessments per IMWG response criteria.	Clarification of efficacy evaluations for disease assessments.
8.4 Treatment of Overdose	Overdose was redefined as any dose higher than the calculated dose for that particular administration within a 12-hour time period.	Redefinition of overdose for stricter limits.
8.8 Biomarkers	Revised instructional guidelines for bone marrow samples used for determining cytogenetic risk factors and minimal residual disease.	Provided revised guidance for bone marrow sampling.
10 Safety Monitoring Committee	Added guidance that based on the safety, PK and Pd data (if available) collected from the participants in a cohort, the SMC may recommend that no further participants are required in a cohort before the planned cohort size is reached.	To clarify that based on the safety, PK and Pd data (if available) collected from the participants in a cohort, the SMC may recommend that no further participants are required in a cohort before the planned cohort size is reached
Appendix 10 Description of Bayesian Dose Escalation Model	Added guidance for the added treatment regimens.	Clarification on how to handle the different regimen in the Bayesian modeling

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma

Short Title:

First in Human Dose Escalation of M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone

Rationale:
M3258 is an oral, potent and selective covalent-reversible inhibitor of the chymotrypsin-like activity of the large multifunctional protease 7 (LMP7, β5i, PSMB8) subunit of the immunoproteasome, which has the potential to deliver a therapeutic benefit to patients with relapsed or refractory multiple myeloma (RRMM).

M3258 demonstrated potent and selective inhibition of LMP7. This indicates that M3258 has a related, yet more selective profile compared to the approved pan-proteasome inhibitors bortezomib, carfilzomib, and ixazomib, which indiscriminately inhibit multiple proteolytic subunits of the immunoproteasome and constitutive proteasome.

M3258 demonstrated strong antitumor activities, up to complete regressions, in nonclinical multiple myeloma models. Optimal efficacy was observed upon once daily (QD) oral dosing of M3258, a schedule associated with sustained suppression of LMP7 activity in tumor cells and peripheral blood mononuclear cells. M3258 also demonstrated superior in vivo efficacy compared to the approved pan-proteasome inhibitors in different nonclinical models including cytogenetic high-risk models, suggesting the potential for M3258 to deliver an efficacy benefit to patients with multiple myeloma (MM) who do not display an optimal response to these approved therapeutic agents.

Objectives and Endpoints:

Study Objectives and Endpoints - Dose Escalation - Part A

Objectives	Endpoints (Outcome Measures)
Primary	
• To determine safety, tolerability and the maximum tolerated dose (MTD) (if observed) of M3258 as a single agent in participants with RRMM	• Occurrence of dose-limiting toxicities (DLTs) in participants receiving M3258 as a single agent during the DLT period • Occurrence of any adverse events (AEs) reported (serious or nonserious) will be considered study treatment-emergent adverse events (TEAEs) and study treatment-related adverse events (TRAEs) (including TEAEs leading to death or discontinuation of treatment) in participants receiving M3258 as a single agent from start of study intervention to 30 days after End of Study Intervention • Occurrence of TEAEs outside of the DLT period that safety monitoring committee (SMC) deems relevant for determination of the MTD • Study treatment-emergent changes in clinical laboratory measures from Baseline, safety electrocardiogram (ECG) measures, vital signs, Eastern Co-operative Oncology Group (ECOG) performance status in participants receiving M3258 as a single agent from start of study intervention to 30 days after end of study intervention
Secondary	
• To investigate the pharmacokinetic (PK) profile of M3258 (single and multiple dose exposure) in participants with RRMM	• PK profile of M3258 in terms of C_{max}, AUC_{0-t}, AUC_{0-24} at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, 6, 8 and 24 h after administration • PK profile of M3258 in terms of C_{max}, AUC_{0-24} at Day 8 Cycle 1 (multiple dose): predose, 1, 2, 3, 4, 5, 6, and 8 h after administration

Objectives	Endpoints (Outcome Measures)
• To investigate the recommended dose and regimen for expansion (RDE) in participants with RRMM	• In addition to safety, tolerability and PK, for selection of recommended dose and regimen for expansion (RDE), changes in pharmacodynamics (Pd) (LMP7 activity) in pre and post study intervention samples on Day 1 Cycle 1 pre and postdose, Day 2 Cycle 1 predose and Day 8 Cycle 1 pre and postdose • Changes from Baseline in serum M-protein or urine M-protein or free light chain protein levels (for free light chain disease) on Day 1 of every cycle
• To evaluate preliminary clinical activity using International Myeloma Working Group (IMWG) criteria	• Overall response (OR), duration of response (DOR), time to response until complete response (CR), stringent complete response (sCR), very good partial response (VGPR), or partial response (PR) according to IMWG

Study Objectives and Endpoints - Dose Expansion - Part B

Objectives	Endpoints
Primary	
• To determine safety and tolerability of M3258 at recommended dose and regimen for expansion (RDE) when co-administered with dexamethasone in participants with RRMM	• Occurrence of DLTs in participants receiving M3258 in combination with dexamethasone during the DLT period • Occurrence of study treatment-emergent serious adverse events (SAEs) (including deaths) in participants receiving M3258 in combination with dexamethasone, from start of study intervention up to 30 days after end of study intervention • Occurrence of TEAEs and TRAEs (including deaths) in participants receiving M3258 in combination with dexamethasone from start of study intervention up to 30 days after end of study intervention • Study treatment-emergent clinically relevant abnormal changes in clinical

Objectives	Endpoints
	laboratory measures from Baseline, ECGs measures, vital signs, ECOG performance status in participants receiving M3258 in combination with dexamethasone from start of study intervention to 30 days after end of study intervention
• To determine recommended Phase II dose of M3258 when co-administered with dexamethasone in participants with RRMM based on early signs of safety and efficacy in the expansion phase	• Occurrence of TEAEs and TRAEs (including deaths) in participants receiving M3258 when given in combination with dexamethasone from start of study intervention to 30 days after end of study intervention • OR, DOR, time to response until CR, sCR, VGPR, or PR according to IMWG
Secondary	
• To collect preliminary efficacy data in participants with RRMM under treatment with M3258, when co-administered with dexamethasone	• OR, DOR, time to response until CR, sCR, VGPR, or PR according to IMWG • Progression-Free Survival (PFS) per Investigator • Overall Survival (OS) censored at End of Study
• To investigate the PK profile of M3258 (single and multiple dose exposure) when co-administered with dexamethasone in participants with RRMM	• PK profile of M3258 in terms of C_{max}, AUC_{0-t}, AUC_{0-24} at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, 6 and 24h after administration • PK profile of M3258 in terms of C_{max}, AUC_{0-24} at Day 8 Cycle 1, (multiple dose): predose, 2, 4, and 6h after administration

Overall Design:

This is a Phase I, open-label, First in Human (FiH), 2-part (dose escalation and expansion), noncontrolled, multicenter clinical study designed to determine the safety, tolerability, PK, Pd and early signs of efficacy of M3258 as a single agent (Part A) and co-administered with dexamethasone (Part B) in participants with RRMM whose disease has progressed following > 3 prior lines of therapy and for whom no effective standard therapy exists.

The dose escalation phase is aimed at determining the recommended dose and regimen for expansion (RDE) based on safety, tolerability, PK, Pd (including LMP7 activity) and initial efficacy data. Following the dose-escalation phase, the safety and tolerability of M3258 with

dexamethasone will be investigated in an expansion cohort for assessment of early clinical activity.

Number of Participants:

In the monotherapy, dose-escalation phase (Part A), approximately 18 participants will be enrolled in cohorts of 3 starting at the 10 mg QD dose level. The recommendation for dosing in the next cohort will be made by the SMC based on safety, tolerability, and preliminary PK and, if appropriate, Pd data. Details are described in the SMC charter. The following dose levels are planned: 10 mg, 20 mg, 35 mg, and 50 mg.

In the dose-expansion phase of M3258 in combination with dexamethasone (Part B), approximately 30 participants with RRMM will be enrolled at the recommended dose and regimen for expansion (RDE) determined in the dose-escalation phase of the study. This number may increase by approximately 3 to 21 participants if a change in dose of M3258 occurs in the expansion cohort. An interim analysis will be conducted when data for 15 participants evaluable for response and treated on the same dose are available. The SMC will monitor the safety of participants during the expansion cohort.

Study Intervention Groups and Duration:

During dose escalation (Part A), M3258 will be administered QD as a single agent in 28-day cycles. In the expansion cohort (Part B), M3258 will be administered in combination with dexamethasone at a cumulative dose of 40mg/week. The treatment period will begin at the first dose of M3258 in Day 1 Cycle 1. Participants tolerating M3258 without significant clinically relevant toxicities may continue to receive assigned M3258 dose until disease progression.

If QD treatment is not tolerated at a dose level showing efficacy and/or Pd marker signals, the following options will be considered by the SMC based on available data:

- QD dosing at doses below the non-tolerated dose (down to 1mg) in 28-day cycles (based on SMC recommendation)

OR

- Twice-per-week dosing on Days 1, 4, 8, 11, 15, 18, 22 and 25 in 28-day cycles

In addition, if a consistent reduction in platelet counts to thrombocytopenia $\geq$ Grade 3 is observed during the 28-day dosing regimen without recovery to baseline or $\leq$ Grade 2 by the end of the cycle, the SMC can consider a drug holiday of at least 7 days in the proposed regimen. Similar to pan-proteasome inhibitors, a transient effect on megakaryocyte function, possibly related to platelet budding needs to be considered rather than a direct cytotoxic effect on megakaryocytes (Lonial et al, 2005). A predicted time for recovery of platelet counts from nadir to baseline values has been described to be around 7 days (Lonial et al, 2005). Thus, a drug holiday (intermittent) of at least 7 days to 10 days is included in the proposed regimen which consequently changes the cycle length to 21 days.

- QD dosing on Days 1 to 14, no dosing on Days 15 to 21, in 21-day cycles

OR

- Twice-per-week dosing on Days 1, 4, 8, 11, no dosing on Days 12 to 21, in 21-day cycles

If a switch in dose and/or regimen is recommended, the first tested dose level in the new regimen must not exceed the highest tested daily dose /or the weekly cumulative dose must be equal to or lower than the highest weekly cumulative dose of regimen(s) tested so far.

The selected M3258 dose and regimen (RDE) will be combined with dexamethasone for the expansion cohort (Part B).

Dexamethasone will be given at a cumulative dose of 40 mg/week:

- 20 mg/day at Days 1, 4, 8, 11, 15, 18, 22 and 25 in a **28-day cycle**

OR

- 20 mg/day at Days 1, 4, 8, 11, 15, and 18 in a **21-day cycle** (regimen with drug holiday)

Dose Escalation Part A

Participants with MM whose disease has progressed following > 3 lines of therapy and for whom no effective standard therapy exists will be enrolled in Part A. The first dose-escalation cohort will receive M3258 at the starting dose of 10 mg QD as a single agent. For further dose cohorts, a SMC will meet and review all available data to provide recommendations on the next dose level. The following prespecified doses of 10 mg, 20 mg (100% increase), 35 mg (43% increase) and 50 mg (30% increase) are planned unless MTD is reached. The SMC, following review of preliminary safety, tolerability, PK and Pd information, will recommend the dose and/or the switch to an alternative regimen prespecified in this protocol for the next cohort as applicable.

This may include proposing smaller dose increases compared to the prespecified doses and de-escalation of the dose potentially down to 1mg.

The SMC may also recommend expanding a given cohort at the same dose level.

If additional dose levels above 50 mg are justified following review of preliminary safety, tolerability, PK, and Pd information from the initial cohorts, a protocol amendment will be submitted.

Depending on the observed toxicity profile, the SMC may decide on different doses as prespecified and/or change to regimens prespecified in this protocol. However, escalation may not proceed to any dose higher than 50 mg. In case escalation should proceed to doses higher than 50 mg, an amendment will be submitted. At each dose level, the first participant enrolled will be observed for acute toxicity for at least 48 hours during the DLT period before further participants are enrolled.

The RDE of single-agent M3258 will be based on all available safety, tolerability, PK, Pd (including LMP7 activity) and initial efficacy data from at least 6 participants at the given dose.

This dose and regimen will be the recommended dose for Part B of the study, pending SMC agreement.

Dose Expansion Part B

Once an RDE (dose and regimen) of M3258 has been defined which is considered safe by the SMC, dose expansion (Part B) may begin. Initiation of Part B may start without reaching the MTD in Part A; dose escalation for defining the monotherapy MTD (Part A) may proceed in parallel.

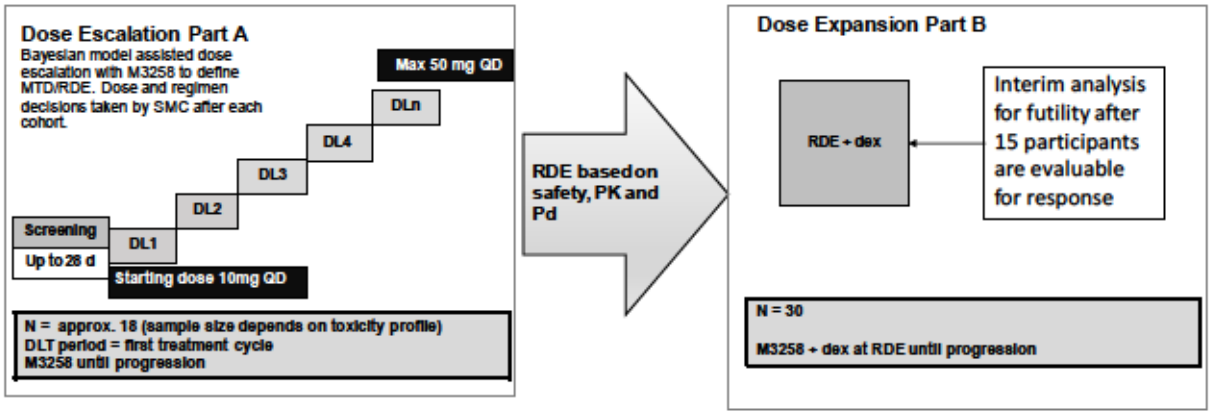
Participants with MM whose disease has progressed following > 3 lines of therapy for whom no effective standard therapy exists will be enrolled. In Part B, participants will receive M3258 at the RDE selected in Part A in combination with dexamethasone at a cumulative dose of 40 mg/week. The first 2 cohorts of 3 participants each (first 6 participants) will be used for a safety run-in. The participants in these 2 cohorts will be enrolled in a sequential approach. Each cohort of the safety run-in will be evaluated by the SMC for the prespecified DLT criteria for this combination before additional participants are enrolled. These SMC meetings will be held after 3 and 6 participants in the safety run-in have finished Cycle 1 or discontinued treatment in order to evaluate safety, cumulative and unacceptable toxicity of participants from their treatment cycles. After the safety run-in, SMC meetings will be held at the completion of Cycle 1 or discontinuation of treatment for every 6 participants (without pausing enrollment) in order to assess safety, cumulative and unacceptable toxicity of all participants in the expansion cohort, unless a change in dosing has occurred. In case dosing in the expansion cohort was changed, the next SMC will be held after 3 participants have finished the DLT period or discontinued.

The SMC decisions in the expansion phase will also be supported by Bayesian modeling. If data obtained during the safety run-in of Part B indicate that a higher dose than the RDE may be tolerated when M3258 is administered in combination with dexamethasone, then a careful escalation beyond the monotherapy RDE in combination with dexamethasone can be recommended in dosing steps of maximum 25% increases in Part B. SMC will review all available data to provide recommendations on the next dose level. When 15 participants treated at the same dose level are evaluable for response, an interim analysis will be performed.

Involvement of Special Committee(s):
The SMC, comprised of internal and external members, will make decisions on dose and regimen of M3258 during the dose-escalation phase (Part A) and will regularly monitor the safety of the participants during the dose-expansion phase (Part B) and decide if the dosing needs to be changed.

1.2 Schema

Figure 1 Overall Study Design



Note: If required in Part A, other dosing and regimen options are presented in Section 1.1. Potential modifications to Part B dosing are also presented in Section 1.1.

3L = third line of therapy;; d = days; dex = dexamethasone; DL = dose level; DLT = dose limiting toxicity; max = maximum; MTD = maximal tolerated dose; N = number; Pd = pharmacodynamics; PK = pharmacokinetics; QD = once daily; RDE = recommended dose and regimen for expansion; SMC = Safety Monitoring Committee.

1.3 Schedule of Activities

Table 1 Schedule of Activities – Dose Escalation - Part A (for 28-day cycles)

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up/ Discontinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days after last intervention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Informed Consent	X																		
Inclusion and Exclusion Criteria	X	X																	Recheck clinical status before first dose of study intervention
Demography/Height	X																		
Physical Examination with Weight	X	X		X [a]	X [a]	X [a]	X		X [a]		X [a]	X [a]	X	X [a]	X [a]	X [a]	X		Details in Section 8.2.1. a = brief physical examination including peripheral motor and sensory nervous system

Assessments & Procedures	Screen-ing	Intervention Period														End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Medical History (includes substance usage and family history of premature CV disease)	X																		Substance usage: Drugs, alcohol, tobacco, and caffeine
Past and Current Medical Conditions	X																		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Every 3rd cycle	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Every 3rd cycle	X	X	See details in Section 8.2.2.
Chest X-ray	X																		To exclude infections, interstitial pneumonitis, and lung infiltration to be done before CT or MRI. See details in Section 8.2.4.
12-lead Safety ECG	X	X	X	X	X	X	X		X		X	X	X	X	X	X Every 3rd cycle			Before any blood sampling

Assessments & Procedures	Screen-ing	Intervention Period														End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6		
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
12-lead QTc Assessment		X	X	X															See Table 5 for details.
Echocardiography or MUGA scan	X																		Echocardiography or MUGA scan to evaluate cardiac left ventricular ejection fraction
MRI (Chest, abdomen, pelvis) or CT scan if contrast can be given	X																		At Screening and to confirm CR, and for PR and MR if extramedullary disease detected at baseline, CT with contrast only if renal activity allows. If performed by PET/CT or MRI, osteolytic lesions and extramedullary disease can be evaluated within the same imaging.

Assessments & Procedures	Screen-ing	Intervention Period															End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Study Intervention M3258		<	-	-	-	-	-	-	-	-	-	-	-	-	-	>			QD In case of toxicity which cannot be managed during treatment alternative dose and regimen will be tested: see Section 4.1. For dose modification, see Section 6.6. For PK and Pd see Table 5 for details.
Antiviral Prophylaxis for Herpes Zoster (valacyclovir or acyclovir)		<	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	->	According to institutional guidelines
AE & SAE Review		<	-	-	-	-	-	-	-	-	-	-	-	-	-	>	X	X	Until 30 days after the last dose
Concomitant Medication Review		<	-	-	-	-	-	-	-	-	-	-	-	-	-	>	X	X	

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up/ Discontinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days after last intervention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Laboratory Assessments (Details regarding local and central laboratory assessments to be found in Appendix 7 and the Laboratory Manual, respectively.)																			
Serum Pregnancy Test (WOCBP only) at Screening and in urine thereafter	X	X					X				X		X	X	X	X	X	X	See Appendix 7.
Urinalysis	X	X									X			X	X	X Every 3rd cycle	X	X	See Appendix 7.
Hepatitis B and C and HIV Screening	X																		See Appendix 7.
Clinical Laboratory Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Hematology, serum chemistry, and coagulation see Appendix 7.
Albumin-corrected Ca		X					X				X		X	X	X	X	X		
PK M3258		X	X	X	X														See Table 5 for details
LMP7 & β5c Activity		X	X	X															See Table 5 for details
L-citrulline		X			X		X				X								Predose

Assessments & Procedures	Screen-ing	Intervention Period														End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6		
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
CCI [redacted]																			
Disease/Efficacy Assessment (Details regarding local and central laboratory assessments to be found in Appendix 7 and the Laboratory Manual, respectively)																			
Assessment for MRD in Bone Marrow		X (- 3 days)																	Bone marrow sample at Day 1 Cycle 1 (window: - 3 days) for assessment of clonality with NGS. Additionally, a bone marrow sample for MRD by NGS and/or flow cytometry at CR (central laboratory, see Section 8.8).
Disease Staging in Bone Marrow		X (- 3 days)																	Morphology, cytogenetics, and either immunohistochemistry or flow cytometry in bone marrow aspirate at predose (local laboratory).

Assessments & Procedures	Screen-ing	Intervention Period														End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6		
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Skeletal Survey	X																		Assessment of osteolytic lesions by imaging at Baseline according to IMWG guidance and suspicion of new lesions (skeletal survey, see Section 8). Follow-Up only when clinical suspicion of new lesions.
Disease/Efficacy Assessment		X					X				X		X	X	X	X	X		
Quantitative Immunoglobulins IgG, IgA, IgM, IgE, IgD in Serum (immunofixation)	X																		When CR is suspected and no detectable M-Protein in serum
Serum-β2 Microglobulin		X																	

Assessments & Procedures	Screen-ing	Intervention Period															End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Free Light Chain in Serum	X																		During study when CR is suspected
Free Light Chain (immunofixation) in Urine	X																		During study, when CR is suspected
Serum M-Protein Electrophoresis	X	X					X				X		X	X	X	X	X		See Section 8 and Appendix 7
Quantitative Urine Ig (immunofixation in 24h urine)	X																		When CR is suspected and no detectable M-Protein in serum
Urine M-Protein Electrophoresis (in 24 h urine sample)	X	X					X				X		X	X	X	X	X		See Section 8 and Appendix 7
In Case of Free Light Chain Disease: Free Light Chain in Serum		X					X				X		X	X	X	X	X		For participants with common MM, the free light chain in serum will be tested when CR is suspected

AE = Adverse event, BID = twice daily; Ca = Calcium, CT = Computed tomography, CV = Cardiovascular, CR = Complete response, HIV = Human immunodeficiency virus, ECG = Electrocardiogram, ECOG = Eastern Co-operative of Oncology Group, Ig = Immunoglobulin, IMWG = International Myeloma Working Group, MRI =Magnetic resonance imaging; MRD = Minimal residual disease, MUGA = Multigated acquisition, NGS = Next-Generation-Sequencing, PK = Pharmacokinetics, Pd = Pharmacodynamics, PR = Partial response, QD = Once daily, SAE = Serious adverse event; WOCBP = Women of childbearing potential.

Table 2 Schedule of Activities – Dose Escalation - Part A (for 21-day cycles)

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Informed Consent	X																
Inclusion and Exclusion Criteria	X	X															Recheck clinical status before first dose of study intervention
Demography/Height	X																
Physical Examination with Weight	X	X		X [a]	X [a]	X		X [a]	X [a]	X [a]	X	X [a]	X [a]	X [a]	X		Details in Section 8.2.1. a = brief physical examination including peripheral motor and sensory nervous system
Medical History (includes substance usage and family history of premature CV disease)	X																Substance usage: Drugs, alcohol, tobacco, and caffeine

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Past and Current Medical Conditions	X																
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X Every 3rd cycle	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X Every 3rd cycle	X	X	See details in Section 8.2.2.
Chest X-ray	X																To exclude infections, interstitial pneumonitis, and lung infiltration to be done before CT or MRI. See details in Section 8.2.4.
12-lead Safety ECG	X	X	X	X	X	X		X	X	X	X	X	X	X Every 3rd cycle			Before any blood sampling
12-lead QTc Assessment		X	X	X													See Table 5 for details.
Echocardiography or MUGA scan	X																Echocardiography or MUGA scan to evaluate cardiac left ventricular ejection fraction

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
MRI (Chest, abdomen, pelvis) or CT scan if contrast can be given	X																At Screening and to confirm CR, and for PR and MR if extramedullary disease detected at baseline. CT with contrast only if renal activity allows. If performed by PET/CT or MRI, osteolytic lesions and extramedullary disease can be evaluated within the same imaging.

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Study Intervention M3258		<	-	-	-	-	-	-	-	-	-	-	-	>			QD In case of toxicity which cannot be managed during treatment alternative regimen will be tested: See Section 4.1. For dose modification, see Section 6.6. For PK and Pd see Table 5 for details.
Antiviral Prophylaxis for Herpes Zoster (valacyclovir or acyclovir)		<	-	-	-	-	-	-	-	-	-	-	-	-	-	->	According to institutional guidelines
AE & SAE Review		<	-	-	-	-	-	-	-	-	-	-	-	>	X	X	Until 30 days after the last dose
Concomitant Medication Review		<	-	-	-	-	-	-	-	-	-	-	-	>	X	X	

Assessments & Procedures	Screening	Intervention Period													End of Study Intervention	Follow-Up/ Discontinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days after last intervention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Laboratory Assessments (Details regarding local and central laboratory assessments to be found in Appendix 7 and the Laboratory Manual, respectively.)																	
Serum Pregnancy Test (WOCBP only) at Screening and in urine thereafter	X	X				X			X		X	X	X	X	X	X	See Appendix 7.
Urinalysis	X	X							X			X	X	X Every 3rd cycle	X	X	See Appendix 7.
Hepatitis B and C and HIV Screening	X																See Appendix 7.
Clinical Laboratory Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Hematology, serum chemistry, and coagulation see Appendix 7.
Albumin-corrected Ca		X				X			X		X	X	X	X	X		
PK M3258		X	X	X	X												See Table 5 for details
LMP7 & β5c Activity		X	X	X													See Table 5 for details
L-citrulline		X			X	X			X								Predose

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
CCI [redacted]																	
Disease/Efficacy Assessment (Details regarding local and central laboratory assessments to be found in Appendix 7 and the Laboratory Manual, respectively)																	
Assessment for MRD in Bone Marrow		X (-3 days)															Bone marrow sample at Day 1 Cycle 1 (window: - 3 days) for assessment of clonality with NGS. Additionally, a bone marrow sample for MRD by NGS and/or flow cytometry at CR (central laboratory, see Section 8.8).
Disease Staging in Bone Marrow		X (-3 days)															Morphology, cytogenetics, and either immunohistochemistry or flow cytometry in bone marrow aspirate at predose (local laboratory).

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Inter-vention	Follow-Up/ Discon-tinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days after last inter-vention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Skeletal Survey	X																Assessment of osteolytic lesions by imaging at Baseline according to IMWG guidance and suspicion of new lesions (skeletal survey, see Section 8). Follow-Up only when clinical suspicion of new lesions.
Disease/Efficacy Assessment		X				X			X		X	X	X	X	X		
Quantitative Immunoglobulins IgG, IgA, IgM, IgE, IgD in Serum (immunofixation)	X																When CR is suspected and no detectable M-Protein in serum
Serum-β2 Microglobulin		X															

Assessments & Procedures	Screening	Intervention Period													End of Study Intervention	Follow-Up/ Discontinuation	Notes
	up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days after last intervention/ intake	30 days after last dose	
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7 d	± 3 d	± 7 d	d = days
Free Light Chain in Serum	X																During study when CR is suspected
Free Light Chain (immunofixation) in Urine	X																During study, when CR is suspected
Serum M-Protein Electrophoresis	X	X				X			X		X	X	X	X	X		See Section 8 and Appendix 7
Quantitative Urine Ig (immunofixation in 24h urine)	X																When CR is suspected and no detectable M-Protein in serum
Urine M-Protein Electrophoresis (in 24 h urine sample)	X	X				X			X		X	X	X	X	X		See Section 8 and Appendix 7
In Case of Free Light Chain Disease: Free Light Chain in Serum		X				X			X		X	X	X	X	X		For participants with common MM, the free light chain in serum will be tested when CR is suspected

AE = Adverse event, BID = twice daily; Ca = Calcium, CT = Computed tomography, CV = Cardiovascular, CR = Complete response, HIV = Human immunodeficiency virus, ECG = Electrocardiogram, ECOG = Eastern Co-operative of Oncology Group, Ig = Immunoglobulin, IMWG = International Myeloma

Working Group, MRI =Magnetic resonance imaging; MRD = Minimal residual disease, MUGA = Multigated acquisition, NGS = Next-Generation-Sequencing, PK = Pharmacokinetics, Pd = Pharmacodynamics, PR = Partial response, QD = Once daily, SAE = Serious adverse event; WOCBP = Women of childbearing potential.

Table 3 Schedule of Activities – Dose Expansion - Part B (for 28-day cycles)

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Informed Consent	X																		
Inclusion and Exclusion Criteria	X	X																	Recheck clinical status before first dose of study intervention.
Demography/ Height	X																		
Physical Examination with Weight	X	X		X [a]	X [a]	X [a]	X		X [a]		X [a]	X [a]	X	X [a]	X [a]	X [a]	X		Details in Section 8.2.1. a = brief physical examination including peripheral motor and sensory nervous system

Assessments & Procedures	Screening	Intervention Period														End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6		
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Medical History (includes substance usage and family history of premature CV disease)	X																		Substance usage: Drugs, alcohol, tobacco, and caffeine
Past and Current Medical Conditions	X																		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Every 3rd cycle	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X Every 3rd cycle	X	X	See Section 8.2.2.
Chest X-ray	X																		To exclude infections, interstitial pneumonitis, and lung infiltration to be done before CT or MRI. See details in Section 8.2.4.

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
12-lead Safety ECG	X	X	X	X	X	X	X		X		X	X	X	X	X	X Every 3rd cycle			ECG before any blood sampling.
12-lead QTc Assessment				X															See Table 6 for details.
Echocardiography or MUGA scan	X																		Echocardiography or MUGA scan to evaluate cardiac left ventricular ejection fraction

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
MRI (Chest, abdomen, pelvis) or CT scan if contrast can be given	X																		At Screening and to confirm CR, and for PR and MR if extramedullary disease detected at baseline, CT with contrast only if renal activity allows. If performed by PET/CT or MRI, osteolytic lesions and extramedullary disease can be evaluated within the same imaging.

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Study Intervention M3258		<	-	-	-	-	-	-	-	-	-	-	-	-	-	>			QD In case of toxicity which cannot be managed during treatment alternative dose and regimen will be tested: See Section 4.1. For dose modification, see Section 6.6. For PK and Pd see Table 6 for details.
Dexamethasone		<	-	-	-	-	-	-	-	-	-	-	-	-	-	>			Dexamethasone will be given at a cumulative dose of 40 mg / week;. see Section 4.1.
Antiviral Prophylaxis (acyclovir or valacyclovir)		<	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	->	According to institutional guidelines

Assessments & Procedures	Screen-ing	Intervention Period															End of Study Intervention	Follow-Up / Discon-tinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
AE & SAE Review		<	-	-	-	-	-	-	-	-	-	-	-	-	-	>	X	X	Until 30 days after the last dose
Concomitant Medication Review		<	-	-	-	-	-	-	-	-	-	-	-	-	-	>	X	X	
Laboratory Assessments (Details regarding local and central laboratory assessments to be found in Appendix 7 and the Laboratory Manual, respectively)																			
Serum Pregnancy Test (WOCBP only) at Screening and in urine thereafter	X	X					X				X		X	X	X	X	X		See Appendix 7.
Urinalysis	X	X									X			X	X	X Every 3rd cycle	X	X	See Appendix 7.
Hepatitis B and C and HIV Screening	X																		See Appendix 7.

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Clinical Laboratory Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Hematology, serum chemistry and coagulation see Appendix 7.

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Albumin-corrected Ca		X					X				X		X	X	X	X	X		
PK M3258		X	X	X			X												See Table 6 for details.
PK Dexamethasone							X												See Table 6 for details.
LMP7 & β5c Activity		X	X	X															See Table 6 for details.
L-citrulline		X			X		X				X								Predose
CCI																			
Food Effect							X												See Table 6.

Assessments & Procedures	Screen-ing	Intervention Period															End of Study Intervention	Follow-Up / Discon-tinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Disease/Efficacy Assessment (Details regarding local and central laboratory assessments to be found in Appendix 7 and the Laboratory Manual, respectively)																			
Assessment for MRD in Bone Marrow		X (-3 days)																	Bone marrow sample at Day 1 Cycle 1 (window: - 3 days) for assessment of clonality for NGS. Additionally, a bone marrow sample for MRD by NGS and/or flow cytometry at CR (central laboratory, see Section 8.8).
Disease Staging in Bone Marrow		X (-3 days)																	Morphology, cytogenetics, and either immunohistochemistry or flow cytometry in bone marrow aspirate at predose (local laboratory).

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Skeletal Survey	X																		Assessment of osteolytic lesions by imaging at Baseline according to IMWG guidance and at suspicion of new lesions (skeletal survey, see Section 8). Follow-Up only when clinical suspicion of new lesions.
Disease/Efficacy Assessment		X					X				X		X	X	X	X	X		
Quantitative Immunoglobulins IgG, IgA, IgM, IgE, IgD in Serum (immunofixation)	X																		When CR is suspected and no detectable M-Protein in serum
Serum-β2 Microglobulin		X																	

Assessments & Procedures	Screening	Intervention Period															End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1					Cycle 2				Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Free Light Chain in Serum and Urine	X																		During study, when CR is suspected
Serum M-Protein Electrophoresis	X	X					X				X		X	X	X	X	X		See Section 8 and Appendix 7.
Quantitative Urine Ig (immunofixation in 24h urine)	X																		When CR is suspected and no detectable M-Protein in serum
Urine M-Protein Electrophoresis (in 24 h urine sample)	X	X					X				X		X	X	X	X	X		See Section 8 and Appendix 7
In case of free light chain disease: Free Light Chain in Serum		X					X				X		X	X	X	X	X		For participants with common MM, the free light chain in serum will be tested when CR is suspected
Survival Follow-Up																		X	Survival Follow-Up every 12 weeks until End of Study.

AE = Adverse event, BID = twice daily; Ca = Calcium, CT = Computed tomography, CV = Cardiovascular, CR = Complete response, HIV = Human immunodeficiency virus, ECG = Electrocardiogram, ECOG = Eastern Co-operative of Oncology Group, Ig = Immunoglobulin, IMWG = International Myeloma Working Group, MRI =Magnetic resonance imaging; MRD = Minimal residual disease, MUGA = Multigated acquisition, NGS = Next-Generation-Sequencing, PK = Pharmacokinetics, Pd = pharmacodynamics; PD = Progressive disease, PR = Partial response, QD = Once daily, SAE = Serious adverse event; WOCBP = Women of childbearing potential.

Table 4 Schedule of Activities – Dose Expansion - Part B (for 21-day cycles)

Assessments & Procedures	Screening	Intervention Period													End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Informed Consent	X																
Inclusion and Exclusion Criteria	X	X															Recheck clinical status before first dose of study intervention.
Demography/ Height	X																
Physical Examination with Weight	X	X		X [a]	X [a]	X		X [a]	X [a]	X [a]	X	X [a]	X [a]	X [a]	X		Details in Section 8.2.1. a = brief physical examination including peripheral motor and sensory nervous system.
Medical History (includes substance usage and family history of premature CV disease)	X																Substance usage: Drugs, alcohol, tobacco, and caffeine

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Intervention	Follow-Up / Discon-tinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Past and Current Medical Conditions	X																
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X Every 3rd cycle	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X Every 3rd cycle	X	X	See Section 8.2.2.
Chest X-ray	X																To exclude infections, interstitial pneumonitis, and lung infiltration to be done before CT or MRI. See details in Section 8.2.4.
12-lead Safety ECG	X	X	X	X	X	X		X	X	X	X	X	X	X Every 3rd cycle			ECG before any blood sampling.
12-lead QTc Assessment				X													See Table 6 for details.

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Intervention	Follow-Up / Discon-tinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Echocardiography or MUGA scan	X																Echocardiography or MUGA scan to evaluate cardiac left ventricular ejection fraction
MRI (Chest, abdomen, pelvis) or CT scan if contrast can be given	X																At Screening and to confirm CR, and for PR and MR if extramedullary disease detected at baseline, CT with contrast only if renal activity allows. If performed by PET/CT or MRI, osteolytic lesions and extramedullary disease can be evaluated within the same imaging.

Assessments & Procedures	Screening	Intervention Period													End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	7d	± 3 d	± 7 d	d = days
Study Intervention M3258		<	-	-	-	-	-	-	-	-	-	-	-	>			QD In case of toxicity which cannot be managed during treatment alternative regimen will be tested: see Section 4.1. . For dose modification, see Section 6.6. For PK and Pd see Table 6 for details.
Dexamethasone		<	-	-	-	-	-	-	-	-	-	-	-	>			Dexamethasone will be given at a cumulative dose of 40 mg / week: see Section 4.1.
Antiviral Prophylaxis (acyclovir or valacyclovir)		<	-	-	-	-	-	-	-	-	-	-	-	-	-	->	According to institutional guidelines
AE & SAE Review		<	-	-	-	-	-	-	-	-	-	-	-	>	X	X	Until 30 days after the last dose

Assessments & Procedures	Screening	Intervention Period													End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Concomitant Medication Review		<	-	-	-	-	-	-	-	-	-	-	-	>	X	X	
Laboratory Assessments (Details regarding local and central laboratory assessments to be found in Appendix 7 and the Laboratory Manual, respectively)																	
Serum Pregnancy Test (WOCBP only) at Screening and in urine thereafter	X	X				X			X		X	X	X	X	X		See Appendix 7.
Urinalysis	X	X							X			X	X	X Every 3rd cycle	X	X	See Appendix 7.
Hepatitis B and C and HIV Screening	X																See Appendix 7.

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Intervention	Follow-Up / Discon-tinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Clinical Laboratory Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Hematology, serum chemistry and coagulation see Appendix 7.

Assessments & Procedures	Screening	Intervention Period													End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Albumin-corrected Ca		X				X			X		X	X	X	X	X		
PK M3258		X	X	X		X											See Table 6 for details.
PK Dexamethasone						X											See Table 6 for details.
LMP7 & β5c Activity		X	X	X													See Table 6 for details.
L-citrulline		X			X	X			X								Predose
CCI																	
Food Effect						X											See Table 6.

Assessments & Procedures	Screen-ing	Intervention Period													End of Study Intervention	Follow-Up / Discon-tinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Disease/Efficacy Assessment (Details regarding local and central laboratory assessments to be found in Appendix 7 and the Laboratory Manual, respectively)																	
Assessment for MRD in Bone Marrow		X (-3 days)															Bone marrow sample at Day 1 Cycle 1 (window: - 3 days) for assessment of clonality for NGS. Additionally, a bone marrow sample for MRD by NGS and/or flow cytometry at CR (central laboratory, see Section 8.8).
Disease Staging in Bone Marrow		X (-3 days)															Morphology, cytogenetics, and either immunohistochemistry or flow cytometry in bone marrow aspirate at predose (local laboratory).

Assessments & Procedures	Screening	Intervention Period													End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Skeletal Survey	X																Assessment of osteolytic lesions by imaging at Baseline according to IMWG guidance and at suspicion of new lesions (skeletal survey, see Section 8). Follow-Up only when clinical suspicion of new lesions.
Disease/Efficacy Assessment		X				X			X		X	X	X	X	X		
Quantitative Immunoglobulins IgG, IgA, IgM, IgE, IgD in Serum (immunofixation)	X																When CR is suspected and no detectable M-Protein in serum
Serum-β2 Microglobulin		X															

Assessments & Procedures	Screening	Intervention Period													End of Study Intervention	Follow-Up / Discontinuation	Notes
	Up to 28 days before Day 1 Cycle 1	Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5	Cycle 6	Every cycle after Cycle 6			
	Day	1	2	8	15	1	8	15	1	15	1	1	1	1	within 7 days of intervention/ intake	30 days, after last dose	Day 2 Cycle1 visit is only for participants in safety run-in or the first 3 participants at a changed dose.
	Visit Window		± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	± 7d	± 3 d	± 7 d	d = days
Free Light Chain in Serum and Urine	X																During study, when CR is suspected
Serum M-Protein Electrophoresis	X	X				X			X		X	X	X	X	X		See Section 8 and Appendix 7.
Quantitative Urine Ig (immunofixation in 24h urine)	X																When CR is suspected and no detectable M-Protein in serum
Urine M-Protein Electrophoresis (in 24 h urine sample)	X	X				X			X		X	X	X	X	X		See Section 8 and Appendix 7
In case of free light chain disease: Free Light Chain in Serum		X				X			X		X	X	X	X	X		For participants with common MM, the free light chain in serum will be tested when CR is suspected
Survival Follow-Up																X	Survival Follow-Up every 12 weeks until End of Study.

AE = Adverse event, BID = twice daily; Ca = Calcium, CT = Computed tomography, CV = Cardiovascular, CR = Complete response, HIV = Human immunodeficiency virus, ECG = Electrocardiogram, ECOG = Eastern Co-operative of Oncology Group, Ig = Immunoglobulin, IMWG = International Myeloma

Working Group, MRI =Magnetic resonance imaging; MRD = Minimal residual disease, MUGA = Multigated acquisition, NGS = Next-Generation-Sequencing, PK = Pharmacokinetics, Pd = pharmacodynamics; PD = Progressive disease, PR = Partial response, QD = Once daily, SAE = Serious adverse event; WOCBP = Women of childbearing potential.

Table 5 Schedule of Electrocardiogram, Pharmacokinetic, and Biomarker Assessments during Dose Escalation - Part A (for 21- and 28-day cycles)

Treatment Day [a]	Time h (± min) [b,c]	ECG [d]	PK M3258	LMP7 & β5c activity	CCI
D1 C1	Predose	X	X	X	
	1 (± 5)		X		
	2 (± 10)	X	X	X	
	3 (± 15)		X		
	4 (± 15)	X	X		
	5 (± 15)		X		
	6 (± 15)	X	X	X	
	8 (± 30)	X	X		
D2 C1	24 (Predose)	X	X	X	
D8 C1	Predose	X	X	X	
	1 (± 5)		X		
	2 (± 10)	X	X	X	
	3 (± 15)		X		
	4 (± 15)	X	X		
	5 (± 15)		X		
	6 (± 15)	X	X	X	
	8 (± 30)	X	X		
D15 C1	Predose		X		

β5c = Constitutive proteasome subunit β5; C = Cycle; D = Day; ECG = Electrocardiogram; LMP7 = Large multifunctional protease 7; CCI ; Pd = Pharmacodynamics; PK = Pharmacokinetics.

a: Table 5 is applicable for all proposed regimens in Part A.

b: At visits where assessment time points (ECG, PK and Pd) coincide with each other:
1) Perform vital signs assessments at first
2) ECG assessments slightly before the specific collection time point
3) PK assessments at scheduled collection time point and
4) Pd assessments as last assessment

c: Actual collection times should be collected in the electronic Case Report Form along with the times of the last dose administration.

d: Triple ECG for the QT/QTc analysis after at least 10 minutes' rest and within 2 minutes and have to be taken before any blood sampling. See Table 1 and Table 2 for 12-lead Safety ECG timing (note that triple ECG for the QT/QTc analysis here is listed as 12-lead QTc Assessment in Tables 1 and 2).

Table 6 Schedule of Electrocardiogram, Pharmacokinetic, and Biomarker Assessments during Dose Expansion - Part B (for 21- and 28-day cycles)

Treatment Day [a]	Time h (± min) [b,c]	ECG [d]	PK M3258	PK dexamethasone	LMP7 activity & β5c	CCI
D1 C1	Predose		X		X	
	1 (± 5)		X			
	2 (± 10)		X		X	
	3 (± 15)		X			
	4 (± 15)		X			
	5 (± 15)		X			
	6 (± 15)		X		X	
D2 C1[f]	24 (Predose)		X		X	
D8 C1	Predose	X	X		X	
	1 (± 5)		X			
	2 (± 10)	X	X		X	
	3 (± 15)		X			
	4 (± 15)	X	X			
	5 (± 15)		X			
	6 (± 15)	X	X		X	
D1 C2	Predose		X[e]	X[e]		
	1 (± 5)		X[e]	X[e]		
	2 (± 10)		X[e]	X[e]		
	3 (± 15)		X[e]	X[e]		
	4 (± 15)		X[e]	X[e]		
	5 (± 15)		X[e]			
	6 (± 15)		X[e]	X[e]		
	8 (± 30)		X[e]			

β5c = Constitutive proteasome subunit β5; C = Cycle; D = Day; ECG = Electrocardiogram; LMP7 = Large multifunctional protease 7; CCI ; Pd = Pharmacodynamics; PK = Pharmacokinetics.

a: Table 6 is applicable for all proposed regimens in Part B.

b: At visits where assessment time points (ECG, PK and PD) coincide with each other

1) Perform vital signs assessments at first

2) ECG assessments slightly before the specific collection time point

3) PK assessments at scheduled collection time point and

4) Pd assessments as last assessment

c: Actual collection times should be collected in the eCRF along with the times of the last dose administration.

d: Triple ECG for the QT/QTc analysis after at least 10-minutes rest and within 2 minutes and have to be taken before any blood sampling. See Table 3 and Table 4 for 12-lead Safety ECG timing (note that triple ECG for the QT/QTc analysis here is listed as 12-lead QTc Assessment in Tables 3 and 4).

e: PK samples for food effect evaluation taken for at least the first 18 participants. Decision on sampling in further participants will be taken during interim analysis.

f: For participants in the safety run-in and the first 3 participants at a new dose.

2 Introduction

Multiple myeloma is characterized by the presence of monoclonal plasma cells in bone marrow, extramedullary organs, or both. Symptomatic MM is defined by end organ damage such as lytic bone lesions, hypercalcemia, anemia, and renal impairment. Relapsed MM is defined as a recurrence of disease after prior response based on objective laboratory and radiological criteria. Refractory MM is defined as disease that becomes nonresponsive or progressive on therapy or within 60 days of last treatment in participants who had achieved a minimal response or better on prior therapy. Once relapse treatment is required, individual participant characteristics will influence the optimal treatment choice. The risk status must be determined based on established criteria. Twenty percent of participants have aggressive relapse according to IMWG criteria, based on unfavorable cytogenetics [del17p, t(4;14), add1q/del1p, t (14;16) and others, high-risk gene expression profile, high b-2-M] or low albumin, high-serum lactate dehydrogenase (Sonneveld 2017).

M3258 is a novel, orally-administered highly selective first in class inhibitor of the immunoproteasome subunit LMP7 that is being developed for the treatment of participants with RRMM.

The combination of M3258 with dexamethasone is expected to deliver increased efficacy with similar safety as compared to M3258 monotherapy. This is based on the precedent of clinical experience with pan-proteasome inhibitors in combination with dexamethasone.

Complete information on M3258 is in the Investigator's Brochure (IB).

2.1 Study Rationale

M3258 is an oral, potent and selective covalent-reversible inhibitor of the chymotrypsin-like activity of LMP7 (β5i, PSMB8) subunit of the immunoproteasome, which has the potential to deliver a therapeutic benefit to patients with RRMM.

M3258 demonstrated potent and selective inhibition of LMP7 in human MM cell lines as well as in peripheral blood mononuclear cell (PBMCs) from various species including human. In contrast to the pan-proteasome inhibitors bortezomib, carfilzomib and ixazomib which indiscriminately inhibit multiple proteolytic subunits of the immunoproteasome and constitutive proteasome, M3258 demonstrated more than 500-fold biochemical selectivity for LMP7 versus the β5c proteolytic subunit of the constitutive proteasome.

M3258 demonstrated strong antitumor activities, up to complete regressions, in nonclinical multiple myeloma models. Optimal efficacy was observed upon QD oral dosing of M3258, a schedule associated with sustained suppression of LMP7 activity in tumor cells and peripheral blood mononuclear cells. M3258 also demonstrated superior in vivo efficacy compared to the approved pan-proteasome inhibitors in different nonclinical models including cytogenetic high-risk models, suggesting the potential for M3258 to deliver an efficacy benefit to patients with MM who do not display an optimal response to these approved therapeutic agents.

LMP7 activity as Pd readout has been demonstrated in several nonclinical species and tissues. Nonclinical data from pharmacology, PK and toxicology studies suggest an acceptable safety profile and window of M3258 in humans. Clinical experience with pan-proteasome inhibitors

suggests no overlapping safety adverse events (AEs) in combination with dexamethasone and immunomodulatory imide drugs (IMiDs) and encouraging clinical antitumor activity in participants with MM.

2.2 Background

Treatment of newly diagnosed and relapsed myeloma has been a rapidly moving field because of an improved understanding of disease biology and access to new drugs (Kumar et al, 2018, Lonial et al, 2015). Prior combination attempts showed that combining multiple cytotoxic drugs would not improve therapy especially when combinations of alkylators with steroids were involved, which instead led to a more pronounced toxicity profile (Oken, 1997).

When the "novel" IMiDs and proteasome inhibitors (PIs) were brought to the field a decade ago, they subsequently demonstrated greater efficacy and were deemed safer in combinations, leading to a push to combine agents for newly diagnosed patients. This much-needed change is now extending to the relapse setting as well. Recent Phase III studies have suggested that combinations of these new agents with each other, or with alkylator based therapy, resulted in greater responses and prolonged duration of remission and OS (Cavo et al, 2011; Sonneveld et al, 2012; Stewart et al, 2015; Lonial et al, 2015). The ubiquitin-proteasome pathway is responsible for degradation of ubiquitinated proteins in eukaryotic cells, including proteins that control cell-cycle progression, apoptosis, and DNA repair and therefore, plays an essential role in maintaining normal cellular homeostasis (Micale et al, 2014). The immunoproteasome and constitutive proteasome are multi-subunit cylindrical complexes that process ubiquitinated proteins and generate peptides which can be presented on major histocompatibility complex Class I. In contrast to the constitutive proteasome, which is broadly expressed, the immunoproteasome is specifically present in normal hematopoietic cells and hematopoietic cancers such as MM. In normal and cancerous cells of nonhematopoietic origin, expression of the immunoproteasome is typically low, but can be induced by inflammatory conditions such as exposure to interferon gamma (Hallermalm et al, 2001).

Pan-proteasome inhibitors such as bortezomib, carfilzomib and ixazomib indiscriminately inhibit the proteolytic activities of multiple subunits of the immunoproteasome and constitutive proteasome (reviewed in Ettari et al, 2018). These agents are approved for use in patients with MM either as monotherapy or in combination with other agents such as IMiDs (e.g., lenalidomide) and the corticosteroid dexamethasone (reviewed in Brayer et al, 2017). Experimental data has indicated that pan-proteasome inhibitors elicit diverse effect on MM cells, which may potentially underpin their therapeutic efficacy (reviewed in Kubiczkova et al, 2014 and McBride et al, 2013). However, the lack of selectivity of these agents, in particular the inhibition of the constitutive proteasome in diverse tissues, is assumed to drive their adverse safety profiles, with common side effects such as peripheral neuropathy, cardiac disorders, gastrointestinal disturbances, fatigue and thrombocytopenia (reviewed in Ettari et al, 2018 and Cengiz Seval et al, 2018). Selective inhibition of the immunoproteasome may potentially maintain antitumor efficacy in MM, while circumventing the severe toxicities associated with pan-proteasome inhibitors (reviewed in Ettari et al, 2018 and Miller et al, 2014).

M3258 is an oral, potent, selective, covalent-reversible inhibitor of the chymotrypsin-like proteolytic activity of LMP7 (β5i, PSMB8) subunit of the immunoproteasome. M3258 displays potent antitumor efficacy, up to complete tumor regression, in nonclinical models of MM, including models harboring the t(4;14)-translocation; a high-risk biomarker commonly

detected in patients with MM displaying poor prognosis and shorter time to progression (reviewed in Bustoros et al, 2017 and Sonneveld, 2017). Furthermore, M3258 demonstrates an improved therapeutic index compared to bortezomib, carfilzomib and ixazomib based on nonclinical animal safety studies. Finally, M3258 is orally bioavailable in animals and demonstrated a drug-drug interaction profile potentially compatible with combination with other agents such as dexamethasone.

CCI [redacted]

Nonclinical studies in different species have confirmed that oral administration of M3258 results in inhibition of LMP7 activity in normal and in tumor tissue. An LMP7 activity assay as Pd readout in human PBMCs is currently validated for clinical use.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

CCI

In the absence of clinical experience with M3258, all study participants will be monitored for any potential occurrence of a SAE irrespective to its attributability to study intervention. When necessary, M3258 administration should be discontinued and appropriate medical interventions initiated in accordance to local medical standards.

CCI

CCI To better understand and characterize the relevant toxicities, in addition to ensuring safety of clinical study participants, AEs such as GI hemorrhage, GI mucositis (diarrhea, vomiting),

opportunistic infections and allergic reactions/hypersensitivity will be considered adverse events of special interest (AESI) and a guidance, in line with standard medical practices, to manage such toxicities are provided in Sections 6.9 and 6.9.1.

During clinical study, a SMC will provide recommendations on dose and regimens during dose escalation based on review of study participant's available data (clinical and PK) in consideration of an anticipated steep dose-response toxicity as well as the potential toxicity due to accumulation over time.

Combination of M3258 with Dexamethasone

Pan-proteasome inhibitors such as bortezomib, carfilzomib and ixazomib are approved in various countries for use in patients with MM in combination with other agents such as the corticosteroid dexamethasone. A detailed retrospective analysis of safety and efficacy signals from multiple second-line clinical studies in participants with MM using either bortezomib or the combination of bortezomib with dexamethasone was published (Dimopoulos et al, 2015). This analysis concluded that the combination of bortezomib with dexamethasone delivered a greater efficacy versus bortezomib monotherapy, exemplified by higher overall response rate (ORR) (75% vs. 41%; odds ratio = 3.467; $P < 0.001$) and longer median time-to-progression (13.6 vs. 7.0 months; hazard ratio [HR] = 0.394; P = 0.003) and PFS (11.9 vs. 6.4 months; HR = 0.595; P = 0.051). Furthermore, the rates of any-grade AEs, most common Grade 3 or higher AEs, and discontinuations due to AEs were comparable in participants receiving bortezomib with dexamethasone compared to bortezomib monotherapy. These findings were broadly supported by a second publication (Harrison et al, 2015).

Based upon available nonclinical data from M3258 and known class effects from approved pan-proteasome inhibitors, the measures for safety reporting, safety monitoring, and risk mitigative activities for this proposed FiH study are considered adequate.

Further, dexamethasone at a cumulative dose of 40mg/week will be administered in the established low-dose regimen in the expansion part of the study, as is used in standard of care in combination with the oral pan-proteasome inhibitor ixazomib.

3 Objectives and Endpoints

Table 7 Study Objectives and Endpoints - Dose Escalation- Part A

Objectives	Endpoints (Outcome Measures)
Primary	
• To determine safety, tolerability and the MTD (if observed) of M3258 as a single agent in participants with RRMM	• Occurrence of DLTs in participants with RRMM receiving M3258 as a single agent during the DLT period • Occurrence of any AEs reported (serious or nonserious) will be considered TEAEs and TRAEs (including TEAEs leading to death or discontinuation of treatment) in participants receiving M3258 as a single agent from start of study intervention to 30 days after End of Study Intervention • Occurrence of TEAEs outside of the DLT period that SMC deems relevant for determination of the MTD • Study treatment-emergent changes in clinical laboratory measures from Baseline, safety ECGs measures, vital signs, ECOG performance status in participants receiving M3258 as a single agent from start of study intervention to 30 days after end of study intervention
Secondary	
• To investigate the PK profile of M3258 (single and multiple dose exposure) in participants with RRMM	• PK profile of M3258 in terms of C_{max}, AUC_{0-t}, AUC_{0-24} at Day 1, Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, 6, 8 and 24 h after administration • PK profile of M3258 in terms of C_{max}, AUC_{0-24} at Day 8 Cycle 1, (multiple dose): predose, 1, 2, 3, 4, 5, 6, and 8 h after administration
• To investigate the recommended dose and regimen for expansion (RDE) in participants with RRMM	• In addition to safety, tolerability and PK, for selection of recommended dose and regimen for expansion (RDE), changes in Pd (LMP7 activity) in pre and post study intervention samples on Day 1 Cycle 1 pre and postdose, Day 2 Cycle 1 predose and Day 8 Cycle 1 pre and postdose

Objectives	Endpoints (Outcome Measures)
	• Changes from Baseline in serum M-protein, urine M-protein, or free light chain protein levels (for free light chain disease) on Day 1 of every cycle
• To evaluate preliminary clinical activity using IMWG criteria	• OR, DOR, Time to Response until CR, sCR, VGPR or PR according to IMWG
Exploratory	
• To investigate the changes in the Pd marker of M3258 as a single agent in participants with RRMM	• Changes in Pd (LMP7 activity) in pre and post study intervention samples on Day 1 Cycle 1 pre and postdose, Day 2 Cycle 1 predose and Day 8 Cycle 1 pre and postdose
• To investigate further PK parameters of M3258 (single and multiple dose exposure) in participants with RRMM	• PK profile of M3258 in terms of t_{max}, t_{lag}, $t_{1/2}$, CL/F, V_z/F at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, 6, 8 and 24 h after administration • PK profile of M3258 in terms of $AUC_{0\rightarrow\infty}$ (if calculable), t_{max}, t_{lag}, $t_{1/2}$, CL_{ss}/F, at Day 8 Cycle 1, (multiple dose): predose, 1, 2, 3, 4, 5, 6 and 8 h after administration • PK profile of M3258 in terms of C_{trough} at Days 8 and 15 (QD regimen only) Cycle 1: predose • PK profile of M3258 in terms of $R_{acc\ (AUC)}$ and $R_{acc\ (Cmax)}$ after Day 1 (single dose) and Day 8 (multiple dose), Cycle 1 and dose-normalized C_{max}, AUC_{0-t}, AUC_{0-24} for single and multiple dose
• To investigate the relationship between exposure of M3258 as a single agent and QTc in participants with RRMM	• Relative changes from Baseline in ECG parameter QTc in relation to M3258 plasma concentration: all times after single and multiple dosing with concurrent QTc and plasma concentration assessments
• To investigate genetic variations that may affect PK of M3258 as a single agent	• Assessment of genetic variations that affect drug metabolism and drug transport of M3258 and other potential genes that may account for differences in the PK profile

Objectives	Endpoints (Outcome Measures)
• To explore potential metabolites of M3258 in plasma in participants with RRMM	• Assessment of potential metabolites of M3258 in plasma
• To explore L-citrulline as an exploratory biomarker	• Changes in the L-citrulline blood levels during the study at Day 1 and Day 15 predose, Cycle 1, and Day 1 predose, Cycle 2 and Cycle 3
• To investigate relationship of drug treatment and Minimal Residual Disease (MRD) in participants with RRMM	• Assessment of MRD upon CR or sCR

Table 8 Study Objectives and Endpoints - Dose Expansion - Part B

Objectives	Endpoints
Primary	
• To determine safety and tolerability of M3258 at the recommended dose and regimen for expansion (RDE) when co-administered with dexamethasone in participants with RRMM	• Occurrence of dose-limiting toxicities (DLTs) in participants receiving M3258 in combination with dexamethasone during the DLT period • Occurrence of study treatment-emergent SAEs including deaths from first dose of study intervention to 30 days after end of study intervention • Occurrence of TEAEs and TRAEs (including deaths) from start of study intervention up to 30 days after end of study intervention • Study treatment-emergent clinically relevant abnormal changes in clinical laboratory measures from Baseline, ECGs measures, vital signs, ECOG performance status from start of study intervention to 30 days after end of study intervention
• To determine recommended Phase II dose of M3258 when co-administered with dexamethasone in participants with RRMM based on early signs of safety and efficacy in the expansion phase	• Occurrence of TEAEs and TRAEs (including deaths) in participants receiving M3258 when given in combination with dexamethasone from start of study intervention to 30 days after end of study intervention

Objectives	Endpoints
	• OR, DOR. Time to Response until CR, sCR, VGPR, or PR according to IMWG
Secondary	
• To collect preliminary efficacy data in participants with RRMM under treatment with M3258, when co-administered with dexamethasone	• OR, DOR. Time to Response until CR, sCR, VGPR, or PR according to IMWG • Progression-Free Survival (PFS) per Investigator • Overall Survival (OS) censored at End of Study
• To investigate the PK profile of M3258 (single and multiple dose exposure) when co-administered with dexamethasone in participants with RRMM	• PK profile of M3258 in terms of C_{max}, AUC_{0-t}, AUC_{0-24} at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, and 6 and 24h after administration • PK profile of M3258 in terms of C_{max}, AUC_{0-24} at Day 8 Cycle 1, (multiple dose): predose, 2, 4, and 6h after administration
Exploratory	
• To investigate the changes in the pharmacodynamic marker of M3258 when co-administered with dexamethasone in participants with RRMM	• Changes in LMP7 activity on Day 1 Cycle 1 pre and postdose and Day 8 Cycle 1 pre and postdose
• To investigate further PK parameters of M3258 (single and multiple dose exposure) when co-administered with dexamethasone in participants with RRMM	• PK profile of M3258 in terms of t_{max}, t_{lag}, $t_{1/2}$, CL/F, V_z/F at Day 1 Cycle 1, (single dose): predose, 1, 2, 3, 4, 5, 6 and 24h after administration • PK profile of M3258 in terms of $AUC_{0\rightarrow\infty}$, t_{max}, t_{lag}, $t_{1/2}$, CL_{ss}/F, at Day 8 Cycle 1, (multiple dose): predose, 2, 4, and 6 h after administration • PK profile of M3258 in terms of dose-normalized C_{max}, AUC_{0-t}, AUC_{0-24} for single and multiple dose
• To investigate the food effect on the PK of M3258 when co-administered with dexamethasone in participants with RRMM	• Area under the plasma concentration-time curve (AUC_{0-8h}) with and without food from time zero (= dosing time) to 8 h and C_{max} of M3258 observed on Day 1 Cycle 2: predose, 1, 2, 3, 4, 5, 6 and 8 h postdose

Objectives	Endpoints
• To investigate the relationship between exposure with M3258 and QTc, when co-administered with dexamethasone in participants with RRMM	• Relative changes from Baseline in ECG parameters (QTc) in relation to M3258 plasma concentration: all times after single and multiple dosing with concurrent QTc and plasma concentration assessments
• To investigate genetic variations that may affect PK of M3258, when co-administered with dexamethasone in participants with RRMM	• Assessment of genetic variations that affect drug metabolism and drug transport of M3258 and other potential genes that may account for differences in the PK profile
• To explore potential metabolites of M3258 in plasma, when co-administered with dexamethasone in participants with RRMM	• Assessment of potential metabolites of M3258
• To investigate the PK profile of dexamethasone when co-administered with M3258 in participants with RRMM	• Area under the plasma concentration-time curve ($AUC_{0\text{-}8h}$) from time zero (= dosing time) to 8 h and C_{max} of dexamethasone observed on Day 1, Cycle 2: predose, 1, 2, 3, 4, and 6 h postdose
• To explore L-citrulline as an exploratory biomarker	• Changes in the L-citrulline blood levels during the study at Day 1 and Day 15 predose, Cycle 1, and Day 1 predose, Cycle 2 and Cycle 3
• To investigate change β5c activity after M3258, when co-administered with dexamethasone in participants with RRMM	• Changes in β5c activity on Day 1 Cycle 1 pre and postdose and Day 8 Cycle 1 pre and postdose
• To investigate relationship of drug treatment and MRD, when M3258 is co-administered with dexamethasone in participants with RRMM	• Assessment of MRD upon CR or sCR

4 Study Design

4.1 Overall Design

This is a Phase I, open-label, FiH, 2-part (dose escalation and expansion), noncontrolled, multicenter clinical study designed to determine the safety, tolerability, PK, Pd and early signs of efficacy of M3258 as a single agent and co-administered with dexamethasone in participants with RRMM whose disease has progressed following > 3 prior lines of therapy and for whom no effective standard therapy exists (Figure 1).

The dose escalation phase is aimed at determining the recommended dose and regimen for the expansion phase (RDE) and the MTD based on safety, tolerability, PK, Pd (including LPM7 activity) and initial efficacy data of M3258 as a single agent. Following the dose-escalation phase, the safety and tolerability of M3258 with dexamethasone will be investigated in an expansion cohort of approximately 30 participants in addition to assessment of early clinical activity. If the dose is modified during the expansion phase, this sample size will increase by approximately 3-21 participants.

Each phase of the study will include a Screening period of up to 28 days, a study intervention period consisting of 21- or 28-day cycles of either M3258 alone (Part A) or M3258 in combination with dexamethasone (Part B), an End of Study Intervention visit (within 7 ± 3 days), and a Safety Follow-Up period of 30 (± 7) days. In Part B, participants will be followed up until 6 months after the last-participant-last-study-intervention intake. Participants who tolerate M3258 ± combination with dexamethasone without significant clinically relevant toxicities may continue to receive their assigned dose if there is no evidence of confirmed disease progression (Section 4.4). Participants who discontinue study intervention for any reason will complete the End of Study Intervention and Safety Follow-Up visits.

Screening Period

Screening will be performed within 28 days prior to Day 1 of M3258 administration. The Screening period should start before the SMC decision to enroll participants to the next study intervention cohort. Treatment of the participants screened for future dosing cohorts will only start after the SMC decision to proceed to the next dosing cohort. If there are no clinically significant findings at Screening and the participant meets all the protocol-defined inclusion criteria and none of the exclusion criteria, the participant will be considered as eligible and will be enrolled into the study. Participants who fail to meet the protocol-specified criteria or who withdraw their consent will be considered Screening Failures.

Treatment Period

During dose escalation (Part A), M3258 will be administered QD as a single agent in 28-day cycles. In the expansion cohort (Part B), M3258 will be administered in combination with dexamethasone at a cumulative dose of 40mg/week. The treatment period will begin at the first dose of M3258 in Day 1 Cycle 1. Participants who tolerate M3258 without significant clinically relevant toxicities may continue to receive their assigned dose if there is no evidence of disease progression.

If QD treatment is not tolerated at a dose level showing efficacy and/or Pd marker signals, the following options will be considered by the SMC based on available data:

- QD dosing at doses below the non-tolerated dose (down to 1mg) in 28-day cycles (based on SMC recommendation)

OR

- Twice-per-week dosing on Days 1, 4, 8, 11, 15, 18, 22 and 25 in 28-day cycles

In addition, if a consistent reduction in platelet counts to thrombocytopenia ≥ Grade 3 is observed during a 28-day dosing regimen without recovery to baseline or ≤ Grade 2 by the end of the cycle, the SMC can consider a drug holiday of at least 7 days in the proposed regimen below. Similar to pan-proteasome inhibitors, a transient effect on megakaryocyte function, possibly related to platelet budding needs to be considered rather than a megakaryocyte cytotoxicity (Lonial et al, 2005). A predicted time for recovery of platelet counts from nadir to baseline values has been described to be around 7 days (Lonial et al, 2005). Thus, a drug holiday (intermittent) of at least 7 to 10 days is included in the proposed regimen below which consequently changes the cycle length to 21 days.

- QD dosing on Days 1 to 14, no dosing on Days 15 to 21, in 21-day cycles

OR

- Twice-per-week dosing on Days 1, 4, 8, and 11, no dosing on Days 12 to 21, in 21-day cycles

If a switch in dose and/or regimen is recommended, the first tested dose level in the new regimen must not exceed the highest tested daily dose or the weekly cumulative dose must be equal to or lower than the highest weekly cumulative dose of regimen(s) tested so far.

The selected M3258 dose and regimen (RDE) will be combined with dexamethasone for the expansion cohort (Part B).

Dexamethasone will be given at a cumulative dose of 40 mg/week:

- 20 mg/day at Days 1, 4, 8, 11, 15, 18, 22 and 25 in a **28-day cycle**

OR

- 20 mg/day at Days 1, 4, 8, 11, 15, and 18 in a **21-day cycle** (regimen with drug holiday)

Dose Escalation Part A

Participants with MM whose disease has progressed following > 3 lines of therapy and for whom no effective standard therapy exists (see definition in Section 5) will be enrolled in the dose-escalation part of this study. The first dose escalation cohort will receive M3258 at the starting dose of 10 mg QD as a single agent. For further dose cohorts, a SMC will meet and review all available data to provide recommendations on the next dose level. The MTD is defined by the SMC with a target DLT rate of 25%. The following prespecified doses of 10

mg, 20 mg (100% increase), 35 mg (43% increase) and 50 mg (30% increase) are planned unless MTD is reached. The SMC, following review of preliminary safety, tolerability, PK and Pd information, will recommend the dose and/or the switch to an alternative regimen pre-specified in this protocol for the next cohort as applicable.

This may include proposing smaller dose increases compared to the prespecified doses and deescalation of the dose potentially down to 1mg.

The SMC may also recommend expanding a given cohort at the same dose level.

If additional dose levels above 50 mg are justified following review of preliminary safety, tolerability, PK, and Pd information from the initial cohorts, a protocol amendment will be submitted.

Depending on the observed toxicity profile, the SMC may decide on different doses as prespecified and/or change to regimens specified in this protocol. However, escalation may not proceed to any dose higher than 50 mg. In case escalation is recommended to proceed to doses higher than 50 mg, an amendment will be submitted. At each dose level, the first participant enrolled will be observed for DLTs for at least 48 hours before further participants are enrolled.

The SMC will recommend a dose and regimen for the expansion cohort based on an integrated review on all available safety, tolerability, PK, Pd (including LMP7 activity) and initial efficacy data.

Residual LMP7 activity reaching a plateau comparing at least 3 increasing dose levels will support the RDE selection.

At least 6 participants need to be treated at the selected RDE as M3258 monotherapy. Additionally, the median estimated DLT rate of the RDE needs to be ≤25% and the 75% percentile of the estimated DLT probability of the RDE needs to be below 30%.

If further data is required to determine the RDE, additional participants may be enrolled in Part A (see Section 9.2).

Dose Expansion Part B

Once an RDE (dose and regimen) of M3258 has been defined which is considered safe by the SMC, dose expansion (Part B) may begin. Initiation of Part B may start without reaching the MTD in Part A; dose escalation for defining the monotherapy MTD (Part A) may proceed in parallel.

Participants with MM whose disease has progressed following > 3 lines of therapy for whom no effective standard therapy exists (see definition in Section 5) will be enrolled. In Part B, participants will receive M3258 at the RDE selected in Part A in combination with dexamethasone at a cumulative dose of 40 mg / week. The first 2 cohorts of 3 participants each (first 6 participants) will be used for a safety run-in. The participants in these 2 cohorts will be enrolled in a staggered approach. Each cohort of the safety run-in will be evaluated by the SMC for the prespecified DLT criteria (see Section 6.6) of this combination before additional participants are enrolled. The SMC meetings will be held after the first 3 and 6 participants have finished Cycle 1 or discontinued treatment. The SMC will evaluate safety, cumulative

and unacceptable toxicity (see definition of acceptable toxicity below). SMC decisions on potential dose adjustments in the safety run-in (and later on) will be supported by Bayesian modeling. After the safety run-in, SMC meetings will be held at the completion of Cycle 1 or discontinuation of treatment for every 6 participants (without pausing enrollment) in order to assess safety, cumulative and unacceptable toxicity of all participants in the expansion cohort, unless a change in dosing has occurred. In case dosing in the expansion cohort was changed, the next SMC will be held after 3 participants have finished the DLT period or discontinued.

The dose-expansion phase of this study is designed to obtain additional safety, tolerability, PK, Pd and preliminary clinical activity data of M3258 in combination with dexamethasone.

The SMC decisions in the expansion phase will also be supported by Bayesian modeling. If data obtained during the safety run-in of Part B indicate that a higher dose than the RDE may be tolerated when M3258 is administered in combination with dexamethasone, then a careful escalation beyond the monotherapy RDE in combination with dexamethasone can be recommended in dosing steps of maximum 25% increases in Part B. SMC will review all available data to provide recommendations on the next dose level.

Unacceptable toxicity in the expansion cohort is defined as AEs that meet the DLT criteria (as defined in Section 6.6) regardless of when they occur during treatment; stopping rules for unacceptable toxicity for participants treated at the same dose are detailed in Section 7.1.

If at any time in the expansion cohort, the number of unacceptable toxicity events indicate that there is a risk of safety to the participants (i.e., if defined boundaries are met, see Section 7.1), accrual to the cohort will be paused and the SMC will meet to review the data, also considering feedback from investigators, to determine if further enrollment should be halted. In this case, the SMC will decide whether participants who are still on treatment and are tolerating the treatment should continue treatment or whether treatment should be reduced or withdrawn. The Health Authorities (HA) will be notified of the SMC decision.

If a situation of unacceptable toxicity occurs that does not meet the defined boundaries for stopping criteria (as outlined in Section 7.1), the SMC will decide whether the dose for newly enrolled participants should be lowered (including to what dose). In case dosing is de-escalated for toxicity in the expansion cohort, only 3 participants will be treated initially with the new dose; enrollment of additional participants will pause until the SMC has evaluated the safety of this cohort. Expansion cohort SMC meetings will also be supported by the results of a Bayesian logistic 2 parameter regression model.

When 15 participants treated at the same dose are evaluable for response (as defined in Section 8.1), according to IMWG, an interim analysis will be performed. At that time the following decision will be made:

i) Continuation on the same dose until additional 15 participants are treated at the same dose and are evaluable for response according to IMWG,

ii) Stop for futility, or

iii) Change the dose of M3258 and enroll participants at the new dose until 15 participants treated at the new dose are evaluable for response according to IMWG. Subsequently a new interim analysis will be performed.

For any other option, a protocol amendment will be submitted. Additionally, the enrollment of participants for investigating the food effect will be evaluated at the interim analysis and decision taken whether enrollment of additional participants is required.

Additional details on the interim analysis can be found in Section 9.4.1.

Food effect

Day 1 Cycle 2 will be an evaluation of the effect of food on PK. If the health of the participant allows, the participant will be allocated to a treatment cohort (administration of M3258 in combination with dexamethasone with or without food at Day 1 Cycle 2, also see Section 5.3.1).

4.2 Scientific Rationale for Study Design

The purpose of this Phase I two-part [dose-escalation for M3258 as a single agent and dose-expansion in combination treatment] study is to establish a safe and tolerable dose of M3258 as a single agent and in combination with dexamethasone and to investigate PK, Pd and the first clinical efficacy signals of M3258 when given in combination with dexamethasone in participants with RRMM. Dose escalation will be followed by a dose expansion once the RDE has been defined.

Rationale for the Combination of M3258 with Dexamethasone

Pan-proteasome inhibitors such as bortezomib, carfilzomib and ixazomib are approved in various countries for use in patients with MM in combination with other agents such as the corticosteroid dexamethasone. A detailed retrospective analysis of safety and efficacy signals from multiple second-line clinical studies in participants with MM using either bortezomib or the combination of bortezomib with dexamethasone was published (Dimopoulos et al, 2015). This analysis concluded that the combination of bortezomib with dexamethasone delivered a greater efficacy versus bortezomib monotherapy, exemplified by higher ORR (75% vs. 41%; odds ratio = 3.467; $P < 0.001$) and longer median time-to-progression (13.6 vs. 7.0 months; HR = 0.394; P = 0.003) and PFS (11.9 vs. 6.4 months; HR = 0.595; P = 0.051). Furthermore, the rates of any-grade AEs, most common Grade 3 or higher AEs, and discontinuations due to AEs were comparable in participants receiving bortezomib with dexamethasone compared to bortezomib monotherapy. These findings were broadly supported by a second publication (Harrison et al, 2015).

M3258, a selective inhibitor of the LMP7 subunit of the immunoproteasome, has a related molecular mechanism of action to the approved pan-proteasome inhibitors bortezomib, carfilzomib and ixazomib. Based on the precedent of clinical experience with pan-proteasome inhibitors in combination with dexamethasone, the combination of M3258 with dexamethasone may potentially deliver increased efficacy and comparable and acceptable safety compared to M3258 monotherapy.

Rationale for Study Population

Participants with MM may have a benefit from a selective drug targeting the immune proteasome function (refer to Section 2.2). The dose escalation will be open to participants with RRMM whose disease has progressed following > 3 prior lines of therapy for MM

including a PI, an IMiD and an anti-CD38 mAb or who are refractory to at least a PI agent (carfilzomib or bortezomib) and IMiD according to the IMWG criteria and for whom no effective standard therapy exists (Kumar et al, 2016). Maintenance is not considered to be a separate line of therapy.

M3258 will be investigated as a single agent in the dose-escalation phase of this study (Part A) and in combination with dexamethasone in the expansion cohort (Part B). Participants in both parts of the study will include participants with MM whose disease has progressed following > 3 prior lines of therapy for MM including a PI, an IMiD and an anti-CD38 mAb or who are refractory to at least a PI agent (carfilzomib or bortezomib) and IMiD according to the IMWG criteria and for whom no effective standard therapy exists (Kumar et al, 2016). Maintenance is not considered to be a separate line of therapy.

Details of the study population are further described in Sections 5.1 and 5.2.

4.3 Justification for Dose

The starting dose for this FiH study of M3258 in participants with advanced disease and limited therapeutic options was determined based on the following approaches:

- CCI [redacted]
- Considering PK/Pd modeling of the predicted pharmacological active dose range in humans.

The ICH S9 has been considered for the determination of the FiH starting dose, i.e., a dose that is expected to have pharmacologic effects and is reasonably safe to use.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the study intervention as defined by the protocol, unless having withdrawn consent, for which the details can be found in the scheduled procedure shown in the Schedule of Activities (SoA).

The End of Study is defined as the date of the last visit of the last participant in the study globally according to the last scheduled procedure shown in the SoA.

Part A of the study will end after all participants have passed the Safety Follow-Up visit or have died or withdrawn consent or study participation, whichever occurs earlier.

Part B of the study will end 6 months after all participants meet at least one of the following criteria:

- Permanently discontinued study intervention
- Died
- Missed at least two consecutive tumor assessments after Baseline
- Withdrawal of consent or withdrawal of study participation
- Start of another anticancer therapy.

The study or either part of it may be stopped upon the Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons or if the Sponsor stops development of M3258 in the population covered by this protocol. The Sponsor may also decide to stop the study if supported by the results of the interim analysis in Part B. For safety stopping rules, see Section 7.1.

5 Study Population

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants who are appropriate for the study, thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Selection of the participant population is based on the expectation that M3258 is well differentiated from pan-proteasome inhibitors, implying that the drug would be efficacious in participants who are refractory to or are progressing under treatment with pan-proteasome inhibitors. M3258 demonstrated superior in vivo efficacy compared to the approved pan-proteasome inhibitors in different nonclinical models including cytogenetic high-risk models, supporting a FiH study in participants with RRMM.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2.

Participants must have documented MM diagnosis as defined by the criteria below:

- Monoclonal plasma cells in the bone marrow ≥ 10% or presence of a biopsy-proven plasmacytoma.
- Measurable disease which can be followed in the blood and urine as defined by any of the following:
- Serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours;

  or
- IgA MM: serum M-protein level ≥ 0.5 g/dL or urine M-protein level ≥ 200 mg/24 hours;

  or
- Light chain MM: Serum immunoglobulin free light chain > 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

Participants must have documented evidence of clinical relapse or progressive disease (PD) on or after their last treatment regimen as defined by the IMWG criteria (Table 16).

Part A

- Participant must have received > 3 prior lines of therapy for MM including a PI, an IMiD and an anti-CD38 mAb and have disease progression during or within 60 days of completing of the most recent regimen or who are refractory to an IMiD and / or a PI agent according to the IMWG criteria and for whom no effective standard therapy exists or who do not tolerate any of the standard treatment. Maintenance is not considered to be a separate line of therapy.
- Participant must have documented evidence or progressive disease as defined by the IMWG criteria either on or after their last regimen (Table 16).
- Participant must have measurable disease as mentioned above.

Part B

- Participant must have received > 3 prior lines of therapy for MM including a PI, an IMiD and an anti-CD38 mAb and have disease progression during or within 60 days of completing of the most recent regimen or who are refractory to an IMiD and / or a PI agent according to the IMWG criteria and for whom no effective standard therapy exists or who do not tolerate any of the standard treatment. Maintenance is not considered to be a separate line of therapy.

- Participant must have documented evidence of progressive disease as defined by the IMWG criteria either on or after their last regimen (Table 16).
- Participant must have measurable disease of MM as mentioned above.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if the above criteria for study population are met at Screening and confirmed at Day 1 Cycle 1 and all the following criteria apply:

Informed Consent

1. Can give signed informed consent, as indicated in Appendix 2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

Part A and B

Age

2. Are participants ≥ 18 years of age, at the time of signing the informed consent.

Weight

No criterion for weight.

Sex

3. Are male or female.

Type of Participant and Disease Characteristics

4. ECOG Performance Status ≤ 1
5. Adequate hematologic function as indicated:
   a. Platelet count ≥ 75,000/mm^3

   Note: Transfusion or use of growth-factors permitted until 5 days before first dose of study intervention

   b. Hemoglobin ≥ 8.0 g/dL
   Note: Transfusions are permitted until 1 week before first dose of study intervention. At Day 1 Cycle 1 the hemoglobin level should meet inclusion criterion without transfusion > 7 days wash-out window.

   c. Absolute neutrophil count (ANC) ≥ 1000/µL
   Note: Use of growth-factors permitted until 5 days before first dose of study intervention.
6. Adequate hepatic function defined: by a total bilirubin level ≤ 1.5 × upper limit of normal (ULN), an aspartate aminotransferase (AST) level ≤ 3.0 × ULN, and an alanine aminotransferase (ALT) level ≤ 3.0 × ULN

- For documented Gilbert's Syndrome a total bilirubin < 3 x ULN is accepted.

7. Creatinine clearance must be ≥ 30 mL/min by calculation using the Cockcroft-Gault formula:

CLcr in mL/min is estimated from a spot serum creatinine (mg/dL) determination using the following formula:

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

8. Male participants:

Agree to the following during the study intervention period and for at least 90 days, after the last dose of study intervention:

Refrain from donating sperm

PLUS either

a. Abstain from intercourse with a female

or

b. Use male condoms

- When having sexual intercourse with a woman of child-bearing potential (WOCBP), who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of <1% per year, as described in Appendix 3, since a condom may break or leak.
- When engaging in any activity that allows for exposure to ejaculate.

9. Female Participants:

Are not pregnant or breastfeeding, and at least one of the following conditions applies:

Not a WOCBP

or

If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:

- **Before** the first dose of the study intervention(s), if using hormonal contraception:
- Has **completed** at least one 4-week cycle of an oral contraception pill and either had or has begun her menses

or

Has used a depot contraceptive or extended-cycle oral contraceptive for least at 28 days and has a documented negative serum pregnancy test using a highly sensitive assay.

- During the intervention period
- After the study intervention period for at least 90 days after the last dose of study intervention

Agree not to donate eggs (ova, oocytes) for reproduction during this period.

The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

Have a negative serum/urine pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention.

Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy

10. Willingness and ability to comply with study procedures including bone marrow biopsy at Day 1 Cycle 1 and at time of response (Part A and Part B mandatory)
11. For participants experiencing toxicities resulting from previous therapy (including peripheral neuropathy), the toxicities must be resolved or stabilized to ≤ Grade 1.

Part A

12. Participant must have received > 3 prior lines of therapy for MM including a PI, an IMiD and an anti-CD38 mAb and have disease progression during or within 60 days of completing of the most recent regimen or who are refractory to an IMiD and / or a PI agent according to the IMWG criteria and for whom no effective standard therapy exists or who do not tolerate any of the standard treatment. Maintenance is not considered to be a separate line of therapy.
13. Participant must have documented evidence progressive disease as defined by the IMWG criteria either on or after their last regimen (Table 16).
14. Participants must have measurable disease of MM as defined above.

Part B

15. Participant must have received > 3 prior lines of therapy for MM including a PI, an IMiD and an anti-CD38 mAb and have disease progression during or within 60 days of completing of the most recent regimen or who are refractory to an IMiD and / or a PI agent according to the IMWG criteria and for whom no effective standard therapy exists or who do not tolerate any of the standard treatment. Maintenance is not considered to be a separate line of therapy.
16. Participant must have documented evidence of progressive disease as defined by the IMWG criteria either on or after their last regimen (Table 16).
17. Participants must have measurable disease of MM as defined above.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any condition, including any uncontrolled disease state that in the Investigator's opinion constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.
2. An active second malignancy or evidence of disease of cancer (other than MM) before the date of enrollment (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the Investigator, with concurrence with the Sponsor's Medical Monitor, is considered cured with minimal risk of recurrence within 3 years).
3. Cerebrovascular accident/stroke (< 6 months prior enrollment) or neurologic instability per clinical evaluation due to tumor involvement of the CNS.
4. Diagnosis of fever within 1 week prior to study intervention administration.
5. Uncontrolled concurrent illness (e.g., serious uncontrolled diabetes [blood glucose > 250 mg/dL], or psychiatric illness/social situations that would limit compliance with the study requirements).
6. Active symptomatic fungal, bacterial and/or viral infection. Individuals with known or seropositive testing for human immunodeficiency virus (HIV) or actively infected viral hepatitis (B or C) are excluded. However, individual with Hepatitis C treated with curative therapy are not considered actively infected.
7. Plasma cell leukemia ($> 2.0 \times 10^9$/L circulating plasma cells by standard differential), active CNS MM or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or amyloidosis.
8. Impaired cardiac function
    - Left ventricular ejection fraction < 45% defined by echocardiography (at Screening)
    - Serious arrhythmia
    - Unstable angina pectoris
    - New York Heart Association heart failure Class III and IV
    - Myocardial infarction within the last 12 months prior to study entry
    - Symptomatic pericardial effusion
9. Peripheral neuropathy of Grade ≥ 2 with pain
10. Active graft versus host disease
11. Life expectancy of < 4 months.

12. Current significant cardiac conduction abnormalities, including corrected QT interval (QTc) prolongation of > 450 ms for males and > 470 ms for females must be confirmed on Day 1 Cycle 1.

Prior/Concomitant Therapy

13. Participant who received chemotherapy, extensive radiation therapy (involving ≥ 30% of bone marrow), vertebroplasty, kyphoplasty or biological therapy (e.g., antibodies, erythropoietin) within 2 weeks (6 weeks for nitrosourea, mitomycin-C) or 5 half-lives prior to dosing or who have been treated with small molecule therapeutics or investigational agents within 4 weeks prior to starting study intervention with M3258 or who have not recovered from the side effects of such therapy to Baseline or Grade 1 (except for alopecia or potentially neuropathy).
14. Hormonal therapies acting on the hypothalamic-pituitary-gonadal axis (i.e., luteinizing hormone-releasing hormone agonist/antagonists).
15. Steroid therapy for antineoplastic intent taken < 7 days prior to the first dose of study intervention. Includes participants who have received a cumulative dose of corticosteroid greater than or equal to the equivalence of 140 mg prednisone or a single dose of corticosteroid greater than or equal to the equivalence of 20 mg/day dexamethasone within the 2-week period before first dose of study intervention.
16. Participant currently receiving (or unable to stop using prior to receiving the first dose of study intervention) medications known to be strong inhibitors or inducers of CYP3A or any herbal supplements known to inhibit or induce CYP3A. Comedication and herbal supplements must stop at least 7 days before the first administration of the study intervention (for details see Section 6.5.3).
17. Participant currently receiving (or unable to stop using prior to receiving the first dose of study intervention) medications or herbal supplements known to be inhibitors of P-gp. Comedication must stop at least 7 days before the first administration of the study intervention (for details see Section 6.5.3).
18. Participant currently receiving (or unable to stop using prior to receiving the first dose of study intervention) medications known to prolong the QT/QTc interval. Comedication must stop at least 7 days before the first administration of the study intervention (a list of medication is attached in the Appendix 4: Prohibited Comedication Prolonging the QT/QTc Interval).
19. Participant has received autologous stem cell transplant within 12 weeks before the first dose of study intervention, or the participant has previously received an allogenic stem cell transplant (regardless of timing).

Diagnostic Assessments

Not applicable

Other Exclusions

Part B only:

20. Participants planning to undergo a stem cell transplant should not be enrolled to reduce disease burden prior to transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants will be instructed to refrain from consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges, St. John's wort as well as any other CYP3A inhibiting/inducing or P-gp inhibiting herbal supplements starting at least 7 days before the first administration of the study intervention and during the study intervention administration.

Part A and Part B

Participants will receive study intervention daily with restriction of food for 1 hour before and 2 hours after dose administration except for the food effect evaluation on Part B Day 1 Cycle 2.

Part B Day 1 Cycle 2 – Food Effect Evaluation

Day 1 Cycle 2 will be an evaluation of a possible effect of food on the PK. All participants will be allocated to 1 of 2 treatment schedule cohorts (as long as safety of the participant is not endangered [i.e., diabetic participant]). The first 9 participants in Part B will be allocated to Schedule A (study treatment without food) and subsequent 9 participants will receive Schedule B (study treatment with food), unless there has been a change in dose. At the interim analysis, the need for additional participants for food effect will be determined without affecting the overall number of participants in the study. Then allocation will be alternating ABAB, etc. Upon enrollment, the site will receive the food-schedule assignment for the participant from the medical monitor or a designee.

- **Schedule A**: all participants of this cohort will receive the regular dose and regimen of M3258 without food. They will fast for 10 hours (i.e., no food [except as noted below] from midnight onwards) before administration of study intervention until at least 4 hours after dosing.
- **Schedule B**: all participants of this cohort will receive the regular dose and regimen of M3258 with food. They will receive a regular breakfast; 30 minutes after start of the breakfast all participants will receive a regular dose of M3258. The regular breakfast contains approximately 400-500 kcal with fat contributing to approximately 150 kcal. M3258 will be taken with 200 mL of water. After administration of study intervention, the participants will fast for at least 4 hours.

During the PK sampling, participants will be allowed to drink water as they desire except 1 hour before and after administration of study intervention.

M3258 will be taken with 200 mL of water.

5.3.2 Caffeine, Alcohol, and Tobacco

No restrictions are applicable.

5.3.3 Activity

Participants will abstain from strenuous exercise for 4 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.4 Screen Failures

Individuals in Part A who do not meet the hematological and/or renal criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants will be assigned a new participant number. Rescreening does not apply to participants intended for Part B.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Study Intervention Name:	M3258 PiCs
Dose Formulation:	Powder in Capsules (PiCs)
Unit Dose Strength(s)/ Dosage Level(s):	1 mg, 5 mg, 30 mg
Route of Administration:	Oral
Dosing Instructions:	See Section 6.6 (Dose Selection and Modification).
Supplier/Manufacturer:	The Sponsor will supply the study intervention.
Packaging and Labeling	PiCs will be supplied in CCI packs. Each CCI pack will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

In addition, commercially available dexamethasone to be given at the regimen proposed in Section 4.1 for oral administration will be provided locally by the site as per local available dosage.

6.1.1 Medical Device(s) Use

Not applicable.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any

discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.

- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, kit numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Operations Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Not applicable.

6.3.2 Blinding

Not applicable.

6.3.3 Emergency Unblinding

Not applicable.

6.4 Study Intervention Compliance

In this study, participants will receive study intervention at the investigational site on visit days. Trained medical staff will monitor and/or perform the on-site study intervention administration. Participants will be instructed by the Investigator/designee regarding off-site self-administration of M3258, and compliance checks performed at all study visits. The information of each study intervention administration (date and dose of study intervention) will be recorded in the participant notes and electronic Case Report Form (eCRF). On days preceding PK, sampling time of drug intake will also be recorded. The Investigator will ensure that the information entered into the eCRF regarding drug administration is accurate for each participant. Any reason for noncompliance should be documented. In the situation where participants discontinue study intervention for more than 5 days per cycle, or if ≥ 6 consecutive planned doses of M3258 are missed for reasons other than toxicity unless, upon consultation with the Sponsor and the review of safety and efficacy, continuation is agreed upon (Sections 7.1 and 8.4).

6.5 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (also for potential enzyme inducers) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the study intervention administration, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study (see Section 6.5.2 for permitted medicines; Section 6.5.3 for prohibited medicines) .

Antiviral prophylaxis for Herpes zoster (e.g., acyclovir, valacyclovir) is permitted.

Antiemetic and antidiarrheal medications may be required and will be administered according to institutional guidelines. A minimal oral hydration of 2 liters/day is recommended for participants to prevent dehydration and hyperviscosity.

Paracetamol/acetaminophen, at doses of ≤ 2 grams/24 hours, is permitted for use any time during the study; Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

6.5.1 Rescue Medicine

Not applicable.

6.5.2 Permitted Medicines

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation. All permitted drugs need to be entered in the eCRF.

Standard supportive care for MM such as transfusions, intravenous Ig, pneumonia prophylaxis, flu and pneumonia vaccines are allowed during treatment. However, treatment with transfusions or growth factors (e.g., granulocyte-colony stimulating factor [G-CSF], erythropoietin) is not permitted during the DLT period.

Bisphosphonates should be considered in all participants with myeloma-related bone disease. Intravenous zoledronic acid or pamidronate are the recommended bisphosphonates can be used at the Investigator's discretion. Nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin/acetylsalicylic acid) use is not prohibited; although their use is generally discouraged in the setting of active renal disease.

6.5.3 Prohibited Medicines

Additional dexamethasone with the intention to treat the underlying disease.

Strong CYP3A inhibitors/inducers must stop at least 7 days before the first administration of the study intervention and during the study intervention administration (i.e., clarithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, diltiazem, idelalisib, as well as carbamazepine, enzalutamide, mitotane, phenytoin, rifampin. For further details and update refer to the Food and Drug Administration Drug Development and Drug Interactions website and the Drug Interactions Table™ website.

All herbal supplements known to inhibit or induce CYP3A are prohibited. Participants will be instructed to avoid any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges, St. John's wort as well as any other CYP3A inhibiting or inducing herbal supplements starting at least 7 days before the first administration of the study intervention and during the study intervention administration.

Any P-gp inhibitors (including herbal supplements) must stop at least 7 days before the first administration of the study intervention and during the study intervention administration (i.e., amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil). For further details and update refer to the Food and Drug Administration Drug Development and Drug Interactions website and the Drug Interactions Table™ website.

Medications known to prolong the QT/QTc interval must stop at least 7 days before the first administration of the study intervention and are not allowed during the study intervention administration. A list of medication is attached in the Appendix 4, for further details and update refer to website at www.crediblemeds.org.

6.5.4 Other Interventions

Not applicable.

6.6 Dose Selection and Modification

Dose escalation will proceed according to the SMC recommendation until the 50 mg dose level or the MTD is reached (whichever is lower). For further dose cohorts, a SMC will meet and review all available data to provide recommendations on the next dose level. In case escalation should proceed to doses higher than 50 mg, a protocol amendment will be submitted. Details are described in the SMC charter. The SMC receives outputs of a Bayesian dose-toxicity model estimated DLT probabilities for potential next dose levels. The Bayesian model will be based on prior, observed number of evaluable participants and number of participants with DLT. Further details on the Bayesian model are provided in Section 9.4.2. Further details on the SMC are provided in Section 10.

A DLT is defined as any of the AEs listed below as assessed by the Investigator and/or the Sponsor at any dose and regimen, and judged not to be related to the underlying disease or any previous or concomitant medication or concurrent condition occurring during the DLT observation period (first treatment cycle), according to the NCI-CTCAE v 5.0. Any DLT must be confirmed by the SMC.

During the DLT assessment period: **Treatment with transfusions or growth factors (e.g., G-CSF, erythropoietin) is not permitted. Transfusions are only permitted if clearly related to multiple myeloma.**

Participants who develop a DLT will permanently discontinue treatment.

Participants who did not receive ≥ 80% of the planned cumulative dose or missed more than 20% of doses in the DLT period will not be considered in the DLT analysis set unless they experienced a DLT.

AEs judged as DLT will include:

- Any Grade ≥ 3 **nonhematologic** AE with **exception** of:
  - Single laboratory values out of abnormal range that have no clinical correlate, and resolve to Grade ≤ 1 or to Baseline within 7 days with adequate medical management
  - Grade 3 diarrhea persisting ≤ 72 hours after initiation of medical management
  - Nausea and vomiting of ≤ 72 h duration with adequate and optimal therapy
  - Transient (< 1 week) Grade 3 fatigue, local reactions, flu-like symptoms, for fever, and headache (≤ 72h) that resolves to Grade ≤ 1 with adequate treatment
  - Grade 3 nonrecurrent skin toxicity that resolves to Grade ≤ 1 in less than 7 days after initiation of medical management
  - Asymptomatic Grade ≥ 3 lipase or amylase elevation not associated with clinical manifestations of pancreatitis.
- Hy's law: Evidence of hepatocellular toxicity without clear alternative reason to explain the observed liver-related laboratory abnormalities, such as increase in AST or ALT of ≥ 3 x

ULN elevation and elevation of serum total bilirubin ≥ 2 x ULN, without initial findings of cholestasis (elevated serum ALP) or other apparent clinical causality (eg viral hepatitis A, B, C or co-medication)

- Any death not clearly due to the underlying disease or extraneous causes
- Any Grade ≥ 4 **hematologic AE**, and:
  - Grade ≥ 3 febrile neutropenia with ANC <1000/mm^3 and a single temperature of >38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 h
  - Grade ≥ 3 thrombocytopenia with medically concerning bleeding
  - Grade 4 thrombocytopenia lasting >7 days, or platelets <10,000/mm^3 at any time

  Except:
    - Isolated Grade 4 lymphopenia without clinical correlate
    - Any Grade 4 neutropenia of < 7 days duration not associated with any clinical symptoms.
- Neuropathic Pain or Peripheral Sensory or Motor Neuropathy:
  - Any aggravation by 2 grades or any Grade ≥ 3 (severe symptoms: limiting self-care Activity of Daily Life [ADL]).
- Any TEAE the SMC deems clinically relevant, that impairs daily function or abnormality occurring in participants treated with M3258 -/+ combination with dexamethasone at any time in Cycle 1 and any toxicity at any time in Cycle 1
- A study intervention-related TEAE (observed in subsequent cycles) that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk.

Any DLT will be confirmed by the SMC.

Table 11 describes the recommended individual dose modifications related to M3258-related neuropathic pain or peripheral sensory or motor neuropathy when experienced by participants outside of DLT period. Table 12 describes the individual dose modifications and temporary or permanent treatment discontinuations for M3258-related hematologic toxicities when experienced by participants outside of DLT period. Table 13 describes the individual recommended temporary treatment discontinuations for M3258-related general toxicities when experienced by participants outside of DLT period.

Table 11 Recommended Dose Modification for New Onset or Worsening Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy (outside of DLT Period)

Severity of Peripheral Neuropathy Signs and Symptoms [a]	Modification of Dose and Regimen
Grade 1 (asymptomatic: loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms: limiting instrumental ADL [b])	Reduce M3258 dose by one dose level (based on dose escalation part) or at least by 50% if no lower dose level is available
Grade 2 with pain or Grade 3 (severe symptoms: limiting self-care ADL [c])	Withhold M3258 therapy until toxicity resolves to Baseline or Grade 1 without pain, then reinitiate with a reduced dose of M3258 by one dose level (based on dose escalation part) or at least by 50% if no lower dose level is available If recurrence to Grade 2 with pain or higher, permanently discontinue M3258.
Grade 4 (life-threatening consequences: urgent intervention indicated)	Permanently discontinue M3258.

ADL = Activities of daily living; DLT = Dose-limiting toxicity; NCI = National Cancer Institute.
a Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
b Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.
c Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 12 Dose Modifications and Temporary/Permanent Treatment Discontinuation for Hematologic Toxicity (outside of DLT Period)

Hematologic Toxicity	Dose Modification
Neutropenia Grade 3 (without complications)	No dose reduction, consider treatment with G-CSF
Grade 3 Neutropenia associated with fever (≥ 38.5 °C) or neutropenia Grade 4	Hold M3258 until recovery to Baseline OR ≤ Grade 2. Upon recovery, restart M3258 at current dose and consider G-CSF support. If recurrence is seen, reduce M3258 by one dose level (based on dose escalation part) or at least by 50% if no lower dose level is available. If second occurrence, permanently discontinue dosing
Thrombocytopenia Grade 3 (without complications)	No dose reduction required
Platelet count < 25,000 /µL (i.e., Grade 4) or Grade 3 thrombocytopenia with bleeding	Hold M3258 until recovery to Baseline Or ≤ Grade 2. Upon recovery, restart at a dose which is one dose level lower (based on dose escalation part) or at least by 50% if no lower dose level is available.

DLT = Dose limiting toxicity; G-CSF = granulocyte-colony stimulating factor.

Table 13 Recommended Temporary Treatment Discontinuation for General Toxicity (outside of DLT Period)

Organ involved	Specifics	Toxicity NCI-CTCAE 5.0 Grade	Management of Toxicity with permanent Discontinuation or Dose Interruption and Modification
Renal	Creatinine increased	Grade 3	Hold the M3258 until recovery to Grade ≤ 1 or Baseline. Upon recovery or returning to baseline, dosing may continue at same or lower level based on clinical judgment.
Hepatic	Increased AST /ALT	Grade 3	Isolated occurrence; repeat test within 72 hours; persistent or worsening, may hold off the M3258 until recovery to Grade ≤ 1 or Baseline, based on Investigator's clinical judgement.
	Increased total bilirubin	Grade 2+	Isolated occurrence; repeat test within 72 hours; persistent or worsening, may hold off the M3258 until recovery to Grade ≤ 1 or Baseline, based on Investigator's clinical judgement.
Other nonhematological toxicities	i.e., diarrhea, vomiting; GI hemorrhage	Grade 2+	Withhold M3258 administration until recovery to Grade ≤ 1; or to Baseline. symptomatic treatment in accordance to standard medical practice
	Other	Grade 3+	Hold M3258 based on Investigator's clinical judgement.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; DLT = Dose-limiting toxicity; G-CSF = granulocyte-colony stimulating factor; GI = Gastrointestinal.

Dose reduction of M3258 for safety and tolerability reasons by one dose level (based on dose escalation part) or at least by 50% if no lower dose level is available or decided by SMC is permitted for individual study participant at any time during the study intervention, except for participants in the first cohort. M3258 dose escalation should not be considered for an individual participant once dose modification has been applied for safety or tolerability reasons.

If M3258 dosing were withheld for more than 2 weeks for scheduled dose for any reason, participant should discontinue the study intervention permanently. The study participant should complete End-of-Treatment visit and then should complete the reminder of the study period as Follow-Up period per the SoA (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B).

Dose modification or deferral should always be discussed with the Sponsor Medical Responsible.

Dexamethasone

Dexamethasone may be dose reduced according to Table 14A and Table 14B or institutional guidelines, if applicable, for toxicities assessed as strictly related to dexamethasone. In those cases, where the toxicity cannot be attributed to dexamethasone, the dose of M3258 should be reduced first (see Section 6.9.1).

Dose modification or deferral should always be discussed with the Sponsor Medical Responsible.

Table 14A Recommended Dose Modification (Delays, Reductions and Discontinuations) due to Dexamethasone-related Adverse Events (Outside the DLT Period)

Organ involved	Specifics	Toxicity NCI-CTCAE v5.0 Grade	Management of Toxicity with permanent Discontinuation or Dose Interruption and Modification
Acute pancreatitis			Permanently discontinue dexamethasone.
Gastrointestinal	Dyspepsia, gastric, or duodenal ulcer, Gastritis (requiring medical management)	Grade 1-2	Institute proton pump inhibitor. If symptoms persist or worsen despite measures, reduce dexamethasone by 50% (eg., 20 mg per week to 10 mg per week).
	Requiring hospitalization or surgery	Grade ≥ 3	Hold dexamethasone until symptoms adequately controlled. Restart and reduce dexamethasone by 50% from initial dose along with the use of proton pump inhibitors.
Metabolic	Hyperglycemia	Grade ≥ 2	Diet control and monitor closely.
		Grade ≥ 3	Treat with insulin or oral hypoglycemics as needed. If uncontrolled despite these measures, reduce dexamethasone by 50% from initial dose.
Cardiovascular	Edema (limiting function and unresponsive to therapy or anasarca)	Grade > 2	Diuretics as needed and dose reduction by 50% should be considered. If edema persists despite these measures, consider reducing dexamethasone dose from 10 mg to 5 mg. Monitor closely (weekly weight, restrict hydration).
Musculoskeletal	Muscle weakness (interfering with function and/or interfering with activities of daily living)	Grade > 2	Reduce dexamethasone by 50%. In case of no improvement or worsening, further (50%) dose reduction is recommended. If weakness persists despite these measures, permanently discontinue dexamethasone.
Neurological	Confusion or mood alteration	Grade > 2	Hold dexamethasone until symptoms resolve. Restart and reduce dexamethasone by 50%. Upon worsening or no improvement, consider further reduction of dose to 5 mg. Permanently discontinue dexamethasone if symptoms recur.
Constitutional	Insomnia	Grade ≥ 2	Advise dexamethasone administration in the morning only. If symptoms persist, reduce the dose by 50% (eg., 20 mg to 10 mg to 5 mg).

Modified from Palumbo and Gay, 2009

Table 14B Recommended Dose Reduction for Dexamethasone

First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Reduce dexamethasone by 50% from starting dose	Give dexamethasone only on Day 8, 15, 21	Discontinue dexamethasone

Refer to Palumbo and Gay, 2009.

Part B

In the expansion cohorts, the SMC will also monitor the safety of the participants treated with M3258 at RDE in combination with 20 mg/day dexamethasone and will meet after 3, 6, and subsequently every 6 participants have finished the DLT period or discontinued, unless a change in dosing has occurred. In case dosing in the expansion cohort was changed, the next SMC will be held after 3 participants have finished the DLT period or discontinued. Thereafter the SMC will evaluate the safety after every 6 participants (see Section 10). The SMC can recommend continuing enrollment at the RDE, changing the dose, or stopping the expansion part of the study. The SMC decisions in the expansion phase will also be supported by Bayesian modeling. Study Intervention after the End of Study.

The Sponsor will not provide any additional care to participants after they leave the study because such care would not differ from what is normally expected for participants with MM.

Part A and B

If a participant receives M3258 QD and misses taking a scheduled dose of M3258, then within a window of 12 hours it is acceptable to replace the missed dose. If in the QD dosing regimen the window is more than 12 hours after the scheduled dose time, then the missed dose should not be taken, and participants should be instructed to take the next scheduled dose.

If a participant receives M3258 twice-per-week and misses taking a scheduled dose within a window of 24 hours, then it is acceptable to replace the missed dose. For the twice-per-week dosing regimens in case of a delay of the scheduled dose, the missed dose should be taken as soon as possible, but at least two days (minimum 36 h) before the next scheduled dose.

If a participant vomits after taking M3258, the participant should not repeat the dose, but resume dosing at the time of the next scheduled dose.

6.7 Study Intervention at the End of the Study

Not applicable.

6.8 Special Precautions

Monitoring of neuropathic pain and/or peripheral sensory or motor neuropathy beyond DLT period in escalation phase and continuously in expansion phase.

6.9 Management of Adverse Events of Special Interest

An AESI (serious or nonserious reaction) is one of the scientific and medical concern specific to the study intervention, for which ongoing monitoring and rapid communication by the

Investigator to the Sponsor will be encouraged. Such events of interest may require further investigation or in-depth evaluations to better characterize and understand the association between the adverse event and M3258. Based on nonclinical data, following AEs will be considered AESI (Table 15).

Table 15 Adverse Events of Special Interest

AE	Management
Myelosuppression (Grade > 3) with complications i.e., cytopenia, febrile neutropenia, thrombocytopenia with clinically significant bleeding	Repeat blood test within 72 hours See Table 12 for guidance on dose modification.
Clinically significant GI Hemorrhage	Routine monitoring of clinical signs and symptoms Symptomatic treatment at Investigator's discretion See Table 13 for guidance on dose modification
GI Mucositis (Diarrhea, vomiting)	Monitor signs and symptoms. Symptomatic treatment at Investigator's discretion is allowed See Table 13 for further guidance.
Opportunistic infections including COVID-19	Monitor signs and symptoms; Testing for COVID-19 according to local medical practice Symptomatic treatment per local medical practice.
Allergic/Hypersensitivity Reaction/Skin Rash	Advised to manage participant in accordance to standard local practice. Premedication (antihistamine/corticosteroid) for the same and/or subsequent participants may be considered if appropriate based on Investigator's clinical judgement limiting dexamethasone to doses not reaching the level required for the treatment of multiple myeloma.

AE = Adverse event, GI = Gastrointestinal.

Investigator must complete the AESI Report Form and communicate with the Sponsor within 24 hours of occurrence of AESI. Serious AESI (based on SAE reporting criteria) should always be reported as SAE as outlined in Section 8.2.

6.9.1 Monitoring and Management of Other Toxicities (e.g., Over-Arching Toxicities in Part B)

Corticosteroid therapy is known to cause mild to severe AEs that affect almost all body systems; however, the incidence of toxicity is dependent on multiple factors including the dose level and duration of treatment. Most common AEs known to occur with dexamethasone (low dose) may include hematological toxicity, i.e., anemia, thrombocytopenia, neutropenia (myelosuppression). Among nonhematological toxicity, i.e., diarrhea, nausea, vomiting, fatigue; systemic infection (specifically opportunistic); thromboembolic events including deep vein thrombosis and pulmonary embolism; and cutaneous rash have been reported; Investigators will be advised to refer to the local product label. Toxicities manifested by administration of dexamethasone in the expansion part of the study will be managed in accordance with the local medical practices and local labels; a guidance on the dose reduction during the study intervention period is provided (Table 14A and Table 14B). Albeit, dose reduction for toxicity deemed to be attributed to dexamethasone alone must be performed as clinically indicated. A deviation from the recommended dose reduction may be performed based on the clinical judgement of the study investigator and after discussion with the Sponsor Medical Monitor.

Since renal impairment is a common complication of MM, abnormalities in renal functions (new or worsening from Baseline) will be carefully monitored throughout the study. If decrease in estimated glomerular filtration rate is > 25% from Baseline or doubling of serum creatinine is observed, laboratory chemistry tests will be repeated within 72 hours from the initial finding in order to confirm the abnormal findings. The study participant will be evaluated thoroughly by the Investigator, i.e., physical examination, review of concomitant medication, etc. Upon recovery to ≤ Grade 1 or pretreatment levels, study intervention may be resumed at the same or a lower dose, if appropriate, based on Investigator's clinical judgement and after discussion with the Sponsor Medical Monitor. Additionally, because of the common occurrence of renal involvement in MM, the use of nephrotoxic agents (e.g., NSAIDs) should be avoided throughout the study.

Grade 3 or 4 (Hematological or Nonhematological) Toxicities

If applicable, repeat laboratory tests in the local laboratory within 72 hours and then repeat tests twice a week until recovery to Grade 2 is observed. Thereafter, repeat laboratory tests as appropriate based on Investigator's clinical judgement.

For clinically evident Grade 4 toxicities occurring after DLT period, discontinuation of M3258 administration is advised. A decision on re-initiation of M3258 should only be considered after recovery of toxicity in question to ≤ Grade 1 is observed within two weeks of discontinuation of M3258 treatment (if a laboratory parameter, recovery should be confirmed by a repeat test), and the dose of M3258 should be reduced by at least 1 dose level. When a dose reduction is required, no re-escalation of the dose will be allowed. If Grade 4 toxicity recurs upon resuming M3258, then administration of study treatment should immediately be discontinued. The decision to continue treatment should be discussed with the Medical Monitor and documented in the study records. In case of the occurrence of overlapping toxicities of M3258 and dexamethasone, the dose reduction of M3258 will occur first (see Table 11, Table 12, and Table 13). Dexamethasone dose should be reduced based on local product label or institutional guidelines only for toxicities which are deemed related to dexamethasone (for related toxicities and guidance on dose reduction, see Table 14A and Table 14B.

In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation and involvement of a pulmonologist should be considered. Participants will be treated according to institutional standards. Since low-grade pulmonary toxicities (Grade 1-2), such as dyspnea and cough, manifest as symptoms of diverse underlying etiologies, the study investigators should bear high suspicion for study treatment-induced pulmonary injury. The study investigator will also be required to discuss any grade pulmonary toxicity with the Sponsor medical representative. Re-initiation of M3258 must be discussed with the Sponsor medical representative. The benefit/risk balance should be considered prior to continuing M3258 therapy.

The adverse events suggestive of lung toxicity with Grade ≥ 3 irrespective of attributability will be reported as SAEs throughout the study.

Grade 4 toxicity should always be reported to the Sponsor as a SAE in expedited manner, within 24 hours of awareness.

Treatment cycles with M3258 -/+ combination with dexamethasone will be repeated every 21 or 28 days; hence, for a cycle of treatment to begin, the participant's blood ANC must be ≥ 1,000 mm^3 and the platelet count must be ≥ 75,000 mm^3. Additionally, all other toxicities considered to be related to study intervention must have resolved to ≤ Grade 1 or to the participant's Baseline value.

If the participant fails to meet the above-cited criteria for treatment, re-initiation of the next cycle of treatment should be delayed for one week. At the end of which, the participant should be re-evaluated to determine whether the criteria for re-treatment have been met. If a delay in the initiation of the next cycle of more than two weeks is required because of incomplete recovery from toxicity, then this event should be considered a DLT. If toxicity does not resolve by two weeks, then the participant should be discontinued from the study. This decision will be made in the context of emerging clinical data and in consultation with Sponsor Medical Responsible. If, in the opinion of the Investigator and the Sponsor Medical Responsible, it is in the participant's best interest to continue the treatment with M3258 -/+ combination with dexamethasone, the study intervention will only be resumed after recovery from toxicity to ≤ Grade 1 or Baseline values. Additionally, the dose of study intervention should be reduced by at least 1 dose levels. If the DLT recurs upon resuming study intervention at a lower dose, the study intervention should immediately be discontinued. For the first study cohort, no dose reduction will be allowed.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Stopping Rules for Individual Participants:

The Investigator must consider discontinuation of study intervention for abnormal liver function when a participant meets one of the conditions outlined in Section 6.6 or if the Investigator believes that it is in best interest of the participant.

All events of ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT > 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured, may indicate potential severe liver injury (possible Hy's Law) and must be reported as an AE and SAE.

If a clinically significant finding in ECG recording is identified (including, but not limited to changes from Baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

The SoA (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B) specifies the data to collect at study intervention discontinuation and Follow-Up, and any additional evaluations that need to be completed.

If a participant's study intervention must be discontinued, this will not result in automatic withdrawal of the participant from the study and the participant should be assessed at the End-of-Treatment visit and Safety Follow-Up visit.

A participant's study intervention should be discontinued if:

- The Investigator believes that for safety reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
  - The participant becomes pregnant.
  - The participant (or the participant's legally authorized representative) withdraws consent for administration of study intervention.
  - The participant's dose is held for more than 5 days per cycle, or if ≥ 6 consecutive planned doses of M3258 are missed for reasons other than toxicity unless, upon consultation with the Sponsor and the review of safety and efficacy, continuation is agreed upon.
  - The participant experiences disease progression.

Safety Stopping Rules for Study Intervention in Part B:

Unacceptable toxicity in the expansion cohort is defined as AEs that meet the DLT criteria regardless of when they occur during treatment (as defined in Section 6.6). The following stopping rules for unacceptable toxicity apply:

- ≥5 participants with observed DLT criteria out of 12 evaluable participants treated on the same dose.
- ≥ 7 participants with observed DLT criteria out of 18 evaluable participants treated on the same dose.
- ≥ 9 participants with observed DLT criteria out of 24 evaluable participants treated on the same dose.
- The chance is >80% that the true DLT rate is ≥ 30% (based on Bayes model).

If at any time in the expansion cohort, the number of unacceptable toxicity events indicate that there is a risk of safety to the participants (i.e., if any of the above boundary is met), accrual to the cohort will be paused and the SMC will meet to determine whether further enrollment should be halted taking into account feedback from study Investigators. In this case, the SMC will decide whether participants still on treatment and tolerating the treatment can stay on treatment or whether treatment needs to be dose reduced or withdrawn. The HA will be notified of the SMC decision.

7.1.1 Temporary Discontinuation

See to Section 6.6.

7.1.2 Rechallenge

See to Section 6.6.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time, at his/her own request (i.e., withdrawal of consent), and without giving a reason.

The participant may be withdrawn by the Investigator due to participation in another clinical study. Participant should have End of Study assessment per study protocol.

The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

The SoA (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B) specifies the data to collect at study discontinuation and Follow-Up, and any additional evaluations that need to be completed.

7.3 Lost to Follow-Up

A participant will be considered lost to Follow-Up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to Follow-Up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoAs (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B).
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All Screening evaluations will be completed and reviewed by the Investigator to confirm that potential participants meet all inclusion and exclusion criteria before submitting eligibility criteria. The eligibility will be confirmed at Day 1 Cycle 1. The Investigator will maintain a Screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for Screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were preformed within the time frame defined in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Unscheduled visits need to be documented in the eCRF.

8.1 Efficacy Assessments and Procedures

- Efficacy assessments and procedures and their timing are summarized in the SoAs (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B).
- Demography: date of birth, sex (gender), race, and ethnicity
- Medical history: previous illness and surgeries (e.g., all during the past year and only major ones prior to that), concomitant illness, allergies, prior therapies for the target indication (i.e., relevant previous medications), therapies stopped or changed at entry into the study, tobacco use, alcohol use, special diets and, for women, menstrual status and date of last menstrual period.
- Disease factors
- Any aspects of the schedule not covered in the SoA (e.g., timing relative to meals or study intervention administration).
- Any necessary conditions (e.g., preparation of participants or materials, laboratory supply, additives in test systems, sample origin, safety measures before, during, and after the procedure, and sample labeling, processing, storage, and transfer).
- Any evaluation criteria.
- If assessments/procedures vary from one time point to another.
- Any qualitative or exit interview evaluations.
- Efficacy assessments per IMWG response criteria (Kumar et al, 2016).

  Assessment of tumor response and disease progression will be conducted in accordance with the IMWG response criteria (Kumar et al, 2016). Disease evaluations will include measurements of myeloma proteins, bone marrow examinations (biopsy and/or aspirate [aspirate preferred] required prior to dosing Day 1 Cycle 1 and at the time of confirmation of CR), assessment of bone lesions, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin (see SoAs: Table 1 and Table 2

for Part A; Table 3 and Table 4 for Part B). Serum and urine tests are to be performed as indicated in the SoAs: Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B. After Cycle 1, immunofixation electrophoresis (IFE) should only be done when M-protein is 0 or nonquantifiable. After Cycle 6, disease assessments serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), and serum calcium corrected for albumin, should be collected every cycle until end of study intervention. All responses (including Pd based on biochemical investigations) require 2 consecutive assessments with the same, worse, or better outcome.

- Disease state
- Survival status and subsequent anticancer treatment data (within the OS Follow-Up of this study) will be collected in Part B censored at the End of Study (Section 9.4.1).

Table 16 International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
sCR	• CR as defined below, plus • Normal FLC ratio, and • Absence of clonal PCs by immunohistochemistry, immunofluorescence or 2 to 4 color flow cytometry
CR[a]	• Negative immunofixation on the serum and urine, and disappearance of any soft tissue plasmacytomas, and < 5% PCs in bone marrow
VGPR[a]	• Serum and urine M-protein detectable by immunofixation, but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus 24-hour urine M-protein <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 not measurable, a decrease of ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size (SPD) of soft tissue plasmacytoma is also required
MR	• In participants with relapsed refractory myeloma adopted from the EBMT criteria (Blade 1998): ≥ 25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at Baseline, ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
SD	• Not meeting criteria for CR, VGPR, PR, MR, or PD • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
PD [b]	• Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL), • Urine M-component (absolute increase must be ≥ 200 mg/24 hours), • Only in participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) • 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) that can be attributed solely to the PC proliferative disorder

CR = Complete response, EBMT = European Group for Blood and Marrow Transplantation; FLC = free light chain; MR = Minimal response, PC = plasma cell, PD = Progressive disease, PR = Partial response, sCR = Stringent complete response, SD = Stable disease, SPD = Sum of the products of the maximal perpendicular diameters of measured lesions, VGPR = Very good partial response.

All response categories (CR, sCR, VGPR, PR, MR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at Baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

a Clarifications to IMWG criteria for coding CR and VGPR in participants in whom the only measurable disease is by serum FLC levels: CR in such participants indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such participants requires a >90% decrease in the difference between involved and uninvolved FLC levels.
b Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in participants without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.
c Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

For the interim analysis the following results are considered a response: PR, VGPR, CR, sCR.

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria (Kumar et al, 2016; Rajkumar et al, 2011). It is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

- Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
- Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
- Hypercalcemia (> 11.5 mg/dL)
- Decrease in hemoglobin of more than 2 g/dL (1.25 mM)
- Rise in serum creatinine by more than or equal to 2 mg/dL
- Hyperviscosity

In some participants, bone pain may be the initial symptom of relapse in the absence of any of the above features. However, bone pain without imaging confirmation is not adequate to meet these criteria in studies.

Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be analyzed according to the Laboratory Manual and as outlined in the SoAs (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B). Only 1 serum and one 24-hour urine sample per time point are required to perform the following tests:

- Serum and urine quantitative immunoglobulins (IgG, IgA, IgM, IgE, and IgD) at Screening and thereafter when CR is suspected and when no M-protein is detectable in serum
- Serum M-protein quantitation by electrophoresis (SPEP)
- Urine M-protein quantitation by electrophoresis (UPEP)

- Serum and urine free light chain assay at Screening and thereafter when CR is suspected. In case of free light chain disease, free light chain assay in serum at Screening, Day 1 of every cycle and when CR is suspected.

Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected as indicated in the SoAs: Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B and analyzed centrally until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) can indicate disease progression or relapse if it is not attributable to any other cause. Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). Calcium will also be analyzed locally for immediate management of participant safety.

Serum β2-microglobulin

Blood samples for β2 microglobulin and albumin are to be collected as indicated in the SoAs: Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B and will be analyzed by the central laboratory.

Bone Marrow Examination

Bone marrow aspirate and/or biopsy (aspirate preferred) will be performed by the local laboratory at Day 1 Cycle 1 (see SoAs: Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B) for clinical staging (morphology, cytogenetics, and either immunohistochemistry or immunofluorescence or flow cytometry) and assessment of MRD (bone marrow aspirate). Bone marrow examination for MRD (bone marrow aspirate) will also be performed after treatment to confirm CR (including sCR). If the participant meets criteria for CR and has a normalized free light chain (FLC) ratio, an additional bone marrow aspirate sample will be required to confirm sCR. For bone marrow handling at CR, refer to the Laboratory Manual.

Assessment of Lytic Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the Investigator suspects involvement by disease) is to be performed and evaluated by the local laboratory by roentgenography as indicated in the SoAs: Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B. Bone lesions can also be assessed by CT, low-dose whole-body CT, PET-CT, whole-body CT, FDG-PET/CT, and MRI. If performed by PET/CT or MRI, osteolytic lesions and extramedullary disease can be evaluated within the same imaging during screening. A Follow-Up during the Treatment Phase with x-rays should be performed whenever clinically indicated based on symptoms, to document response or progression.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of Baseline medical conditions, AEs, physical examination findings, vital signs, ECGs, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

8.2.1 Physical Examinations

- A complete physical examination will be conducted as outlined in the SoA (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B). It will include, at a minimum, assessments of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous systems of a participant. Weight will also be measured and recorded. Height will be measured and recorded at Screening only.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver and spleen) and peripheral motor and sensory nervous system. Brief examination may also include targeted system examination as appropriate. For instance, Investigator may examine the participant with a medical history of peripheral neuropathy for worsening.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Body temperature (use one method for a participant [oral preferred]), pulse rate, respiratory rate, and blood pressure will be assessed as outlined in the SoA (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B).
- Blood pressure and pulse measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a sitting position and in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of pulse rate and blood pressure measurements. The readings will be recorded on the eCRF.

8.2.3 Electrocardiograms

Safety ECGs

Safety ECGs are standard single 12-lead ECGs obtained for safety monitoring according to the SoAs (Table 1 and Table 2 for Part A, Table 3 and Table 4 for Part B). Participants will rest in recumbent position for at least 10 minutes. Safety ECGs will be read locally and all ECGs should be assessed on the day of collection to determine continued eligibility. The calculated QTc average of 12-lead ECGs must be $\leq$ 450 ms for males and $\leq$ 470 ms for female participants' eligibility. Participants, in whom the calculated QTc average increases to $>$ 500 ms or $>$ 60 ms change over baseline during treatment with M3258, must interrupt study treatment until further clinical evaluation. ECGs should be repeated if QTc is outside the range

until resolution. To assess the safety and tolerability of the study intervention, an ECG can be repeated at the Investigator's discretion at unscheduled visits. Start and end of resting time and ECG time will be recorded in the eCRF.

QT/QTc Evaluation

Triple ECG monitoring will be performed with a provided Holter ECG at the time points specified in the SoAs (Table 1/Table 2 and Table 5 for Part A and Table 3/Table 4 and Table 6 for Part B). Participants will rest in recumbent position for at least 10 min. Start and end of resting time will be documented in the eCRF.

ECGs will be stored digitally for a later independent analysis: ECG extractions will be made by the central ECG laboratory and over-read of interval measurements will be provided by experienced, qualified, and certified cardiac safety specialists. The central readers will be blinded to participant details, treatment, visit day, and time points of the ECG recording, and a single reader will read all ECGs of a given participant.

8.2.4 Chest X-Ray at Pretreatment

A pretreatment (screening) chest radiograph serves to identify pneumonitis, interstitial pneumonia and lung infiltration for eligibility of participants and as a baseline for potential post-treatment pulmonary changes.

In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnea), a prompt diagnostic evaluation and involvement of a pneumologist should be considered. Participants treated according to institutional standards. The study investigator will also be required to discuss any grade pulmonary toxicity with the Sponsor medical representative. Re-initiation of M3258 must be discussed with the Sponsor medical representative. The benefit/risk balance should be considered prior to continuing M3258 therapy.

8.2.5 Clinical Safety Laboratory Assessments

- Appendix 7 lists the laboratory tests that will be analyzed for the study for each panel (e.g., hematology, chemistry, urinalysis).
- Hematology includes complete blood count with differential and platelet counts. Blood samples for hematology will be obtained prior to administration of study intervention.
- Urinalysis assessments are listed in Appendix 7 and are required at the timepoints listed in the SoAs (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B).
- β-human chorion gonadotropin must be determined from serum at Screening and from urine thereafter in WOCBP (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B). Appropriate menopausal status of women can be confirmed by testing for increased FSH levels at Screening. A negative urine pregnancy test on Day 1 of each cycle prior to study intervention administration needs to be available. Results of the most recent pregnancy test (within the last 7 days) must be available prior to next administration of the study drug.
- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 7, at the time points listed in the SoA (Table 1 and Table 2 for Part A;

Table 3 and Table 4 for Part B). Blood samples for PK will be obtained prior to the administration of the study intervention. All samples should be clearly identified.

- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the local laboratory. The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the designated organization.
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.2.6 Suicidal Ideation and Behavioral Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 5.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the 30-Day Follow-Up Safety Visit.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 5, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 5.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and all nonserious AESIs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 5.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 and are assessed for their outcome at the 30-Day Follow-Up Safety Visit. All SAEs ongoing at

the 30-Day Follow-Up Safety Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to Follow-Up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and Follow-Up procedures are performed. Further information on Follow-Up procedures is given in Appendix 5.

Based on the nonclinical toxicology studies, adverse events of myelosuppression, GI toxicity, opportunistic infections and allergic reactions are considered AESI (Section 6.9). These events must be reported on AESI Forms to Merck Healthcare Global Patient Safety throughout the study until resolution or permanent outcome of the event.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the study.

In accordance with ICH Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy

Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 5, section on Reporting Serious Adverse Events.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

8.4 Treatment of Overdose

For this study, any dose higher than the calculated dose for that particular administration within a 12-hour time period is considered an overdose.

The Sponsor does not recommend specific treatment for an overdose, but the Investigator should use his or her clinical judgment when treating an overdose of the study intervention considering the presenting symptoms and standard evaluation results.

For monitoring purposes, any case of overdose, even if it not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 5, section on reporting SAEs.

8.5 Pharmacokinetics

Sampling time schedules for determination of M3258 can be found in Table 5 for Part A and for M3258 and dexamethasone in Table 6 for Part B. Whole blood samples of approximately 40 mL in Cycle 1 of Part A will be collected for measurement of plasma concentrations of M3258; whole blood sample of approximately 30 mL in Cycle 1 and 30 mL on Cycle 2 of Part B will be collected for measurement of plasma concentrations of M3258 and dexamethasone. The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. Details on processes for collection and shipment of these samples are in Laboratory Manual.

The quantification of M3258 and dexamethasone in plasma will be performed using a validated assay method. Concentrations will be used to evaluate the PK of study intervention.

Remaining samples collected for analyses of plasma concentration may also be used to evaluate metabolites safety or efficacy aspects related to concerns arising during or after the study.

The definitions for PK parameters are listed in Appendix 8.

Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.6 Pharmacodynamics

Pharmacodynamic markers are described in Section 8.8, and details on processes for collection and shipment of these samples are in the Laboratory Manual.

CCI [redacted]

8.8 Biomarkers

- Collection of participant samples for biomarker research is also part of this study and is governed by the appropriate ICF.
- The following participant samples for biomarker research are required and will be collected from all participants in this study, as specified in the SoAs (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B):
    - Blood samples for analysis of L-citrulline, β5c activity in whole blood and LMP7 activity in PBMCs.
    - Bone marrow sample for determining cytogenetic risk factors and minimal residual disease (MRD).
        - Baseline bone marrow samples to identify cytogenetic risk factors in order to evaluate associations with drug response.
        - Baseline bone marrow samples to determine MM clonality before treatment, which is needed as a reference when evaluating MRD (i.e. disease burden) using next generation sequencing (NGS) for participants that experience a CR or sCR.
        - On-study bone marrow aspirate to determine MRD in participants experiencing CR or sCR using NGS and/or next generation flow cytometry. Of note, only participants that experience a CR or sCR will have their baseline sample analyzed using NGS, whereas next generation flow cytometry does not require a baseline sample.

A portion of the bone marrow sample to confirm CR (including sCR), as described in Section 8.1, will be sent to a laboratory for MRD assessment by next generation flow cytometry and/or next generation sequencing.

In addition, participant samples may be used for additional research, as specified in the ICF.

Details on processes for collection and shipment of these samples are in Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.9 Health Economics

Not applicable.

8.10 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

9.1 Statistical Hypotheses

This is an exploratory study. No formal statistical hypothesis will be tested.

9.2 Sample Size Determination

Dose Escalation Part A

The planned cohort size is 3 participants at a given dose. Parallel screening and enrollment of participants will allow eligible participants to enroll, the cohort size may therefore increase to a maximum of 4 participants. Any additional participants enrolled in the study at a given dose, will complete all study procedures and assessments as per protocol and are considered in the Bayesian model if they fulfill the criteria for inclusion in the DLT set.

The total sample size will depend on the number of cohorts and regimens to be evaluated. It is anticipated that 15 to 21 participants (4 projected dose levels with 3 to 9 participants each) may be needed. If change(s) in regimen would occur, the sample size may increase.

The following scenario is anticipated:

2 dose levels with 3 participants each and 2 dose levels with 6 participants each, resulting in 18 participants.

Considering for example one change in regimen after the first dose level, the sample size may increase by 3 if in the new regimen, the above scenario holds.

Dose Expansion Part B

Part B begins with a safety run-in of 6 participants. Dose adjustments during Part B may occur.

Part B will include 30 participants treated at the same dose who are evaluable for response in a two-stage design. This sample size will give a posterior probability of 85% that the ORR ≥ 20% if 8/30 responses are seen at the final analysis.

An interim analysis will occur after enrollment of 15 participants treated at the same dose are evaluable for response. The cut-off for the interim analysis was chosen to balance sufficient information for decision with the potential of sparing participants an inefficient treatment. The boundary and operational characteristics are described in Section 9.4.1.

If in the course of the expansion and/or at the interim analysis, the M3258 dose is modified, then only participants treated at the same dose will be considered in the two-stage design. Therefore, the number of participants in the expansion cohort might increase by approximately 3 to 21 participants to reach the required number of 30 participants treated on the same dose who are evaluable for response according to IMWG.

Additionally, in Part B (as well as in Part A) the SMC may recommend to end the enrollment in the expansion cohort due to safety concerns.

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.
DLT	The Dose Escalation Set will include all participants who received at least one dose of study intervention and meet at least one of the following criteria: • Experienced at least one DLT during the DLT period, regardless of the administered number of doses of study intervention/completion of the DLT period • Received at least 80% of the planned cumulative dose and 80% of planned administrations of each treatment during the DLT period and completed the DLT period.
PK	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable postdose concentration. Participants will be analyzed per the actual study intervention they received.
Pd	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting Pd, and provide at least one measurable Pd endpoint postdose.

DLT = Dose-limiting toxicity; Pd = Pharmacodynamics; PK = Pharmacokinetics.

9.4 Statistical Analyses

There is no formal significance level for this study, and all analyses are considered descriptive.

9.4.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	No primary efficacy endpoint is specified

Secondary	Will be specified in the Integrated Analysis Plan finalized before database lock. In general, continuous variables will be summarized using number of participants (n); mean, standard deviation; median, 25th Percentile to 75th Percentile (Q1-Q3), minimum, and maximum. If there are less than 5 observations available, only mean and the observed data will be given. Categorical variables will be summarized using frequency counts and percentages. The calculation of proportions will be based on the number of participants in the analysis set of interest, unless otherwise specified in the study Integrated Analysis Plan. Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of PFS and OS together with a summary of associated statistics (median survival time, 6-, 12-month survival rate estimates and estimates for every 6 months thereafter if applicable) including the corresponding 2-sided 95% CIs.
Tertiary/Exploratory	Will be specified in the Integrated Analysis Plan finalized before database lock.

CI = Confidence Interval; PFS = Progression-Free Survival; OS = Overall Survival.

In Part B, a two-stage design with an interim analysis after 15 participants treated on the same dose and evaluable for response is foreseen. If less than 3 responses are seen out of 15 participants evaluable for response, the expansion cohort is stopped for futility or dose is increased. This gives a probability of falsely stopping the study if the drug were effective (assuming an ORR of 35%) of 6%, while already correctly stopping the study if the drug is not sufficiently effective (assuming an ORR of 15%) of 60%. Else the study continues, until 30 participants are evaluable for response.

At this interim analysis there is the possibility to:

- If ≥3 responders are seen (in participants treated on the same dose) and there are no safety concerns, continue the study on the same dose until 15 additional participants are treated at the same dose who are evaluable for response according to IMWG, or
- If <3 responders are seen, either:
  - Stop the study for futility, or
  - Increase the dose (within the limits specified in Section 4.1 and only to doses with an estimated 75% percentile of the DLT rate below 30% from the Bayesian model in combination will be considered). Enroll participants at the new dose until 15 participants treated at the new dose are evaluable for response according to IMWG. Subsequently a new interim analysis is performed. The following options at that second interim analysis are possible (the same futility rule as for the first interim applies after 15 participants treated on the same dose who are evaluable for response):
    - If ≥3 responders (in participants treated on the same dose) are seen and there are no safety concerns: Continue at the same dose until additional 15 participants are evaluable for response (to reach overall 30 participants on the changed dose evaluable for response), or
    - If <3 responders are seen, stop the study for futility.

If any other option is deemed necessary, a protocol amendment will be submitted.

No more than 2 such interim analyses will be performed, unless a protocol amendment is submitted.

Treated on the same dose includes all participants who were planned to receive the same dose.

9.4.2 Safety Analyses

Analyses to decide on dose escalation will be based on safety, PK, and Pd data.

To support the decision on dose escalation, the SMC will receive results of a Bayesian dose-toxicity model, including the recommendation of next dose level from the model.

The Bayesian dose-toxicity analysis will be performed on the dose escalation set.

More details of this Bayesian two-parameter logistic regression model (Neuenschwander et al. 2008) are further specified in Appendix 10.

For each SMC meeting, the model will be updated with the number of DLTs and evaluable participants per dose level. Based on the observed data the model will suggest the next dose level. The following dose levels are foreseen: 10 mg, 20 mg, 35 mg, and 50 mg. However, the SMC may decide to have different or additional dose levels or skip dose levels, except escalation may not proceed to any dose higher than 50 mg. In case escalation should proceed to doses higher than 50 mg, an amendment will be submitted.

The dose suggested by the model for the next cohort will be the dose with minimal Bayesian Risk (among all considered doses).

The target DLT toxicity for the MTD is 25%.

The SMC may choose a different dose than suggested by the Bayesian escalation approach (not higher than 50 mg). Also, the SMC may decide to change the dosing regimen as specified in Section 4.1. In such a case the dose toxicity model will be extended, or a separate model will be set up.

Usually decisions on dose escalation are taken once all participants of the most recent cohort have completed the DLT period or discontinued. In exceptional cases, however, the SMC may recommend on the next cohort earlier, i.e., before the last participant of a cohort has finished the DLT period (considering the available data from the current and previous cohorts as well as model recommendation). Per definition of the Dose Escalation set, participants who have not completed the DLT period are not included for update of the model, unless they experienced a DLT. However, data of such participants will be included at next SMC (if criteria for the Dose Escalation set are then fulfilled).

Before first dosing, the assumed relationship between dose level and toxicity is specified through the prior distribution. The prior distribution chosen for this study correspond to the following mean/median estimates of DLT probability:

Probability for DLT	10 mg	20 mg	35 mg	50 mg
Prior mean	15%	19%	24%	28%
Prior median	8%	13%	18%	22%

DLT = Dose-limiting toxicity.

Details of the model, including the prior distribution can be found in Appendix 10.

Decisions of the SMC in the expansion cohort will also be aided by a Bayesian two-parameter logistic regression model with the same specifications as for the dose escalation, except the prior. The prior will be based on the data seen in the monotherapy dose escalation and specified in the SMC charter before the first SMC for the expansion cohort occurs. The model will be updated at times of SMCs in the expansion cohort. Additional stopping rules in Part B apply (see Section 7.1).

Other specifications are as for dose escalation and can be found in Appendix 10.

Details on analyses for SMCs will be described in the SMC Integrated Analysis Plan.

All other safety analyses will be performed on the Safety Analysis population.

Endpoint	Statistical Analysis Methods
Primary (DLTs)	After end of dose escalation and main analysis, the number and proportion of participants experiencing DLTs will be reported by dose level, based on observations during the first study intervention cycle. Posterior probabilities (2.5%, 25%, 50%, 75%, and 97.5% quantiles) for DLT probabilities at selected doses will be estimated from the Bayesian logistic regression model. A sensitivity analysis will be performed using frequentist modeling (without prior).
Secondary	In general, continuous variables will be summarized using number of participants (n); mean, standard deviation; median, 25th Percentile to 75th Percentile (Q1-Q3), minimum, and maximum. If there are less than 5 observations available only mean and the observed data will be given. Categorical variables will be summarized using frequency counts and percentages. The calculation of proportions will be based on the number of participants in the analysis set of interest, unless otherwise specified in the study Integrated Analysis Plan. Details will be specified in the Integrated Analysis Plan finalized before database lock.
Tertiary/Exploratory	Details will be specified in the Integrated Analysis Plan finalized before database lock.

DLT = Dose-limiting toxicity.

QT/QTc Analysis

The ECG parameter will be summarized by descriptive statistics per time point; changes from Baseline will be calculated.

Time-matched, replicate ECGs and PK samples collected in the dose escalation phase will be used to analyze for cQTc responses using slope analysis of exposure/response. This analysis may be reported separately.

9.4.3 Other Analyses

PK, Pd, and biomarker exploratory analyses will be specified in the Integrated Analysis Plan finalized before database lock. Integrated analyses across studies, such as the population PK analysis and Pd analyses will be presented separately from the main clinical study report.

9.4.4 Sequence of Analyses

This is an exploratory study.

The SMC will review available data during study conduct. The cut off for dose escalation assessments in Part A by the SMC will be triggered by the completion of the DLT period (or discontinuation) of the last participant in the respective dose escalation cohort. If enrollment of the last participant in a dosing cohort is delayed, the SMC may decide on available data for enrollment and dose of the next dosing cohort before all participants in a cohort have completed Cycle 1. In these cases, cut-off can be earlier (after DLT period of the first 2 participants is finished or they experienced a DLT).

For Part A, the cut off for an exploratory interim analysis of the safety, available PK, available Pd and preliminary antitumor activity data from the complete dose escalation will be triggered when all participants enrolled in the dose escalation:

- Had the first on-study intervention tumor assessment or
- Experienced death or
- Withdrew for any reason

whichever comes first.

In Part B, an interim analysis will be conducted after 15 participants who are treated at the same dose are evaluable for response. If at this interim analysis, the dose is increased, one additional interim analysis may occur after 15 participants are treated on the new dose and are evaluable for response. Additionally, there are SMCs planned after 3, 6, and in the following every 6 participants have finished the DLT period. For all SMCs the analyses necessary for these SMCs will be conducted (as described in the integrated analysis plan for SMCs).

Additional analysis during the study might be conducted, e.g., for publication purposes.

The primary analysis will be performed once all participants have completed the second response evaluation (or discontinued prematurely).

Follow-Up analyses to further efficacy and safety data will be done once the End of Study has been reached.

The preliminary food effect will be evaluated at the time of interim analysis in the available participants in Part B. The results will be indicative of whether to evaluate further participants on food effect or stop the food effect evaluation.

More details will be described in the Integrated Analysis Plan.

10 Safety Monitoring Committee

The SMC consists of core (internal and external voting) members for the Sponsor (Global Patient Safety Product Leader [Chair], Medical Responsible, Clinical Pharmacologist and Biostatistician), the Coordinating Investigator, and the Medical Monitor of the Contract Research Organization. Ad hoc members may be invited as needed.

During the dose-escalation Part A of the study, the SMC will evaluate the safety data (including DLTs) and available PK and Pd data, as defined in the SMC charter, in order to make recommendations on the dosing of the next participant cohort.

A Bayesian two-parameter logistic regression model (Neuenschwander et al. 2008) will be used to assist the SMC with dose selection. Further details on the Bayesian model are provided in Section 9.4.2 and Appendix 10 Description of the Bayesian Dose Escalation Model0.

The SMC may choose a different dose than suggested by the Bayesian escalation model (however, not higher than 50 mg).

Based on the observed toxicity profile and available PK and Pd, dose level(s) that are different than the prespecified doses may be recommended by the SMC. However, escalation may not proceed to any dose higher than 50 mg. In case escalation should proceed to doses higher than 50 mg, an amendment will be submitted. Based on observed toxicity profile, PK and Pd data, the SMC may recommend changing the dosing regimen as specified in Section 4.1.

The planned cohort size is 3 participants at a given dose. Parallel screening and enrollment of participants will allow eligible participants to enroll, the cohort size may therefore increase to 4 participants. Any additional participants enrolled in the study at a given dose, will complete all study procedures and assessments as per protocol. Based on the safety, PK and Pd data (if available) collected from the participants in a cohort, the SMC may recommend that no further participants are required in a cohort before the planned cohort size is reached. In cases where enrollment of the last participant in a dosing cohort was delayed, the SMC may decide (based on available data) upon enrollment and dose for the next dosing cohort before all participants in a cohort have completed the DLT period. For this participant, the SMC will consider all available data (and any subsequent emerging data at a subsequent meeting). An ad-hoc meeting will be convened if this participant experiences a DLT.

Participants who did not experience a DLT and who either did not receive at least 80% of the planned cumulative dose of treatment during the DLT period, or at least 80% of the planned

administrations, or did not complete the DLT observation period will not be considered for DLT evaluation and in the Bayesian model. An SMC meeting with selection of dose for next cohort will also be held if not all participants in a cohort are evaluable (e.g., if a participant missed more than 20% of treatment in the first cycle for any reason other than a DLT).

The SMC might modify the schedule of PK and Pd sampling based on emergent data. However, the total blood volume taken for PK and Pd samples will not exceed blood volume described in this protocol or the Laboratory Manual.

For the expansion part of the study, the SMC will monitor the safety of M3258 at the recommended dose with dexamethasone and may recommend by consensus on continuation at the same dose, change in dose (only to doses declared safe by SMC in monotherapy), modifications of the study protocol, or stop of expansion cohort. The same DLT criteria as for the monotherapy dose escalation will apply. Additional safety stopping rules apply as outlined in Section 7.1.

The SMC will evaluate the safety of the combination therapy after 3, 6, (safety run-in) and subsequently every 6 participants finished their DLT period or discontinued, unless a change in dosing has occurred. In case the dosing in the expansion cohort was changed, the next SMC will be held after the next 3 participants have finished the DLT period or discontinued and then the SMCs are scheduled every 6 participants having finished the DLT period or discontinued.

For SMCs in the safety run-in and the first SMC after a dose change, dosing of new participants can only start after SMC has decided to proceed (including on what dose). For all other SMCs there is no pause in enrollment.

The SMC decisions in expansion cohort will also be supported by a two-parameter Bayesian logistic regression model. For details on the model, see Section 9.4.2.

The SMC may modify the frequency of meetings as deemed appropriate during the study.

After the evaluation of the food effect in 15 participants in Part B, the SMC will take the decision whether to increase the number of participants which are to be included in the food effect evaluation.

The specific working procedures will be described in an SMC charter, which will be established prior to the start of dosing.

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12 Appendices

Appendix 1 Abbreviations

ADL	Activity of Daily Life
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area under the Concentration-Time Curve
BED	Biologically Effective Dose
CL/f	Apparent Total Body Clearance
CLss	Clearance at Steady State
C_{max}	Maximum Observed Concentration
CR	Complete Response
CSR	Clinical Study Report
(e)CRF	(electronic) Case Report Form
CT	Computed Tomography
CV	Coefficient of Variation
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FiH	First in Human
FLC	Free Light Chain
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GI	Gastrointestinal
HA	Health Authorities
HIV	Human Immunodeficiency Virus
CCI [redacted]	[redacted]
HR	Hazard Ratio

HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFE	Immunofixation Electrophoresis
IMiD	Immunomodulatory Imide Drug
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IRB	Institutional Review Board
LMP7	Large Multifunctional Protease 7
MM	Multiple Myeloma
M-protein	Monoclonal Paraprotein
MR	Minimal Response
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition
NA	Not Applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next-Generation-Sequencing
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PC	Plasma Cell
Pd	Pharmacodynamics
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Proteasome Inhibitors
PiC	Powder in Capsule

PK	Pharmacokinetics
PR	Partial Response
QD	Once Daily
QTc	QT Interval Corrected
QTcF	QT Interval Corrected using Fridericia's Formula
RDE	Recommended Dose and Regimen for Expansion
RRMM	Relapsed Refractory Multiple Myeloma
SAE	Serious Adverse Event
sCR	Stringent Complete Response
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SPD	Sum of the Products of the Maximal Perpendicular Diameters of Measured Lesions
SPEP	Serum Protein Electrophoresis
STD	Severely Toxic Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TRAE	Treatment-Related Adverse Event
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
US	United States
VGPR	Very Good Partial Response
WOCBP	Woman/Women of Childbearing Potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally-authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.
- A copy of the ICF(s) will be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and will be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

- The Investigator will complete the participant registration form and fax it to the medical monitor. If the participant meets all inclusion criteria and does not meet any of the exclusion criteria, the medical monitor will inform the Investigator and the Sponsor of the registration number by email or fax. If the participant is ineligible for the study, a participant number will be allocated and documented.

Study Administrative

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report (CSR).

The study will appear in the following clinical studies registries: EudraCT 2019-000947-28; ClinicalTrail.gov

Details of structures and associated procedures will be defined in a separate Operations and Study Reference Manual.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The Investigator will submit the protocol, protocol amendments (if applicable), ICF, IB, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC will review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
- Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
- Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact the medical monitor. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate medical monitor to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a CSR in consultation with the Coordinating Investigator.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck Healthcare to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- After completion of the study, a CSR will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.

- Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.
- The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Operations Manual.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan or contracts.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file will identify each participant, contain the following demographic and medical information for the participant, and will be as complete as possible:
- Participant's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identifier (i.e., the Sponsor's study number) and participant's study number.
- Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
- Any medical examinations and clinical findings predefined in the protocol
- All AEs
- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data will be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document will have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records will be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- The Study Monitors will use printouts of electronic files for source data verification. These printouts will be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in eCRF guidelines.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is when the first site is opened and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination.
    - Reasons for the early closure of a study site by the Sponsor or Investigator may include:
    - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
    - Inadequate recruitment of participants by the Investigator
    - Discontinuation of further development of the Sponsor's compound.
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is not:

1. Premenarchal
2. A premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

3. A postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
- A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

All study participants will be provided with the information on acceptable methods of contraception as part of the informed Consent Form (ICF) process. Each study participant will be asked to read and sign ICF stating that they understand the requirements for avoidance of pregnancy, donation of ova or sperm during the study until 90 days after the last dose of study intervention.

Appendix 4: Prohibited Comedication Prolonging the QT/QTc Interval

Medications known to prolong the QT/QTc interval must stop at least 7 days before the first administration of the study intervention and are not allowed during the study intervention administration:

Generic Names: Aclarubicin (Only on Non US Market), Amiodarone, Anagrelide, Arsenic trioxide, Astemizole (Removed from US Market), Azithromycin, Bepridi (Removed from US Market), Chloroquine, Chlorpromazine, Cilostazol, Ciprofloxacin, Cisapride (Removed from US Market), Citalopram, Clarithromycin, Cocaine, Disopyramide, Dofetilide, Domperidone (Only on Non US Market), Donepezil, Dronedarone, Droperidol, Erythromycin, Escitalopram, Flecainide, Fluconazole, Gatifloxacin (Removed from US Market), Grepafloxacin (Removed from US Market), Halofantrine (Only on Non US Market), Haloperidol, Hydroquinidine, dihydroquinidine (Only on Non US Market), Ibogaine (Only on Non US Market), Ibutilide, Levofloxacin, Levomepromazine (methotrimeprazine) (Only on Non US Market), Levomethadyl acetate (Removed from US Market), Levosulpiride (Only on Non US Market), Mesoridazine (Removed from US Market), Methadone, Moxifloxacin, Ondansetron, Oxaliplatin, Papaverine HCl (Intra- coronary), Pentamidine, Pimozide, Probucol (Removed from US Market), Procainamide, Propofol, Quinidine, Roxithromycin (Only on Non US Market), Sevoflurane, Sotalol, Sparfloxacin (Removed from US Market), Sulpiride (Only on Non US Market), Sultopride (Only on Non US Market), Terfenadine (Removed from US Market), Terlipressin (Only on Non US Market), Terodiline (Only on Non US Market), Thioridazine, Vandetanib.

For further details and update refer to the website "crediblemeds.org" (www.crediblemeds.org).

Appendix 5 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (NCI-CTCAE), version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate

Grade 3 or Severe

Grade 4 or Life-threatening

Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

Mild:

The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate:

The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe:

Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the M3258 include, but may not be limited to, temporal relationship between the AE and the M3258, known side effects of M3258 or dexamethasone, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm

requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs, AESIs and DLTs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalization to observe, administer or simplify study intervention or study procedure (for instance, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAE.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the participant's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the adverse event reporting period, as defined in Section 8.3.2.

Adverse Events of Special Interest

Based on theoretical safety concerns related to a M3258, Investigator should report AESIs (Section 6.9) to the Sponsor in an expedited manner, regardless if they satisfy the standard definition of an SAE. AEs of special interest for monitoring are then reported following the procedure for an SAE specified below for reporting SAEs, AESI, and DLTs.

Recording and Follow-Up of AE and/or SAE

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, whether reported by the participant or observed by the Investigator.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented. If an AE constitutes a DLT this is documented accordingly.

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the electronic SAE report form in the Electronic Data Capture (EDC) system.

Reporting of SAEs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

In exceptional circumstances, an SAE (or Follow-Up information) may be reported by telephone; in these cases, an electronic SAE report form must be completed immediately thereafter.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for Follow-Up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for Follow-Up will usually be made via the study monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will notify the Sponsor/designee by completing the electronic AESI Report Form in the EDC system within 24 hours of occurrence of an event. Serious AESIs must be reported in an expedited manner as SAEs, as outlined above.

Reporting of non-serious AESIs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper report form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

Dose Limiting Toxicities

Each event meeting the criteria of a DLT, as specified in Section 6.6, must be recorded in the CRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs, as outlined above.

Appendix 6 Liver Safety: Suggested Actions and Follow-Up Assessments

If a study participant is noted to have ALT or AST elevated > 3 x ULN (new or worsening of preexisting), the abnormality should be recorded as an AE, regardless if clinical symptoms are present or not. If a study participant is noted to have ALT or AST > 3 times ULN and total bilirubin > 2 ULN for which an alternative etiology has not been identified, the event should be reported as a SAE. The Investigator must contact the Sponsor Medical Responsible for discussion.

Appendix 7 Laboratory Tests

Assessments in Appendix 7 to be performed by the local laboratory.

Serum Chemistry	Hematology	Coagulation
Albumin	Absolute lymphocyte count	Activated partial thromboplastin time
Alkaline phosphatase	Absolute neutrophil count	Prothrombin time/International normalized ratio (Quick, INR)
Alanine aminotransferase	Hematocrit	
Amylase	Hemoglobin	
Aspartate aminotransferase	Platelet count	
Gamma glutamyltransferase	Red blood cell count	
Blood urea nitrogen/total urea	White blood cell count and differential count	
Calcium	Red blood cell morphology	
Chloride	Reticulocytes	
Creatinine[a]	Mean corpuscular hemoglobin	
C-reactive protein	Mean corpuscular volume	
Ferritin	Mean corpuscular hemoglobin concentration	
Glucose		
Lactate dehydrogenase	**Serum quantitative immunoglobulins for IgG, IgA, IgM, IgD,IgE**	**Urine quantitative immunoglobulins for M-protein**
Lipase	Serum M-protein quantitation by electrophoresis (SPEP) every cycle (Part A only)	24-hour urine M-protein quantitation by electrophoresis (UPEP) every cycle (Part A only)
Phosphorus/phosphates		
Magnesium		
Potassium	**Serology (at Screening only)**	**Serum and urine pregnancy test**
Sodium	HBsAg, HBcAb	Serum pregnancy test at Screening
Total bilirubin/indirect bilirubin	HBV DNA (quantitative PCR)	Urine pregnancy test at Follow-Up
Total protein	HCVAb, HCV RNA (quantitative PCR)	
Uric acid	HIV test	

HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HCVAb = Hepatitis C virus antibody; HIV = Human immunodeficiency virus.

Full hematology, serum chemistry and coagulation will be performed at Screening, on every timepoint of SoAs (Table 1 and Table 2 for Part A; Table 3 and Table 4 for Part B) including at the End-of-Treatment and Safety Follow-Up visits.

a Creatinine clearance will be calculated using the Cockcroft-Gault formula.

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Details of liver chemistry stopping criteria and required actions and Follow-Up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 6.	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase specific gravity, protein, blood, and glucose and a basic urinalysis (protein content only) esterase by dipstick • Microscopic examination (if blood or protein is abnormal).

Appendix 8 Pharmacokinetic Parameters

Single Dose Parameters

Symbol	Definition
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
AUC_{0-t} /Dose	The Dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, using the formula AUC_{0-t} /Dose.
$AUC_{0-\infty (Pred)}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, $AUC_{0-\infty}=AUC_{0-t}+C_{last\ obs}/\lambda_z$ Predicted/observed $AUC_{0-\infty}$ should be selected as appropriate.
$AUC_{0-\infty}$ /Dose	The Dose normalized AUC from time zero extrapolated to infinity. Normalized using actual dose, using the formula $AUC_{0-\infty}$ /Dose.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. AUCextra = (extrapolated area/$AUC_{0-\infty}$)*100.
$CL_{/f}$	The apparent total body clearance of study intervention following extravascular administration, taking into account the fraction of dose absorbed. CL/f = Dose $_{p.o.}$ /$AUC_{0-\infty}$. Either the observed or predicted $AUC_{0-\infty}$ should be used, depending on the study specific requirements.
C_{last}	The observed concentration at the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification
C_{max}	Maximum observed concentration
C_{max} /Dose	The Dose normalized maximum concentration. Normalized using the actual dose, and the formula C_{max} /Dose.
C_{min}	The minimum observed concentration during a complete dosing interval
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$
t_{lag}	The time prior to the first measurable (non-zero) concentration (for extravascular input only)
t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)

Symbol	Definition
$V_{Z/f}$	The apparent volume of distribution during the terminal phase following extravascular administration, based on the fraction of dose absorbed. $V_{z/f}$ = Dose/($AUC_{0-\infty}$*λ_z) following single dose. $V_{z/f}$ = Dose/(AUC_τ*λ_z) following multiple dose.
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve

Multiple Dose Parameter of M3258 and Dexamethasone

Symbol	Definition
AUC_τ	The area under the concentration-time curve (AUC) over the dosing interval from T_1=0 h to T_2=τ h. Calculated using the mixed log-linear trapezoidal rule (linear up, log down). For single dose, AUCτ is calculated as a partial area with the defined time range. In multiple dose profiles AUC_τ is calculated at steady state from one predose time point to the dosing interval time. In cases where the actual observation time is not equal to the scheduled observation time AUC_τ will be calculated based on the estimated concentration at τ hours, and not the concentration at the actual observation time.
AUC_τ /Dose	The Dose normalized AUC over the interval from T_1=0 h to T_2=τ h. Normalized using actual dose, using the formula AUC_τ /Dose.
$CL_{SS/f}$	The apparent total body clearance of study intervention at steady state following extravascular administration, taking into account the fraction of dose absorbed. $CL_{ss/f}$ = Dose $_{p.o.}$ / AUC_τ.
C_{max}	Maximum observed concentration
C_{max} /Dose	The dose normalized maximum concentration. Normalized using the actual dose, and the formula C_{max} /Dose.
C_{trough}	The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing)
$R_{acc(AUC\tau)}$	The accumulation factor to assess the increase in exposure until steady state is reached. $R_{acc(AUC\tau)}$= (AUC_τ after multiple dose (at steady state)) / (AUC_τ after single dose)
$R_{acc(Cmax)}$	The accumulation factor to assess the increase in maximum concentration until steady state is reached. $R_{acc(Cmax)}$ = (C_{max} after multiple dose (at steady state))/ (C_{max} after single dose)

Symbol	Definition
$R_{acc(AUC0-\infty)}$	The accumulation factor to assess the increase in exposure via $AUC_{0-\infty}$. $R_{acc(AUC0-\infty)}$= (AUC_{τ} after multiple dose (at steady state)) / ($AUC_{0-\infty}$ after single dose)
$t_{1/2}$	Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve
τ	Dosing interval


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Appendix 10 Description of the Bayesian Dose Escalation Model

The Bayesian model is based on the number of DLTs and evaluable participants per dose level. The SMC will receive results of a Bayesian two-parameter logistic regression model updated with the observed DLT data (Neuenschwander et al. 2008), including a recommendation for the next dose. For a dose level dj, the relationship between dose and probability of toxicity P (DLT) is defined by:

$$P(DLT|d_j,\alpha,\beta) = \frac{exp\left(\alpha+exp(\beta)*log\left(\frac{d_j}{d_{ref}}\right)\right)}{1+exp\left(\alpha+exp(\beta)*log\left(\frac{d_j}{d_{ref}}\right)\right)},$$

with bivariate normally distributed parameters (α, β) using the following parameterization:

- preselected dose level dj ε{10 mg, 20 mg, 35 mg, 50 mg} subject to change by SMC)
- Reference dose dref = 90 mg
- E(α) = -0.708, E(β) = -0.389
- SD(α) = 1.2, SD(β) = 0.9, Cov(α, β) = 0.

The target DLT toxicity is 25%. The following toxicity regions for use in dose suggestion will be defined:

Toxicity Intervals	Probability of DLT	Loss term (weight in loss function)
Under-Dosing	[0.0, 0.20]	1
Targeted toxicity	(0.20, 0.35]	0
Excessive toxicity	(0.35, 0.60]	2
Unacceptable toxicity	(0.60, 1.00]	3

Recommendation on the next dose level by the model is determined as follows:

- Select the dose level that minimizes the loss function. The loss function is defined as the sum of products of the probability to lie within each of the toxicity regions, and the associated loss term:

1 × P (under-dosing) + 0 × P (targeted toxicity) + 2 × P (excessive toxicity) +

3 × P (unacceptable toxicity).

The model will be provided with the following preselected dose levels: 10 mg, 20 mg, 35 mg and 50 mg. The set of doses can be changed any time by the SMC.

The SMC will be notified of a potential candidate dose for MTD once

- the upper bound of the 95% credible interval of a potential MTD is not more than 40% and the estimated DLT probability for the suggested MTD is above or equal to 17%.

In case information arises from other studies that changes current knowledge on the dose toxicity relationship, the prior distribution can be updated prior to the first participant being treated in this study. If a change in regimen occurs, a separate model will be set up for each regimen. Any change in prior and the priors for changed regimens will be documented in the SMC charter.

Decisions of the SMC in the expansion cohort will also be aided by a Bayesian two-parameter logistic regression model with the same specifications as for the dose escalation, except the prior. The prior will be based on the data seen in the dose escalation and be specified in the SMC charter. The model will be updated at times of SMCs in the expansion cohort.

Posterior distribution and the recommended next dose level suggested by the model will be calculated using EAST version 6.4 or higher/ R version 3.4.2 or higher with library package bcrm (Sweeting et al, 2013) or package CRMpack or SAS version 9.4 (or higher) proc MCMC.

Appendix 11 Protocol Amendment History

Protocol Version 3.0 (12-Sep-2019)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Revision of the original protocol is to include changes requested by ANSM. Changes to the protocol; the rationale for the changes are listed in the table below.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Tables 1 and 2	Inclusion of monthly pregnancy tests after Cycle 6.	Request by regulatory agency in order to allow for early detection while a participant is receiving study intervention.
	Expansion of chest X-ray examination to exclude not only infection but also interstitial pneumonitis and lung infection.	Request by regulatory agency because of mechanism of action between pan-proteasome inhibitors and M3258.
	Addition of a -3-day window for assessment for MRD in bone marrow, disease staging in bone marrow, and skeletal survey at screening.	Clarification
	Additional guidance added for evaluation of osteolytic lesions and extramedullary disease for the MRI or CT scan assessments.	Clarification
6.6 Dose Selection and Modification	Description of Grade ≥3 febrile neutropenia changed to Grade ≥ 3 febrile neutropenia with ANC <1000/mm^3 and a single temperature of >38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 h.	Clarification. Revised description of Grade ≥3 febrile neutropenia to align with CTCAE v5.0
	Expanded the guidance on dexamethasone dose adjustments, Added table.	Request by regulatory agency to provide a general guidance on dexamethasone dose reduction and to clarify on sequence of dose reduction of dexamethasone versus M3258 upon observation of overlapping toxicities.
6.9.1. Monitoring and Management of Other Toxicities (e.g., Over-Arching Toxicities in Part B)	Expanded the guidance on dexamethasone dose adjustments.	Request by regulatory agency to give general guidance dose reduction of dexamethasone and to clarify on sequence of dose reduction of dexamethasone vs M3258 when overlapping toxicities of these compounds occur.
8.9.1 Efficacy Assessments and Procedures	Additional guidance added for evaluation of osteolytic lesions and extramedullary disease for the MRI or CT scan assessments.	Clarification.

8.2.4 Chest X-Ray at Pretreatment	New section added to describe and provide rationale for chest X-ray at screening as baseline to exclude infection and other acute pulmonary abnormalities.	Considering the request from the regulatory agency, the role and relevance of the chest X-ray at pretreatment and information for the investigator regarding the potential occurrence of pulmonary toxicity is included.
8.2.5 Clinical Safety Laboratory Assessments	Adjusted wording to allow for monthly pregnancy testing.	Request by regulatory agency in order to allow for early detection of pregnancy while a participant is receiving study intervention.

Protocol Version 2.0 (01-Jul-2019)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Revision of the original protocol is mainly to include changes requested by US FDA. Major changes to the protocol and the rationale for the changes are listed in the table below.

Section Number and Name	Description of Change	Brief Rationale
Multiple sections	Dexamethasone was removed from the dosing regimen in Part A Dose Escalation.	At the request of US FDA, participants in the dose-escalation phase will receive M3258 monotherapy.
Multiple sections	A safety run-in for the combination of M3258 and dexamethasone was added to Part B Dose Expansion.	Because the combination with dexamethasone was removed from Part A, a safety run-in with the combination with dexamethasone was added to Part B.
Multiple sections	Addition of stopping rules for Part B and definition of unacceptable toxicity for Part B.	At the request of US FDA.
Multiple sections	Details added of the meeting schedule for the Safety Monitoring Committee (SMC) in Part B.	With the addition of the safety run-in, clarification of the SMC schedule was necessary.
Multiple sections	In order to dose in Part A above 50mg M3258 QD, a protocol amendment must be submitted.	At the request of US FDA.
Multiple sections	Interim analysis for Part B was adapted to changes in study design and described with more detail.	To accommodate the changes requested in Parts A and B.
Multiple sections	Pharmacokinetic analysis adjusted in Parts A and B to accommodate the change in dosing regimens in Parts A and B and inclusion of the Part B safety run-in.	To accommodate the changes requested in Parts A and B.
Multiple sections	The approximate number of participants in Parts A and B and guidance for enrolling was adjusted to accommodate the change in study design.	To accommodate the changes requested in Parts A and B.
Multiple sections	The targeted DLT rate for defining the MTD was changed from 30% to 25%.	At the request of US FDA.
Multiple sections	The food-effect assessment will be conducted during Part B Day 1 Cycle 2, rather than Day 1 Cycle 1 in order to accommodate the change in dosing regimen in the study.	To accommodate the requested change in Part B.

1.1 Synopsis, Objectives and Endpoints, Study Objectives and Endpoints – Dose Escalation – Part A 3 Objectives and Endpoints, Table 5 Study Objectives and Endpoint - Dose Escalation – Part A	"tolerability and PK" added to Part A secondary objective to investigate the recommended dose for expansion.	Reflects the change in study design and clarification of endpoints to objectives.
1.1 Synopsis, Objectives and Endpoints, Study Objectives and Endpoints – Dose Expansion – Part B 3 Objectives and Endpoints, Table 6 Study Objectives and Endpoint - Dose Expansion – Part B	Primary safety objective added (originally a secondary objective) with the addition of safety endpoints.	Reflects start of combination with dexamethasone in expansion cohort where safety of combination becomes a primary objective.
	Primary objective and corresponding endpoints added to determine the recommended Phase II dose of M3258 when co-administered with dexamethasone.	Reflects the change in study design for Part B.
	Endpoint for determining overall response, duration of response, and time to response added for secondary efficacy objective	Clarification of endpoints to objective.
	Revised secondary PK objective for Part B.	Reflects the change in study design.
3 Objectives and Endpoints, Table 5 Study Objectives and Endpoints – Dose escalation – Part A, Exploratory	Added an objective and endpoint for investigating the genetic variations that may affect M3258 as a single agent.	Added in order to assess genetic variations that affect drug metabolism and drug transport of M3258 and other potential genes that may account for differences in the PK profile.
3 Objectives and Endpoints, Table 6 Study Objectives and Endpoint - Dose Expansion – Part B, Exploratory	Added PK objective (and endpoints) in order to evaluation further PK parameters in addition to those investigated in the secondary objective.	Added to allow for a more complete PK profile of M3258 when administered with dexamethasone.
	Clarified the endpoint for the QTc exploratory objective	Reflects the change in study design.
	Added an objective (and endpoints) for the investigation of the PK profile for dexamethasone when given with M3258.	Reflects the change in study design: Dexamethasone PK evaluated in expansion phase.
	Added an objective (and endpoint) to explore L-citrulline as an exploratory biomarker	Added to investigate L-citrulline correlation with early clinical signs of gastrointestinal toxicity.
5.1 Inclusion Criterion 7	Deletion of serum creatinine ≤ 1.5 x ULN.	Requested by US FDA.
	Deletion that creatinine clearance could be calculated using the 24-hour urine collection.	Clarification that only serum creatinine would be used to calculate creatinine clearance.

5.2 Exclusion Criterion 12	Added exclusion for current significant cardiac conduction abnormalities.	Requested by US FDA.
5.2 Exclusion Criteria 16 and 17	Strengthened the restrictions concerning herbal supplements, CYP3A inhibitors and inducers, and P-gp inhibitors.	Requested by US FDA.
5.2 Exclusion Criterion 18	Added exclusion for medications known to prolong the QT/QTc interval.	Requested by US FDA.
5.3.1 Meals and Dietary Restrictions	Additional dietary restrictions for CYP3A inhibitors and inducers added.	Requested by US FDA.
6.5.3 Prohibited Medicines	Revised to indicate that both strong inhibitors and inducers of CYP3A must be stopped at least 7 days before initiation of study intervention.	Requested by US FDA.
	Addition that herbal supplements that are known to inhibit or induce CYP3A are prohibited.	Requested by US FDA.
	Addition that all P-gp inhibitors are prohibited at least 7 days before the first administration of the study intervention and throughout the study.	Requested by US FDA.
	Addition that medications known to prolong the QT/QTc interval are prohibited at least 7 days before the first administration of the study intervention and throughout the study.	Requested by US FDA.
6.6 Dose Selection and Modification	Hy's Law was added to the list of AEs judged as DLTs.	Requested by US FDA.
Appendix 4: Prohibited Comedication Prolonging the QT/QTc Interval	Added appendix which lists and gives reference for medications known to prolong the QT/QTc interval.	Requested by US FDA.

Appendix 12 Sponsor Signature Page

Study Title:	A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma
Regulatory Agency Identifying Numbers:	IND CCI [redacted] EudraCT 2019-000947-28
Clinical Study Protocol Version:	11 May 2020/Version 4.0

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD [redacted]
Function/Title:	Medical Responsible
Institution:	Merck Healthcare KGaA
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
Telephone number:	PPD [redacted]
Fax number:	PPD [redacted]
E-mail address:	PPD [redacted]

Appendix 13 Coordinating Investigator Signature Page

Study Title:	A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma
Regulatory Agency Identifying Numbers:	IND CCI EudraCT 2019-000947-28
Clinical Study Protocol Version:	11 May 2020/Version 4.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

Signature _____ Date of Signature _____

Name, academic degree:	PPD
Function/Title:	Coordinating Investigator
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix 14 Principal Investigator Signature Page

Study Title:	A Phase I Open Label First in Human Dose Escalation of the Immunoproteasome Inhibitor M3258 as a Single Agent and Expansion Study of M3258 in Combination with Dexamethasone in Participants with Relapsed Refractory Multiple Myeloma
Regulatory Agency Identifying Numbers:	IND [redacted] EudraCT 2019-000947-28
Clinical Study Protocol Version:	11 May 2020/Version 4.0
Site Number:	

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: