Title: An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 With Cyclophosphamide and Dexamethasone In Patients With Newly Diagnosed or Relapsed and/or Refractory Multiple Myeloma Requiring Systemic Treatment

NCT Number: NCT02046070

Protocol Approve Date: 6 May 2014

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

CLINICAL STUDY PROTOCOL C16020 AMENDMENT 1

MLN9708

An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 With Cyclophosphamide and Dexamethasone In Patients With Newly Diagnosed or Relapsed and/or Refractory Multiple Myeloma Requiring Systemic Treatment

Protocol Number:	C16020
Indication:	Newly Diagnosed or Relapsed and/or Refractory Multiple Myeloma
Phase:	2
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2013-003113-17
Therapeutic Area:	Oncology

Protocol History

Original	23 July 2013
Amendment 1	6 May 2014

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Approved by:

Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

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[redacted], Clinical Research (or designee) Signature *Date DD Month YYYY*

[redacted], MD
[redacted] Signature *Date DD Month YYYY*
(or designee)

Rationale for Amendment 1

The protocol is being amended to allow for the enrollment of patients with relapsed and/or refractory multiple myeloma (RRMM) into the study and the evaluation of oral MLN9708 when added to a regimen of cyclophosphamide and low-dose dexamethasone (Cd) in this patient population. Consequently, study objectives and endpoints are added and study procedures described for this patient population. The amendment also contains minor updates in study procedures to improve protocol clarity and compliance and align the study conduct with the sponsor's current guidelines and practices.

Purposes for Amendment 1

The purposes of this amendment are to:

- Revise the protocol title to reflect the added population of patients with RRMM
- Revise the Study Overview Diagram to include the patient population with RRMM
- Clarify the description of VELCADE/cyclophosphamide/dexamethasone (VCD) as a therapeutic option for frontline treatment of patients with multiple myeloma
- Update the details of the clinical experience with MLN9708
- Add a brief description of treatment options and prognosis for patients with RRMM
- Provide a rationale for adding patients with RRMM to the study
- Revise the description of the study purpose to include patients with RRMM
- Add the RRMM population to the discussion of the rationale for the combination therapy under evaluation in the study
- Add the RRMM population to the discussion of dose intensity schedules for cyclophosphamide
- Add the primary study objective for patients with RRMM and delineate the primary objective for the 2 patient populations
- Add the secondary study objectives for patients with RRMM and delineate the secondary objectives for the 2 patient populations
- Remove the European Organization for Research and Treatment of Cancer (EORTC) Multiple Myeloma Module (MY-20) from the assessments to determine changes in global health status
- Describe the tertiary/exploratory objectives for the 2 patient populations and add an additional tertiary objective of health care utilization assessments
- Align the primary, secondary, and tertiary study endpoints with the primary, secondary, and tertiary study objectives
- Clarify the study design for patients with newly diagnosed multiple myeloma (NDMM) and describe the study design for patients with RRMM
- Revise the anticipated number of enrolled patients and investigative sites
- Revise the description for anticipated duration of study and timing of the clinical study report
- Add patients with RRMM to the description of the study population and clarify the

inclusion criteria for the 2 patient populations

- Describe the inclusion criteria that pertain to both patient populations (NDMM and RRMM)
- Add the pregnancy prevention guidelines for cyclophosphamide and dexamethasone
- Clarify the exclusion criteria for the 2 patient populations
- Revise and update the guidelines for study drug administration
- Describe and clarify the MLN9708 administration guidelines for the 2 patient populations
- Describe and clarify the cyclophosphamide administration guidelines for the 2 patient populations
- Describe and clarify the dexamethasone administration guidelines for the 2 patient populations
- Clarify the study enrollment guidelines for the 3 treatment arms
- Describe and/or clarify the dose modification guidelines for the 3 treatment arms
- Clarify the permitted medications and procedures for patients in the 3 treatment arms
- Revise and update the subheading pertaining to infection and add transverse myelitis to the discussion of clinical events for MLN9708
- Revise the description of capsule sizes and capsule colors for MLN9708 to align with the certificate of analysis provided by the manufacturer
- Clarify MLN9708 preparation, reconstitution, and dispensation guidelines
- Clarify the storage, handling, and accountability requirements for MLN9708
- Clarify and/or define treatment assignments for the 3 treatment arms
- Clarify timing for performing study procedures
- Clarify that assessment of comorbid conditions pertains to patients with NDMM only (Arms A and B)
- Clarify the guidelines for monitoring of peripheral neuropathy (PN) and PN-related events for the 2 patient populations
- Revise the definition of enrollment in the study for the 3 treatment arms
- Clarify the guidelines for clinical laboratory evaluations
- Clarify the procedure for performing the skeletal survey at screening
- Clarify that the blood sample for genotyping is optional and not required for study enrollment
- Revise and clarify disease response assessments for the 3 treatment arms
- Add description of health care utilization assessments
- Clarify follow-up assessments for progression-free survival and serious adverse event (SAE) reporting during follow-up
- Describe and/or clarify the statistical considerations to determine sample size for the 2 patient populations (NDMM and RRMM)
- Revise and clarify the randomization or enrollment process for the 3 treatment arms

- Revise the description of analysis populations
- Revise the proposed pooling of the study data and presentation of study results for the 3 treatment arms
- Add text to clearly delineate the primary efficacy endpoint for the 2 patient populations
- Revise and update the description of secondary study endpoints
- Describe the analysis of health care utilization data
- Revise and update the description of safety analysis
- Revise the description of assessments pertaining to drug exposure
- Revise and update stopping rules for patients in the 3 treatment arms
- Update the SAE Reporting contact information to align with the sponsor's current guidelines and practices
- Revise and update the reporting guidelines for new malignancies
- Add a Schedule of Events for patients enrolled in Arm C (patients with RRMM)
- Revise and update footnotes in the Schedule of Events to clarify study procedures
- Add health care utilization assessments to the Schedule of Events (NDMM)
- Revise table title for the PK sampling schedule to include all 3 treatment arms
- Revise and update the timing of predose PK assessments
- Correct typographical errors, punctuation, grammar, and formatting

For specific examples of changes in text and where the changes are located, see Section 14.8.

PROTOCOL SUMMARY

Study Title: An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 With Cyclophosphamide and Dexamethasone In Patients With Newly Diagnosed or Relapsed and/or Refractory Multiple Myeloma Requiring Systemic Treatment

Number of Patients: It is anticipated that approximately 148 patients, 70 patients with newly diagnosed multiple myeloma (NDMM) and 78 patients with relapsed and/or refractory multiple myeloma (RRMM), will be enrolled in the study.

Study Objectives

Primary:
For Patients With Newly Diagnosed Multiple Myeloma (NDMM)

- To determine the combined response rate of complete response (CR) (including stringent CR [sCR]) + very good partial response (VGPR) following treatment with oral MLN9708 when added to a regimen of cyclophosphamide and low-dose dexamethasone (Cd) during the induction phase.

For Patients With Relapsed and/or Refractory Multiple Myeloma (RRMM)

- To determine overall response rate (ORR) following treatment with oral MLN9708 when added to a regimen of Cd.

Secondary:
For Patients With NDMM

- To evaluate the tolerability and toxicity of the combination of oral MLN9708 and Cd
- To characterize the pharmacokinetics (PK) in plasma of oral MLN9708 in combination with Cd
- To determine overall response rate (ORR) (CR + VGPR + PR), CR, VGPR, and PR during the induction phase and the ORR (CR + VGPR + PR), CR + VGPR, CR, VGPR, and PR throughout the entire treatment period
- To determine time to response for patients who respond during the induction phase
- To determine duration of response (DOR) for patients who respond during the induction phase
- To determine time to progression (TTP)
- To evaluate progression-free survival (PFS)
- To describe the safety, tolerability, and efficacy of MLN9708 as maintenance therapy in patients who continue treatment beyond 13 cycles of induction therapy
- To assess change in global health status, as measured by the patient-reported outcome (PRO) instruments European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30).

For Patients With RRMM

- To evaluate the tolerability and toxicity of the combination of oral MLN9708 and Cd

- To characterize the PK in plasma of oral MLN9708 in combination with Cd
- To determine CR + VGPR, CR, VGPR, and PR
- To determine time to response for patients who respond
- To determine DOR for patients who respond with a best response of a CR, VGPR or PR
- To determine TTP
- To evaluate PFS
- To assess change in global health status, as measured by the PRO instruments, EORTC QLQ-C30.

Exploratory:
For Patients With NDMM and Patients with RRMM**:**

- [redacted]
- [redacted]

Overview of Study Design: This is a phase 2 study in patients with NDMM who have not received prior systemic treatment for multiple myeloma (MM) and are ineligible for high-dose therapy (HDT)-stem cell transplantation (SCT) due to age or comorbid disease(s), and in patients with RRMM who have received 1 to 3 lines of prior therapy and whose disease is not refractory to proteasome inhibitors.

Patients With NDMM (Arms A and B):

In patients with NDMM, MLN9708 in combination with Cd will be explored as induction therapy for approximately 1 year (13 × 28-day cycles). Eligible patients will be randomized 1:1 to either Arm A or Arm B.

The safety and efficacy of a weekly planned dose of MLN9708 (4.0 mg) administered orally on Days 1, 8, and 15 in combination with cyclophosphamide (300 mg/m^2 [Arm A] OR 400 mg/m^2 [Arm B] both on Days 1, 8, and 15) and dexamethasone (40 mg on Days 1, 8, 15, and 22; 20 mg for patients > 75 years of age) of a 28-day cycle will be evaluated.

The study will begin with a safety lead-in evaluation performed after at least 6 patients from each arm have had the opportunity to complete at least 1 cycle of therapy. Dose-limiting toxicities (DLTs) observed in the first 6 patients from each treatment arm will be used to determine the safety

and overall tolerability of the regimen and the feasibility of continued recruitment to the study.

At the end of the induction phase, patients who have at least stable disease with an acceptable toxicity profile will continue treatment in the maintenance therapy phase of the study. Patients will be administered single-agent MLN9708 only (at the dose tolerated at the end of induction) on Days 1, 8, and 15 of 28-day cycles as maintenance until disease progression, death or unacceptable toxicity.

Patients With RRMM (Arm C)

The safety and efficacy of MLN9708 in combination with Cd will also be explored in patients with RRMM. Eligible patients with relapsed and/or refractory disease will be enrolled in Arm C. Enrolled patients will receive a weekly planned dose of MLN9708 4.0 mg on Days 1, 8, and 15 administered orally in combination with cyclophosphamide 300 mg/m^2 on Days 1, 8, and 15 and dexamethasone (40 mg on Days 1, 8, 15, and 22; 20 mg for patients > 75 years of age) of a 28-day cycle. Patients with an acceptable toxicity profile will continue treatment until they experience disease progression, death or unacceptable toxicity.

A safety lead-in evaluation will be performed after at least 6 patients with RRMM have had the opportunity to complete at least 1 cycle of therapy. DLTs observed in the first 6 patients in this treatment arm will be used to determine the safety and overall tolerability of the study regimen and the feasibility of continued recruitment of patients to Arm C.

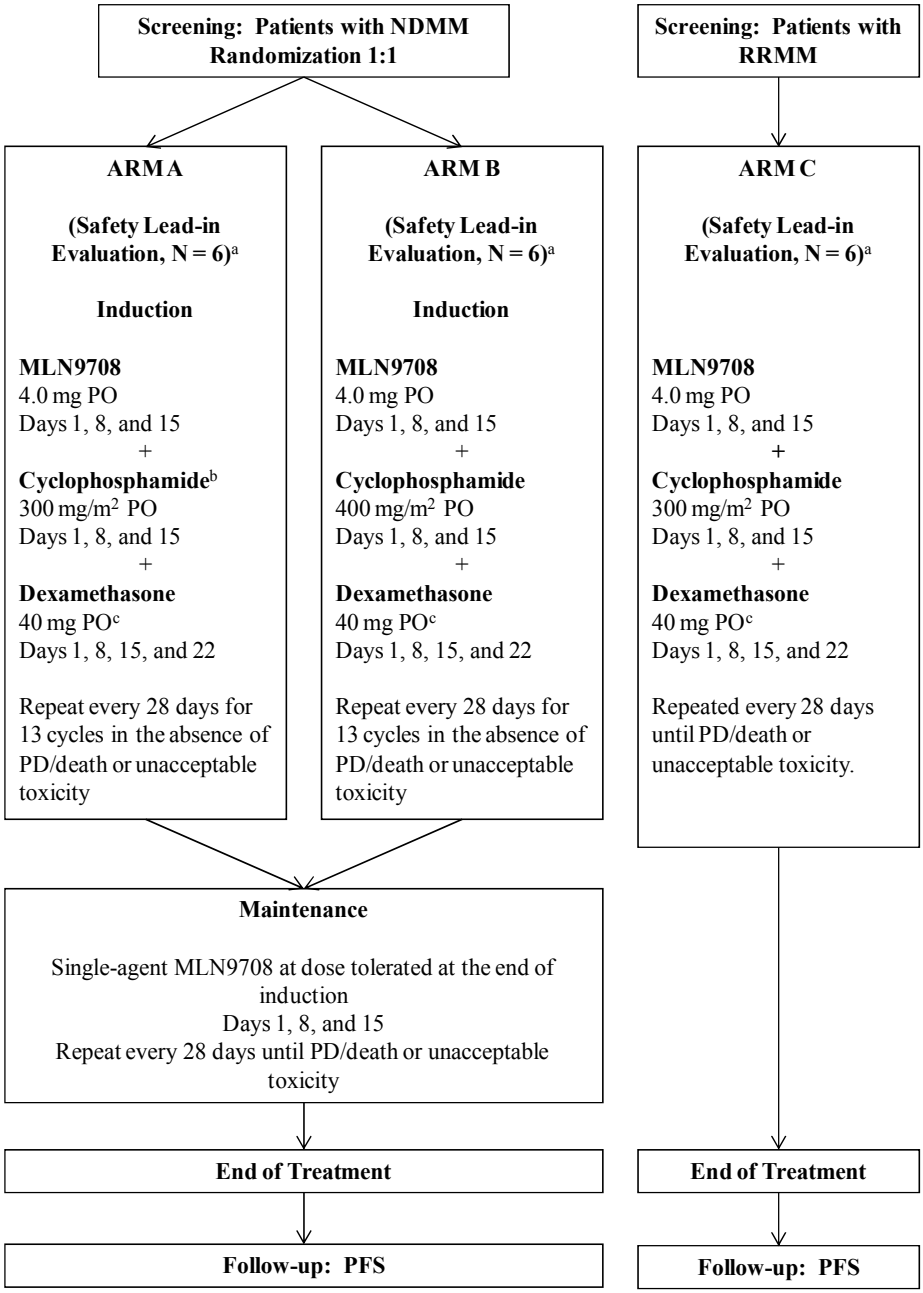
Study Population:
Patients With NDMM (Arms A and B)
Adult patients with a confirmed diagnosis of symptomatic MM who have received no prior antimyeloma treatment and who are not candidates for HDT-SCT due to age (≥ 65 years) or comorbidities.

Patients With RRMM (Arm C)
Adult patients with a confirmed diagnosis of symptomatic MM and relapsed and/or refractory disease (RRMM) after 1 to 3 lines of prior therapy and whose disease is not refractory to proteasome inhibitors.

All enrolled patients must have an Eastern Cooperative Oncology Group (ECOG) status of 0 to 2 and adequate renal, hepatic, cardiac, and hematological function/status. Patients with Grade 1 peripheral neuropathy (PN) with pain or Grade 2 or higher PN of any cause on clinical examination will be excluded.

Duration of Study: It is anticipated that the total duration of the study will be approximately 60 months. This includes approximately 24 months of enrollment and up to 36 months of treatment and/or PFS follow-up.

STUDY OVERVIEW DIAGRAM



Abbreviations: NDMM = newly diagnosed multiple myeloma; PD = progressive disease; PFS = progression-free survival; PO = orally; RRMM = relapsed and/or refractory multiple myeloma.

a The safety evaluation will be performed after at least 6 patients in each arm have had the opportunity to complete Cycle 1 of therapy.

b Intrapatient dose escalation is not planned; however, it may be considered for Arm A depending on the safety profile and efficacy observed for Arm B during induction.

c Patients over 75 years of age at the time of enrollment will receive a reduced dexamethasone dose of 20 mg.

SCHEDULE OF EVENTS: ARMS A AND B (NDMM)

SCHEDULE OF EVENTS: ARMS A and B (NDMM)									
		Treatment Period (28-Day Cycles)							
		INDUCTION[b] CYCLES 1-13				MAINTENANCE[b] CYCLE 14 and BEYOND			
Study Procedures	**Screening[a]**	**Day 1[c]**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Cycles 14, 15 Only Days 8, 15, 22**	**End of Treatment[d]**	**PFS Follow-up[e] Every 8 Weeks**
Window	**-28 to -1**							**± 1 Week**	**± 1 Week**
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics	X								
Complete Medical History and Disease Staging	X								
Assessment of Comorbid Condition(s)	X								
Physical Exam[f]	X							X	
Symptom-directed Physical Exam		X				X			
Neurologic Assessment[g]	X	X				X		X	X
ECOG Performance Status	X	X				X		X	
Vital Signs	X	X				X		X	
Height (cm)	X								
Weight (kg), BSA[h]	X	X[h]				X		X	
Serum Pregnancy Test[i]	X	X						X	
12-Lead ECG[j]	X	X[j]						X[j]	
Hematology[k,l]	X					X[k]	X	X	

SCHEDULE OF EVENTS: ARMS A and B (NDMM)

Study Procedures	Screening[a]	Treatment Period (28-Day Cycles)						End of Treatment[d]	PFS Follow-up[e]
		INDUCTION[b] CYCLES 1-13				MAINTENANCE[b] CYCLE 14 and BEYOND			
		Day 1[c]	Day 8	Day 15	Day 22	Day 1	Cycles 14, 15 Only Days 8, 15, 22		Every 8 Weeks
Window	**-28 to -1**							**± 1 Week**	**± 1 Week**
Cycles 1-3		X[k]	X	X	X				
Cycles 4-13		X[k]		X[k]					
Clinical Chemistry[k]	X					X[k]		X	
Cycles 1-3		X[k]	X	X	X				
Cycles 4-13		X[k]							
Urinalysis[m]	X	X[m]							
QOL Assessments[n] (EORTC QLQ-C30)	X	X				X		X	X
Health Care Utilization Assessment[n]		X				X		X	X
Skeletal Survey	X	Once annually for all patients and at the discretion of the investigator[n]							
Radiographic Disease Assessment for Extramedullary Plasmacytoma	X	X[p]				X[p]		X	X
β_2-microglobulin	X								
M-protein Measurements (SPEP)[q]	X	X				X		X	X
M-protein Measurements (UPEP [24-hr Urine Collection])[q]	X	X				X		X	X
Serum Free Light Chain Assay[q]	X	X				X		X	X
Immunofixation - Serum and Urine[q]	X	X				X		X	X
Quantification of Ig[q]	X	X				X		X	X
[redacted]									

SCHEDULE OF EVENTS: ARMS A and B (NDMM)

Study Procedures	Screening[a]	Treatment Period (28-Day Cycles)						End of Treatment[d]	PFS Follow-up[e]
		INDUCTION[b] CYCLES 1-13				MAINTENANCE[b] CYCLE 14 and BEYOND			
		Day 1[c]	Day 8	Day 15	Day 22	Day 1	Cycles 14, 15 Only Days 8, 15, 22		Every 8 Weeks
Window	**-28 to -1**							**± 1 Week**	**± 1 Week**
[redacted]									
Skeletal-related Events	Recorded from the first dose of drug in the study drug regimen until progressive disease								
New Primary Malignancy Assessment	Continuous from the start of study drug regimen until death or termination of the study by the sponsor								
AE Reporting[e]	Recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen								
	Serious adverse events and serious pretreatment events will be collected from signing of the informed consent form through 30 days after the last dose of drug in the study drug regimen								
Concomitant Medications/Procedures	Recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen								

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BSA = body surface area; C1D1 = Cycle 1, Day 1; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMD = extramedullary disease; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; Ig = immunoglobulin; MM = multiple myeloma; MRD = minimal residual disease; MRI = magnetic resonance imaging; OS = overall survival; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PN = peripheral neuropathy; PR = partial response; QLQ-C30 = Quality of Life Questionnaire; QOL = quality of life; SAE = serious adverse event; SPEP = serum protein electrophoresis; TEAE = treatment-emergent adverse event; UPEP = urine protein electrophoresis; VGPR = very good partial response.

Tests and procedures should be performed on schedule, but occasional changes may be allowed (± 3 days) for holidays, vacations, and other administrative reasons. If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessments is completed prior to dosing. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the Millennium project clinician or designee.

a Evaluations during the Screening period are to be conducted within 28 days before randomization, unless otherwise noted. The date of randomization or enrollment should be within 7 days of Cycle 1, Day 1 (C1D1).

b During induction and maintenance, there will be a ± 3-day window for study visits unless otherwise noted.

SCHEDULE OF EVENTS: ARMS A and B (NDMM)									
		Treatment Period (28-Day Cycles)							
		INDUCTION[b] CYCLES 1-13				MAINTENANCE[b] CYCLE 14 and BEYOND		End of Treatment[d]	PFS Follow-up[e]
Study Procedures	**Screening[a]**	**Day 1[c]**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Cycles 14, 15 Only Days 8, 15, 22**		**Every 8 Weeks**
Window	**-28 to -1**							**± 1 Week**	**± 1 Week**

c Cycle 1, Day 1 is baseline. All baseline evaluations/procedures are to be conducted at C1D1 before dosing or within 3 days before the first dose of drug unless otherwise specified.

d Patients who do not continue the study drug regimen must complete the end-of-treatment (EOT) visit, which should occur within 30 days (± 1 week) after the last dose of study drug or before the start of subsequent antineoplastic therapy.

e [redacted]

f The symptom-directed physical exam may be performed at other visits during the treatment cycle at the discretion of the investigator.

g To assess both MM-related symptoms and TEAEs.

h Body surface area (BSA) will be calculated at C1D1 and at any subsequent visit that the patient experiences a > 5% change in weight from the weight used for the most recent BSA calculation.

i A serum pregnancy test will be performed for women of childbearing potential during screening, predose on C1D1, and at EOT. The serum pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the study drug regimen is administered.

j A 12-lead ECG will occur at screening, C1D1, C5D1, C9D1, C13D1, and EOT.

k Clinical laboratory evaluations will be performed locally and centrally as indicated in Section 7.4.13. Labs should be collected prior to dosing. During induction, hematology should occur weekly on Days 1, 8, 15, and 22 for Cycles 1 through 3 and on Days 1 and 15 for Cycles 4 through 13. During Maintenance, hematology should occur weekly on Days 1, 8, 15, and 22 for Cycles 14 and 15, and on Day 1 of each cycle thereafter until EOT. During induction, chemistry should occur weekly on Days 1, 8, 15, and 22 for Cycles 1 through 3 and on Day 1 for Cycles 4 through 13. During Maintenance, chemistry should occur on Day 1 of every other cycle starting with Cycle 14 until EOT. Hematology and chemistry may be collected up to 3 days prior to MLN9708 dosing. Criteria for retreatment are provided in Section 6.3.1. Hematology is also to be collected upon occurrence of an adverse event (AE) or serious adverse event (SAE), suggestive of renal toxicity. For dosing decisions, local hematology and chemistry laboratory results may be used.

l For patients in Arm A, if intrapatient dose escalation of cyclophosphamide occurs, hematology labs will be obtained weekly for the first 3 cycles following the escalation.

m A urinalysis is to be done predose on Day 1 of each cycle during induction for all patients. Urinalysis is also to be done upon occurrence of an AE (or

SCHEDULE OF EVENTS: ARMS A and B (NDMM)									
		Treatment Period (28-Day Cycles)							
		INDUCTION[b] CYCLES 1-13				MAINTENANCE[b] CYCLE 14 and BEYOND		End of Treatment[d]	PFS Follow-up[e]
Study Procedures	Screening[a]	Day 1[c]	Day 8	Day 15	Day 22	Day 1	Cycles 14, 15 Only Days 8, 15, 22		Every 8 Weeks
Window	**-28 to -1**							**± 1 Week**	**± 1 Week**

SAE) suggestive of renal toxicity.

n Patient-reported outcomes assessments and health care utilization assessments should be completed before any other study procedures are performed and before the study drug regimen is administered.

o To be performed at screening (within 8 weeks prior to randomization), once annually, and if at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions. Plain films of symptomatic sites for signs or symptoms of new bone lesions may be obtained instead of a full skeletal survey. At the discretion of the investigator and where regionally permitted, a computed tomography (CT) scan, a positron emission tomography computed tomography (PET-CT) scan, or a whole body magnetic resonance imaging (MRI) may be done at screening in place of a skeletal survey, provided that the same modality for assessment is used throughout the study.

p For those with documented extramedullary disease, radiographic assessments should be made at screening, at every other cycle during induction and maintenance starting at Cycle 2, Day 1, at EOT, and every 8 weeks during progression-free follow-up. The same imaging modality used at screening (CT/PET-CT/MRI) should be used for all follow-up assessments.

q To be performed prior to dosing during induction, every other cycle during maintenance starting with Cycle 14, at EOT, and during PFS follow-up. Note: The collection of these samples is required to be repeated at C1D1 only if the collection during screening was done > 14 days before the first dose of the study drug regimen. Serum-only patients will have 24-hour urine collected for UPEP and urine immunofixation at screening, noted complete response (CR) or progressive disease (PD), and at EOT. All other patients should have the M component quantification by UPEP and urine immunofixation performed prior to dosing in every cycle in induction and every other cycle during maintenance starting with Cycle 14, at EOT, and during PFS follow-up.

r [redacted]

s [redacted].

STUDY DRUG REGIMEN ADMINISTRATION: ARMS A AND B (NDMM)

		INDUCTION				MAINTENANCE			
		CYCLES 1-13				CYCLE 14 and BEYOND			
Study Drug	**Route**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**
MLN9708	PO	X	X	X		X	X	X	
Cyclophosphamide	PO	X	X	X					
Dexamethasone	PO	X	X	X	X				

Abbreviations: NDMM = newly diagnosed multiple myeloma; PO = per os (by mouth; orally).

SCHEDULE OF EVENTS: ARM C (RRMM)

SCHEDULE OF EVENTS: ARM C (RRMM)							
		Treatment Period[b] (28-Day Cycles)					
		CYCLE 1 and BEYOND					
Study Procedures	**Screening[a]**	**Day 1[c]**	**Day 8**	**Day 15**	**Day 22**	**End of Treatment[d]**	**PFS Follow-up[e] Every 8 Weeks**
Window	**-28 to -1**					**± 1 Week**	**± 1 Week**
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Demographics	X						
Complete Medical History and Disease Staging	X						
Physical Exam[f]	X					X	
Symptom-directed Physical Exam		X					
Neurologic Assessment[g]	X	X				X	X
ECOG Performance Status	X	X				X	
Vital Signs	X	X				X	
Height (cm)	X						
Weight (kg), BSA[h]	X	X[h]				X	
Serum Pregnancy Test[i]	X	X				X	
12-Lead ECG[j]	X	X[j]				X[j]	

SCHEDULE OF EVENTS: ARM C (RRMM)							
		Treatment Period[b] (28-Day Cycles)					
		CYCLE 1 and BEYOND					
Study Procedures	**Screening[a]**	**Day 1[c]**	**Day 8**	**Day 15**	**Day 22**	**End of Treatment[d]**	**PFS Follow-up[e] Every 8 Weeks**
Window	**-28 to -1**					**± 1 Week**	**± 1 Week**
Hematology[k]	X					X	
Cycles 1-3		X[k]	X	X	X		
Cycle 4 and beyond		X[k]		X[k]			
Clinical Chemistry[j]	X					X	
Cycles 1-3		X[k]	X	X	X		
Cycle 4 and beyond		X[k]					
Urinalysis[l]	X	X[l]					
QOL Assessments[m] (EORTC QLQ-C30)	X	X				X	X
Health Care Utilization Assessment[m]		X				X	X
Skeletal Survey	X	Once annually for all patients and at the discretion of the investigator[n]					
Radiographic Disease Assessment for Extramedullary Plasmacytoma	X	X[o]				X	X
β_2-microglobulin	X						
M-protein Measurements (SPEP)[p]	X	X				X	X
M-protein Measurements (UPEP [24-hr Urine Collection])[p]	X	X				X	X
Serum Free Light Chain Assay[p]	X	X				X	X
Immunofixation - Serum and Urine[p]	X	X				X	X

SCHEDULE OF EVENTS: ARM C (RRMM)

Study Procedures	Screening[a]	Treatment Period[b] (28-Day Cycles) CYCLE 1 and BEYOND Day 1[c]	Day 8	Day 15	Day 22	End of Treatment[d]	PFS Follow-up[e] Every 8 Weeks
Window	**-28 to -1**					**± 1 Week**	**± 1 Week**
Quantification of Ig[p]	X	X				X	X
[redacted]							
Blood Sample for Genotyping	X						
Skeletal-related Events	Recorded from the first dose of drug in the study drug regimen until progressive disease						
New Primary Malignancy Assessment	Continuous from the start of study drug regimen until death or termination of the study by the sponsor						
AE Reporting[e]	Recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen						
	Serious adverse events and serious pretreatment events will be collected from signing of the informed consent form through 30 days after the last dose of drug in the study drug regimen						
Concomitant Medications/Procedures	Recorded from the first dose of drug in the study drug regimen through 30 days after last dose of drug in the study drug regimen						

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BSA = body surface area; C1D1 = Cycle 1, Day 1; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMD = extramedullary disease; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; Ig = immunoglobulin; MM = multiple myeloma; MRD = minimal residual disease; MRI = magnetic resonance imaging; OS = overall survival; PD = progressive disease; PET = positron emission tomography; PFS = progression-free survival; PN = peripheral neuropathy; PR = partial response; QLQ-C30 = Quality of Life Questionnaire; QOL = quality of life; SAE = serious adverse event; SPEP = serum protein electrophoresis; TEAE = treatment-emergent adverse event; UPEP = urine protein electrophoresis; VGPR = very good partial response.

Tests and procedures should be performed on schedule, but occasional changes may be allowed (± 3 days) for holidays, vacations, and other administrative reasons. If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessments is completed prior to dosing. If

SCHEDULE OF EVENTS: ARM C (RRMM)							
		Treatment Period[b] (28-Day Cycles)					
		CYCLE 1 and BEYOND					
Study Procedures	**Screening[a]**	**Day 1[c]**	**Day 8**	**Day 15**	**Day 22**	**End of Treatment[d]**	**PFS Follow-up[e] Every 8 Weeks**
Window	**-28 to -1**					**± 1 Week**	**± 1 Week**

extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the Millennium project clinician or designee.

a Evaluations during the Screening period are to be conducted within 28 days before enrollment, unless otherwise noted. The date of randomization or enrollment should be within 7 days of Cycle 1, Day 1 (C1D1).

b During the treatment period, there will be a ± 3-day window for study visits unless otherwise noted.

c Cycle 1, Day 1 (C1D1) is baseline. All baseline evaluations/procedures are to be conducted at C1D1 before dosing or within 3 days before the first dose of drug unless otherwise specified.

d Patients who discontinue the study drug regimen must complete the end-of-treatment (EOT) visit, which should occur within 30 days (± 1 week) after the last dose of study drug or before the start of subsequent antineoplastic therapy.

e [redacted]

f The symptom-directed physical exam may be performed at other visits during the treatment period at the discretion of the investigator.

g To assess MM-related clinical symptoms and TEAEs.

h Body surface area (BSA) will be calculated at C1D1 and at any subsequent visit that the patient experiences a > 5% change in weight from the weight used for the most recent BSA calculation.

i A serum pregnancy test will be performed for women of childbearing potential during screening, predose on C1D1, and at EOT. The serum pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the study drug regimen is administered.

j A 12-lead ECG will occur at screening and every 4 cycles thereafter during the treatment period, and at EOT.

k Clinical laboratory evaluations will be performed locally and centrally as indicated in Section 7.4.13. Labs should be collected prior to dosing. Hematology should occur weekly on Days 1, 8, 15, and 22 for Cycles 1 through 3 and on Days 1 and 15 for Cycle 4 and beyond until EOT. Chemistry should occur weekly on Days 1, 8, 15, and 22 for Cycles 1 through 3 and on Day 1 for Cycle 4 and beyond until EOT. Hematology and chemistry may be collected up to

SCHEDULE OF EVENTS: ARM C (RRMM)							
		Treatment Period[b] (28-Day Cycles)					
		CYCLE 1 and BEYOND					
Study Procedures	**Screening[a]**	**Day 1[c]**	**Day 8**	**Day 15**	**Day 22**	**End of Treatment[d]**	**PFS Follow-up[e]** Every 8 Weeks
Window	**-28 to -1**					**± 1 Week**	**± 1 Week**

3 days prior to MLN9708 dosing. Criteria for retreatment are provided in Section 6.3.1. Hematology is also to be collected upon occurrence of an adverse event (AE) or serious adverse event (SAE) suggestive of renal toxicity. For dosing decisions, local hematology and chemistry laboratory results may be used.

l A urinalysis is to be done predose on Day 1 of each cycle during the treatment period for all patients. Urinalysis is also to be done upon occurrence of an AE (or SAE) suggestive of renal toxicity.

m Patient-reported outcomes assessments and health care utilization assessments should be completed before any other study procedures are performed and before the study drug regimen is administered.

n To be performed at screening (within 8 weeks prior to enrollment), once annually, and if at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions. Plain films of symptomatic sites for signs or symptoms of new bone lesions may be obtained instead of a full skeletal survey. At the discretion of the investigator and where regionally permitted, a computed tomography (CT) scan, a positron emission tomography computed tomography (PET-CT) scan, or a whole body magnetic resonance imaging (MRI) may be done at screening in place of a skeletal survey, provided that the same modality for assessment is used throughout the study.

o For those with documented extramedullary disease, radiographic assessments should be made at screening, at every other cycle, starting at Cycle 2, Day 1, at EOT, and every 8 weeks during progression-free follow-up. The same imaging modality used at screening (CT/PET-CT/MRI) should be used for all follow-up assessments.

p To be performed prior to dosing during the treatment period, at EOT, and during PFS follow-up. Serum only patients will have 24-hour urine collected for UPEP and urine immunofixation at screening, noted CR or PD, and at EOT. All other patients should have the M component quantification by UPEP and urine immunofixation performed prior to dosing in every cycle during the treatment period, at EOT, and during PFS follow-up.

q [redacted] d

r [redacted]

STUDY DRUG REGIMEN ADMINISTRATION: ARM C (RRMM)

		Treatment Period			
		CYCLE 1 and BEYOND			
Study Drug	**Route**	**Day 1**	**Day 8**	**Day 15**	**Day 22**
MLN9708	PO	X	X	X	
Cyclophosphamide	PO	X	X	X	
Dexamethasone	PO	X	X	X	X

Abbreviations: PO = per os (by mouth; orally); RRMM = relapsed and/or refractory multiple myeloma.

Pharmacokinetic Sampling Schedule for All Patients in Safety Lead-In (Arms A, B, C)

PK Sampling Time Point Drug Administration	Cycle 1										Cycle 2
	D1	D2	D3	D5	D8	D15	D16	D17	D19	D22	D1
Predose[a]	X										
15 min postdose (± 3 min)	X										
30 min postdose (± 5 min)	X										
1 h postdose (± 15 min)	X										
1.5 h postdose (± 15 min)	X										
2 h postdose (± 15 min)	X										
4 h postdose (± 45 min)	X										
8 h postdose (± 1 h)	X										
24 h postdose (± 1 h)		X									
48 h postdose (± 2 h)			X								
96 h postdose (± 4 h)				X							
168 h postdose (± 4 h) (prior to Day 8 dose)					X						
Predose[a]						X					
15 min postdose (± 3 min)						X					
30 min postdose (± 5 min)						X					
1 h postdose (± 15 min)						X					
1.5 h postdose (± 15 min)						X					
2 h postdose (± 15 min)						X					
4 h postdose (± 45 min)						X					
8 h postdose (± 1 h)						X					
24 h postdose (± 1 h)							X				
48 h postdose (± 2 h)								X			
96 h postdose (± 4 h)									X		
168 h postdose (± 4 h)										X	
Predose[a]											X

Abbreviations: D = day; PK = pharmacokinetic(s).

a Predose PK assessments should occur within 2 hours before dosing.

Pharmacokinetic Sampling for All Patients (Arms A, B, and C) (Excluding Safety Lead-in Patients)

	Cycle 1				Cycles 2-3			
PK Sampling Time Point	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**
Predose[a]		X	X		X	X	X	
1 h postdose (± 15 min)	X							
Collect at any time during clinic visit				X				X

Abbreviations: D = day; PK = pharmacokinetics.

a Predose PK assessments should occur within 2 hours before dosing.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
AL	light-chain
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCRP	breast cancer resistance protein
BMA	bone marrow aspirate
BSA	body surface area
BUN	blood urea nitrogen
C1D1	Cycle 1, Day 1
CBC	complete blood count
Cd	cyclophosphamide and low-dose dexamethasone
CCd	combination with cyclophosphamide/dexamethasone
CI	confidence interval
CL	clearance, IV dosing
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
CR	complete response
CrCL	creatinine clearance
CSR	clinical study report
CT	computed tomography
CyBorD	cyclophosphamide, bortezomib and dexamethasone
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMD	extramedullary disease
EORTC	European Organization for Research and Treatment of Cancer

Abbreviation	Term
EOT	End of Treatment (visit)
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
HDT	high-dose therapy
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMWG	International Myeloma Working Group
IR	immunophenotype
IRB	institutional review board
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous; intravenously
IWRS	interactive web response system
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MP	melphalan/prednisone
MPR	MP/lenalidomide
MPR-R	MP/lenalidomide followed by lenalidomide continuous therapy
MPT	melphalan/prednisone/thalidomide
MRD	minimal residual disease
MRP2	multidrug resistance associated protein
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	overall response

Abbreviation	Term
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
Pgp	P-glycoprotein
PI	(United States) Package Insert
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	*per os*; by mouth (orally)
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
QLQ-C30	Quality of Life Questionnaire
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RevDex	Revlimid (lenalidomide)/dexamethasone
RP2D	recommended phase 2 dose
RRAL	relapsed and/or refractory systemic light chain amyloidosis
RRMM	relapsed and/or refractory multiple myeloma
RVd	Revlimid/VELCADE/dexamethasone
SAE	serious adverse event
sCR	stringent complete response
SCT	stem cell transplantation
SMA	Safety Management Attachment
SmPC	Summary of Product Characteristics
SPEP	serum protein electrophoresis
SRE	skeletal-related events
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
ThalDex	thalidomide/dexamethasone
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
TTP	time to progression
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
UPS	ubiquitin-proteasome system
US	United States
VCD	VELCADE/cyclophosphamide/dexamethasone
VDD	VELCADE, doxorubicin and dexamethasone

Abbreviation	Term
VelDex	VELCADE/dexamethasone
VGPR	very good partial response
VMP	VELCADE/melphalan/prednisone
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Multiple myeloma (MM) is a B-cell tumor characterized by the accumulation of plasma cells in the bone marrow (and other organs) and can result in bone marrow failure, bone destruction, hypercalcemia, and renal failure. It constitutes approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide.[1] In the Americas, Canada, and Western European countries, approximately 5 to 7 new cases of MM are diagnosed per 100,000 people each year.[1, 2, 3] Although less common in Asian countries, incidences of MM have increased almost 4-fold in the past 25 years and are characterized by younger onset age, more invasive disease, and a less favorable prognosis.[4, 5]

MM is sensitive to many cytotoxic drugs, including alkylating agents and anthracyclines, and to corticosteroids for both initial treatment and relapsed disease. Over the past decade, the treatment of newly diagnosed multiple myeloma (NDMM) has evolved due to availability of the proteasome inhibitor VELCADE® (bortezomib), and the immunomodulatory agents thalidomide and lenalidomide (Revlimid). These, along with the use of high-dose therapy and autologous stem cell transplant (ASCT) in selected patients, have led to improved survival in myeloma.[6, 7, 8] Therapeutic regimens for NDMM recommended by the National Comprehensive Cancer Network (NCCN) include VELCADE/dexamethasone (VelDex), thalidomide/dexamethasone (ThalDex), Revlimid (lenalidomide)/dexamethasone (RevDex), VELCADE/cyclophosphamide/dexamethasone (VCD), Revlimid/VELCADE/dexamethasone (RVd); VELCADE/melphalan/prednisone (VMP), melphalan/prednisone/thalidomide (MPT), and VELCADE, doxorubicin and dexamethasone (VDD). Among these regimens, VMP and MPT are used for transplant-ineligible patients only, while others are used for both transplant-eligible and transplant-ineligible patient populations. VCD is one of several preferred therapeutic options available as frontline therapy for transplant-eligible patients.

Although these new treatments have significantly changed the outcome for patients with NDMM, this malignant disease remains incurable and requires long-term treatment. In the elderly patient population strategies to optimize the initial induction therapy with the development of new agents and new combination therapies and the role of maintenance treatment continue to be evaluated, with the goal to identify the most effective approach

while maximizing the quality of life (QOL). For patients with relapsed and/or refractory multiple myeloma (RRMM) who experience disease progression after their initial therapy, response to subsequent treatments varies with a decreased likelihood of response and a tendency towards a shorter duration of response (DOR). Ultimately, RRMM becomes refractory to approved therapies, and patients have no alternative treatment options.

MLN9708, a small molecule 20S proteasome inhibitor has been developed by Millennium Pharmaceuticals, Inc. (Millennium) in an effort to expand the therapeutic armamentarium against MM.

1.1.2 MLN9708

Protein homeostasis that occurs through regulation of protein production and destruction is one of the critical biological processes that play a role in cell survival, growth, and signaling. The ubiquitin-proteasome system (UPS) is the major regulatory system through which protein homeostasis occurs and represents the primary mechanism by which cells degrade proteins, including those involved in growth control, cell cycle regulation, and apoptosis. The 26S proteasome is comprised of a catalytic proteolytic core (20S) and 2 regulatory subunits (19S). Inhibition of the 20S core with first generation VELCADE (a potent, reversible, and specific inhibitor of the proteasome), results in the inhibition of protein degradation and the disruption of several distinct cell regulatory mechanisms, further resulting in inhibition of cell growth and survival pathways, dysregulation of the cell cycle, and induction of apoptosis. Inhibition of the 20S proteasome pathway has been proven useful in the treatment of MM and mantle cell lymphoma.

As an example and for patients with NDMM who are not eligible for ASCT, adding VMP not only improved response rates, but also prolonged overall survival.[9] Final results of the international, multicenter, phase 3 VISTA trial confirmed that after 5 years of follow-up, VMP was associated with a persistent, significant overall survival (OS) benefit versus melphalan/prednisone (MP) with a median 13.3 month increase (43.1 vs 56.4 months, hazard ratio [HR] 0.695, $p = 0.0004$). The OS benefit with VMP was seen across prespecified patient subgroups (age $\geq$ 75 years, stage III myeloma, creatinine clearance $<$ 60 mL/min) and maintained, despite substantial use of novel agent-based salvage therapies.[10] In an effort to improve tolerability and to lower the discontinuation rate due to treatment-related side effects, reported as 33% with VMP, a once-weekly dosing regimen of VELCADE instead of the typical twice-weekly schedule (as used in the VISTA trial) was tested in combination with MP. Reduced toxicity, specifically reduced Grades 3 to 4

peripheral neuropathy (PN) was observed and similar efficacy demonstrated.[11, 12] Weekly administration of VELCADE is now being commonly used in clinical practice. Recently, results of a pivotal study have also shown similar efficacy with reduced incidence of PN with subcutaneous VELCADE leading to its approval as new route of administration.[12]

MLN9708 is a next-generation oral proteasome inhibitor that is in clinical development for the treatment of both hematologic and nonhematologic malignancies and represents the first orally bioavailable proteasome inhibitor to enter clinical development. MLN9708 was developed to build upon the attributes of VELCADE and to address its limitations with a more convenient dosing schedule. When hydrolyzed from its citrate ester form (MLN9708) to its boronic acid form (MLN2238), like VELCADE, MLN2238 is active against the β5 subunit of the 20S proteasome. MLN2238 produces reversible inhibition and, in contrast to VELCADE, rapidly dissociates from the β5 subunit. It is expected that the different binding kinetics and pharmacologic profile compared with VELCADE will translate into similar efficacy and potentially better safety profiles; therefore, MLN9708 is being tested as a therapeutic treatment for nonhematologic and hematologic malignancies.

1.2 Nonclinical Experience

Detailed information regarding the nonclinical pharmacology and toxicology of MLN9708 may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

MLN9708 has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapsed and/or refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent MLN9708 and MLN9708 in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, two phase 3 trials in NDMM (C16014) and RRMM (C16010) patient populations are currently evaluating MLN9708 in combination with RevDex versus placebo/RevDex. Both trials are combining MLN9708 at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies include evaluation of drug-drug interactions with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetic (PK) of MLN9708 alone (in Japanese patients) and in combination with

lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of NDMM are ongoing.

As of 27 March 2013, preliminary clinical data are available for a total of 653 patients across 13 studies. The emerging safety profile indicates that MLN9708 is generally well tolerated. The adverse events (AEs) are consistent with the known effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic antiemetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose(MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of antiemetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of antiemetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms will be mitigated by the use of the lower MTD/RP2D (as per each study) and standard clinical usage of antiemetics and/or antidiarrheal medications as deemed appropriate.

The most frequent (at least 20% of patients) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to MLN9708, were nausea (___ of patients), fatigue (___), diarrhea (___), vomiting (___), thrombocytopenia (___), decreased appetite (___), fever and anemia

(___ each). The most frequent (at least 20% of patients) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to MLN9708, were diarrhea (___), fatigue (___), nausea___), peripheral edema (___), constipation___), insomnia (___), thrombocytopenia (___), anemia and vomiting (__% each), neutropenia (___), back pain (___, pyrexia (___), peripheral edema (___), and fever, cough, hypokalemia, neutropenia, and upper respiratory tract infection___ each). Overall, rash of all grades is reported in approximately 50% of patients and is more common when MLN9708 is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of MLN9708 may be found in the IB, including information on the IV formulation.

1.3.1 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multiexponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration (T_{max}) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days.[13] Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[14] Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. Please refer to the current MLN9708 IB and Safety Management Attachment (SMA) for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that MLN9708 is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 treatment to produce drug-drug interactions (DDIs) via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or inducer

because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN2238 may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN2238 is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

1.4 Study Rationale

Induction

Over the last decade, progress in treatment paradigms for MM comes through a series of investigations examining the efficacy of proteasome inhibitors and immunomodulatory drugs used in various combinations and sequences. After confirmation of significant activity in the relapsed setting, these new drugs were examined in combination with dexamethasone in the frontline setting and consistently demonstrated higher and deeper response rate and improved progression-free survival (PFS). This has been followed by 3-drug combination regimens that either combined the drugs or added the new drug to an alkylating based backbone (MP or cyclophosphamide and low-dose dexamethasone [Cd]).

VELCADE, in combination with an alkylating agent has shown to be a highly effective initial therapy. As discussed in Section 1.1.2, results of VELCADE plus MP in patients with NDMM not eligible for transplantation have demonstrated improved response rate and prolonged overall survival.[9] Although VMP is standard of care in patients with NDMM, the use of melphalan as a backbone is declining in recent years due to the impact on the stem cells and the known risk of secondary leukemia and myelodysplastic syndrome (MDS) with the use of melphalan. Increased interest emerges for Cd as a combination partner because of less myelosuppression and a more favorable long-term toxicity profile (lower incidence of secondary leukemia) compared to melphalan, and it also demonstrated good efficacy.

Over the last few years, encouraging results from phase 2 trials exploring the combination of VELCADE, with Cd have shown to induce a high rate of deep responses when administered

as induction before ASCT. Reeder et al. have reported high overall response (OR), very good partial response (VGPR), and complete response (CR) rates of 90%, 60%, and 41%, respectively in frontline transplant-eligible patients treated with a cyclophosphamide, bortezomib (VELCADE), and dexamethasone (CyBorD) regimen.[15] Similar results were reported in the Evolution trial on the VCD-mod arm.[16] Common adverse reactions included in both trials were hematological toxicities, PN, GI disturbances, and fatigue, all considered clinically manageable. These encouraging preliminary safety and efficacy results prompted the evaluation of the fully oral combination of MLN9708 with Cd as induction therapy in a transplant-ineligible patient population with NDMM.

Maintenance

The goal of treatment in elderly patients is to achieve CR, ultimately resulting in improved survival. Complete response achievement, however, is not the only objective of treatment, as it is possible to further improve the depth of response and the outcome by prolonged therapy or maintenance after a CR is achieved.[12, 17] Mateos reported an upgrade in responses in elderly patients with untreated MM with a VELCADE-based maintenance therapy after induction with either VMP or MPT and a benefit in terms of PFS. Maintenance therapy greatly increased the number of CRs.[9, 12] Positive results for a maintenance setting were also reported with lenalidomide. Palumbo demonstrated that adding lenalidomide to MP with lenalidomide as maintenance significantly improved PFS in the same patient population: median PFS was significantly longer with MP/lenalidomide followed by lenalidomide continuous therapy (MPR-R) (31 months) than with MP/lenalidomide (MPR) (14 months; HR, 0.49; $p < 0.001$) or MP (13 months; HR, 0.40; $p < 0.001$).[17]

Relapsed and/or Refractory Disease

Although multiple therapies are available for patients with RRMM, the frequent relapses that characterize this disease highlight a need for new therapies for patients in whom prior treatments have failed.[18] VCD has been shown to be an effective treatment in patients with RRMM and has a favorable toxicity profile. VCD is recognized by the NCCN as salvage therapy for patients with RRMM with an ORR of 75% to 83%.[19, 20]

The early development program of MLN9708 in patients with RRMM investigated 2 dose schedules commonly used with the first-in-class proteasome inhibitor, VELCADE. In the open-label, dose-escalation, phase 1 studies, C16003 and C16004, MLN9708 was administered on a twice-weekly (Days 1, 4, 8, and 11 of a 21-day cycle) schedule and on a

weekly schedule (Days 1, 8, and 15 of a 28-day cycle), respectively. In both studies, patients had MM that had relapsed following at least 2 lines of therapy that included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, the MTD cohorts were expanded. Patients enrolled in these expansion cohorts had relapsed or refractory disease (refractory was defined as disease progression while on therapy or within 60 days after the last dose of therapy), and included patients who had been previously treated with a proteasome inhibitor such as VELCADE or carfilzomib and considered to be sensitive to a proteasome inhibitor or patients who were proteasome inhibitor naive. Preliminary data suggest that MLN9708 has antitumor activity in heavily pretreated patients with MM, with an ORR of 27% for the MTD expansion cohort in Study C16004. In both studies, durable responses and disease control have been observed with a generally acceptable toxicity profile.

The inclusion of an RRMM treatment arm in this study is proposed on the basis of results of VELCADE in patients with previously treated MM and the emerging activity seen with MLN9708 in patients with previously treated and untreated MM.

The purpose of Study C16020 is to determine the safety, tolerability, and efficacy of oral MLN9708 when added to a Cd backbone in patients with NDMM and RRMM. For patients with NDMM, extending the duration of the response through prolonged use of single-agent MLN9708 as maintenance therapy following induction will also be evaluated. Patients with NDMM who are stable or responding at the end of induction therapy will continue to receive MLN9708 as maintenance treatment.

1.4.1 Feasibility of Combination of MLN9708, Cyclophosphamide, and Dexamethasone Therapy

Treatment with oral Cd is generally well tolerated. The primary side effect of cyclophosphamide is bone marrow suppression, particularly neutropenia and GI disturbances such as nausea, vomiting, and diarrhea. Treatment with dexamethasone can induce steroid side effects, such as hyperglycemia, fluid retention, increased appetite, or behavioral changes in susceptible patients. Adverse events reported in MLN9708 clinical trials are generally consistent with the known effects of proteasome inhibition and are generally similar to what has been previously reported with VELCADE, though the severity of some may vary, for example GI toxicity is more, while PN is less with MLN9708. The most common and significant AEs reported include GI disorders, thrombocytopenia, and rash.

When VELCADE was added to cyclophosphamide/dexamethasone (CyBorD and VCD regimen) the combination was shown to be tolerable, although neuropathy was common. All AEs reported were expected from each drug administered as a single agent and considered manageable with either appropriate clinical support or dose reduction. The discontinuation rate due to AE was ≤ 12%. For CyBorD, the most commonly reported AEs Grade 3 or higher were cytopenia and hyperglycemia. The major reason for dose reduction of cyclophosphamide included thrombocytopenia and neutropenia, which appeared in early cycles, whereas neuropathy was the major cause for dose reduction of VELCADE in later cycles. A similar safety profile was observed with VCD. Based on the available safety data on the combination of VELCADE/cyclophosphamide/dexamethasone, the expected overlapping toxicities such as hematological toxicities when MLN9708 is combined with cyclophosphamide are anticipated to be similar as with CyBorD or VCD regimen and manageable. Standard clinical usage of antiemetic and/or antidiarrheal agents to control potential increased GI toxicities seen with MLN9708 compared with VELCADE may be necessary though not expected to be dose limiting in the dose and schedule being tested. Given the similar safety and tolerability profile of MLN9708 compared with VELCADE, adding MLN9708 to a Cd backbone is anticipated to be feasible from a safety perspective in both the NDMM and RRMM settings.

1.4.2 Rationale for the Combination of MLN9708, Cyclophosphamide, and Dexamethasone Dose and Dosing Schedule

MLN9708

Oral MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle is supported by nonclinical data and clinical trial results in which MLN9708 has been given either as a single agent or in combination with a standard dose of RevDex (C16005) or MP (C16006). A weekly dose of MLN9708 at 4.0 mg was consistently declared as MTD or RP2D across the MLN9708 program (single agent or in combination) and is currently the RP3D tested in the ongoing registration trials (C16010, C16011, and C16014) in patients with either MM or AL amyloidosis. Most relevant to the dosing schedule selected is the previously mentioned Study C16006, an ongoing, open-label, multi-arm, dose-escalation, phase 1/2 study in which MLN9708 is tested in combination with MP in elderly patients with NDMM, ineligible for transplant. After an induction therapy of the combination for 1 year, single-agent MLN9708 is administered as maintenance therapy. In Arm B of the phase 1 portion of the study, patients were enrolled in each of the following cohorts: Cohort 1 (MLN9708 3.0 mg), Cohort 2 (MLN9708 4.0 mg) and Cohort 3 (MLN9708 5.5 mg) given weekly on Days 1, 8, and 15 on a 28-day cycle, in combination with melphalan (6 mg/m^2) and prednisone

(60 mg/m^2). MLN9708 4.0 mg was determined to be the MTD and the RP2D, with no DLT reported in that cohort, while DLTs reported in 2 of 5 patients in the 5.5-mg cohort included Grade 4 esophageal ulcer and Grade 3 thrombocytopenia, with Grade 3 hematemesis; Grade 3 nausea, vomiting, and diarrhea; and Grade 3 ileus and neurogenic bladder. Preliminary results in the ongoing MTD cohort suggest an overall safe and well tolerated induction regimen with comparable efficacy as to historical controls. Selection of the same weekly RP2D dose of MLN9708 at 4.0 mg on Days 1, 8, and 15 of a 28-day cycle has been shown to be safe and tolerable when added to MP was logically considered for the Cd combination.

Cyclophosphamide

The dose-intensity schedules for cyclophosphamide tested in the myeloma setting are numerous and there is no dosing regimen that can be considered standard in either the frontline or relapsed and/or refractory disease setting. Recent studies evaluating the combination of Cd with VELCADE in a transplant-eligible patient population (CyBorD and VCD-mod) combined standard twice-weekly VELCADE dosing to weekly cyclophosphamide administration of either 300 mg/m^2 or 500 mg/m^2 continuously or with a 1-week break. As mentioned previously, both dosing regimens were tolerable with manageable toxicities. More recently, preliminary results exploring carfilzomib, another proteasome inhibitor in combination with cyclophosphamide/dexamethasone (CCd) in a NDMM elderly patient population were presented at the European Hematology Association Congress 2013.[(21)] A weekly cyclophosphamide dose of 300 mg/m^2 on Days 1, 8, and 15 and a dexamethasone dose of 40 mg weekly in a 28-day cycle was used. This combination was shown to have a good efficacy and safety profile: discontinuation rate for AEs of 11%. No differences in response rate and safety between patients younger and older than 75 years were observed. On the basis of available data on weekly cyclophosphamide tested in combination with a proteasome inhibitor in both transplant-eligible and transplant-ineligible patients with NDMM, weekly cyclophosphamide at a dose of 300 mg/m^2 on Days 1, 8, and 15 on a 28-day cycle was a safe and tolerable dose to consider and was selected for Arm A and the population with relapsed and/or refractory disease to be enrolled in Arm C. Because cyclophosphamide was also successfully tested at a dose of 500 mg/m^2 weekly in patients with NDMM considered for transplantation, and because depth of response matters, a weekly dose of cyclophosphamide of 400 mg/m^2 will be explored in Arm B to determine whether an increased dose of the backbone agent may translate into better efficacy while providing an acceptable safety/tolerability profile.

Although various dose schedules have been used for cyclophosphamide in combination with VELCADE in the relapsed and/or refractory disease setting, including the 500 mg weekly dose[19] or 50 mg daily dose,[20] a weekly dose of 300 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle is expected to be tolerable in combination with a proteasome inhibitor, based on the toxicity profile observed in patients with NDMM. An alternative dose schedule may be considered for Arm C if the planned dosage is not tolerated.

Dexamethasone

Dexamethasone enhances the activity of MLN9708 and of cyclophosphamide, and is used at the proposed study dose and schedule (40 mg on Days 1, 8, 15, and 22) in other MLN9708 clinical studies (C16010, C16011, and C16014). An open-label, randomized, controlled, Eastern Cooperative Oncology Group (ECOG) clinical trial using this dose and schedule reported better short-term OS and lower toxicity than the high-dose dexamethasone schedule (40 mg on Days 1-4, 9-12, and 17-20) when added to lenalidomide.[22]

1.5 Rationale for Biomarker Measurements

Minimal Residual Disease Assessment

Residual disease, present yet undetected by conventional techniques following therapy, leads to disease relapse and mortality. Complete response remains the optimal objective in front-line treatment of myeloma to improve survival. The definition of CR has evolved in recent years from normalization of serum protein electrophoresis and bone marrow morphology with negative immunofixation, to normal serum free light-chain ratio test (stringent CR; sCR), and more recently to normal immunophenotype (IR).[23] Emerging data assessing the presence of minimal residual disease (MRD) using flow cytometric techniques to immunophenotype bone marrow aspirate material obtained during CR assessment in combination with k/λ ratio are starting to demonstrate the potential value of being able to assess the presence of MRD.

Immunophenotyping defines a tumor's surface marker profile via flow cytometry and is highly sensitive to the presence of tumor cells in marrow specimens. Patients with tumor cells below the detection threshold (1 in ~10,000 plasma cells) are considered to be MRD negative.[23] Although the long-term utility of this approach is still in its early days in MM, several studies have indicated that MRD-negative patients experienced longer PFS and OS than flow cytometric-positive patients.[24] Recently, Paiva and colleagues have investigated the impact of IR versus CR and sCR in 260 newly diagnosed elderly (> 65 years) patients

with MM treated with novel agents in the PETHEMA/GEM 05 trial. In this trial, IR showed significant increased 3-year rates of PFS and (time to progression [TTP] compared with those in sCR or CR (90% vs 69% and 60%, and 96% vs 71% and 68% [$p < 0.001$]) respectively. On a multivariate COX regression analysis for PFS, only IR status was an independent prognostic factor (relative risk, 4.1; 95% CI, 1.4-12.0; $p < 0.01$).[24]

Blood Sample Genotyping

[redacted]

1.6 Rationale for Pharmacokinetic Measurements

[redacted]

1.7 Potential Risks and Benefits

[redacted]

[redacted]

Further information can be found in Section 1.4.1 and Section 1.4.2 and in the MLN9708 IB and SMA.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective for patients with newly diagnosed multiple myeloma (NDMM) is:

- To determine the combined response rate of CR (including stringent CR [sCR]) + VGPR following treatment with oral MLN9708 when added to a regimen of cyclophosphamide and low-dose dexamethasone (Cd) during the induction phase

The primary objective for patients with relapsed and/or refractory multiple myeloma (RRMM) is:

- To determine overall response rate (ORR; CR + VGPR +partial response [PR]), following treatment with oral MLN9708 when added to a regimen of Cd

2.2 Secondary Objectives

For patients with NDMM, the secondary objectives are:

- To evaluate the tolerability and toxicity of the combination of oral MLN9708 with Cd
- To characterize the PK in plasma of oral MLN9708 in combination with Cd
- To determine overall response rate (ORR; CR + VGPR + PR), CR, VGPR, and PR during the induction phase and the ORR (CR + VGPR + PR), CR + VGPR, CR, VGPR, and PR throughout the entire treatment period

- To determine time to response for patients who respond during the induction phase
- To determine duration of response (DOR) for patients who respond during the induction phase
- To determine TTP
- To evaluate PFS
- To describe the safety, tolerability, and efficacy of MLN9708 as maintenance therapy in patients who continue treatment beyond 13 cycles of induction therapy
- To assess change in global health status, as measured by the patient-reported outcome (PRO) instruments European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30)

For patients with RRMM, the secondary objectives are:

- To evaluate the tolerability and toxicity of the combination of oral MLN9708 with Cd
- To characterize the PK in plasma of oral MLN9708 in combination with Cd
- To determine CR + VGPR, CR, VGPR, and PR
- To determine time to response for patients who respond
- To determine DOR
- To determine TTP
- To evaluate PFS
- To assess change in global health status, as measured by the patient-reported outcome (PRO) instruments European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30)

2.3 Exploratory Objectives

For patients with NDMM and patients with RRMM, the exploratory objectives are:

- [redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoint

For patients with NDMM, the primary endpoints are:

- Combined response rate of CR (including sCR) + VGPR during the induction phase in patients treated with MLN9708 when added to a regimen of Cd.

For patients with RRMM, the primary endpoint is:

- ORR (CR + VGPR +PR) in patients treated with MLN9708 when added to a regimen of Cd.

3.2 Secondary Endpoints

For patients with NDMM, the secondary endpoints are:

- All AEs, Grade 3 or higher AEs, AEs resulting in discontinuation, AEs resulting in dose reduction, serious adverse events (SAEs), and assessments of clinical laboratory values

- PK parameters including, but not limited to single-dose maximum (peak) concentration (C_{max}), T_{max}, and AUC

- ORR (CR + VGPR + PR), CR, VGPR, PR, stable disease (SD), progressive disease (PD) during the induction phase; ORR, CR + VGPR, CR, VGPR, PR, SD and PD and throughout the entire study

- Time to response, defined as the time interval from the date of enrollment to the date of first documented response during the induction phase

- DOR, defined for responders as the time interval from the date of first response to the date of disease progression

- TTP, defined as the time interval from the date of enrollment to the date of first documented disease progression

- PFS, defined as the time interval from the date of enrollment to the date of first documented disease progression or death

- AEs, SAEs, AEs resulting in discontinuation, AEs resulting in dose reduction in patients remaining on treatment after 13 cycles, ORR, CR, VGPR, and PR of single-agent MLN9708 as maintenance therapy in patients remaining on treatment after 13 cycles

- Comparison of change in global health status between baseline and each postbaseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30.

For patients with RRMM, the secondary endpoints are:

- All AEs, Grade 3 or higher AEs, AEs resulting in discontinuation, AEs resulting in dose reduction, serious adverse events (SAEs), and assessments of clinical laboratory values
- PK parameters including but not limited to single-dose maximum (peak) concentration (C_{max}), T_{max}, and AUC
- CR + VGPR, CR, VGPR, PR, SD, PD
- Time to response
- DOR
- TTP
- PFS
- Comparison of change in global health status between baseline and each postbaseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30.

3.3 Exploratory Endpoints

For patients with NDMM and patients with RRMM, the exploratory endpoints are:

[redacted]

- [redacted]

[redacted].

4. STUDY DESIGN

4.1 Overview of Study Design

This is a phase 2, multicenter, open-label study in patients with NDMM who have not received prior systemic treatment for MM and who are ineligible for high-dose therapy (HDT)-SCT due to age (ie, ≥ 65 years) or comorbid disease(s) and in patients with RRMM who have received 1 to 3 lines of prior therapy and whose disease is not refractory to proteasome inhibitors. It is expected that approximately 148 patients will be enrolled in this study.

Patients With NDMM (Arms A and B)

Patients with NDMM will be randomized 1:1 to either Arm A or Arm B. Each 28-day treatment cycle consists of oral MLN9708 (4.0 mg on Days 1, 8, and 15) administered in combination with cyclophosphamide (300 mg/m^2 [Arm A] OR 400 mg/m^2 [Arm B] both on Days 1, 8, and 15) and dexamethasone (40 mg on Days 1, 8, 15, and 22). Patients over 75 years of age will receive a reduced dose of dexamethasone 20 mg on the same weekly schedule. Patients may receive MLN9708 in combination with Cd for an induction phase of approximately 1 year (13 × 28-day cycles) and if at least stable disease has been reached with an acceptable toxicity profile, patients will be administered, as maintenance, single-agent MLN9708 (at the dose tolerated at the end of induction) on Days 1, 8, and 15 in 28-day treatment cycles until disease progression, death, or unacceptable toxicity.

Patients With RRMM (Arm C)

Patients with RRMM will receive MLN9708 4.0 mg weekly on Days 1, 8, and 15, in combination with cyclophosphamide 300 mg/m^2 on Days 1, 8, and 15, and dexamethasone 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle (all orally administered). Patients over 75 years of age will receive the reduced dose of dexamethasone 20 mg on the same weekly

schedule. Patients with an acceptable toxicity profile will continue treatment until disease progression, death, or unacceptable toxicity.

All Patients (Arms A, B, and C)

For all 3 treatment arms (Arms A, B, and C), a safety lead-in evaluation will be performed after at least 6 patients in each treatment arm have had the opportunity to complete at least 1 cycle of therapy. Dose-limiting toxicities (DLTs) observed in the first 6 patients from each treatment arm will be used to determine the safety and overall tolerability of the regimen and the feasibility of continued recruitment to the study.

No formal interim analysis is planned; however, both safety and efficacy will be continually monitored (see Section 8.1.11) throughout study conduct.

Response will be assessed according to the International Myeloma Working Group (IMWG) criteria. For patients with NDMM (Arms A and B), these assessments will be performed at every cycle during the induction phase and at every other cycle during the maintenance phase. For patients with RRMM (Arm C), response will be assessed at every cycle during the treatment period. Radiographic disease assessments are to be performed for patients with documented extramedullary disease. Patients discontinuing study drug before disease progression (ie, for withdrawal of consent or unacceptable toxicity) will be followed for PFS until disease progression or death.

Eastern Cooperative Oncology Group performance score and AEs will be assessed, and laboratory values, urine analysis, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of the combination therapy. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective 14 June 2010.[31]

Serial blood samples for determination of the plasma concentration of MLN9708 and tumor specific markers, will be obtained at prespecified time points as described in Schedule of Events.

The study drug regimen will be discontinued for a patient in any of the 3 treatment arms who experiences disease progression or unacceptable study drug-related toxicities. This includes MLN9708 in combination with Cd during the induction period for patients with NDMM (Arms A and B) or the treatment period for patients with RRMM (Arm C). MLN9708 will also be discontinued for patients with NDMM (Arms A and B) who

experience disease progression during the maintenance phase. Patients may discontinue therapy at any time. Patients will attend the end of treatment (EOT) visit 30 days (± 7 days) after receiving their last dose of study drug regimen.

4.2 Number of Patients

It is anticipated that approximately 148 patients, 70 patients with NDMM and 78 patients with RRMM, will be enrolled in this study from approximately 30 study centers globally.

4.3 Duration of Study

It is anticipated that the total duration of the study will be approximately 60 months. This includes 24 months of enrollment and up to 36 months of treatment and/or PFS follow-up.

The analyses for the clinical study report (CSR) will be conducted after all enrolled patients have had the opportunity to complete 13 cycles of the study drug regimen.

5. STUDY POPULATION

Two patient populations will be enrolled in this study:

- Adult patients with a confirmed diagnosis of symptomatic MM who have received no prior antimyeloma treatment (NDMM) and are not candidates for HDT-SCT due to age (≥ 65 years) or comorbidities; and
- Adult patients with a confirmed diagnosis of symptomatic MM and relapsed and/or refractory disease (RRMM) after 1 to 3 lines of prior therapy and whose disease is not refractory to proteasome inhibitors

5.1 Inclusion Criteria

Each patient with NDMM must meet all of the following inclusion criteria to be enrolled in the study:

1. Adult male or female patients 18 years of age or older with a confirmed diagnosis of symptomatic MM according to standard criteria (see Section 14.1 and Section 14.5).

2. Patients for whom cyclophosphamide and dexamethasone treatment is appropriate and who are considered not eligible for HDT-SCT for 1 or more of the following reasons:

    - The patient is 65 years of age or older.
    - The patient is less than 65 years of age but has significant comorbid condition(s) that are, in the opinion of the investigator, likely to have a negative impact on tolerability of HDT-SCT.

Each patient with RRMM must meet all of the following inclusion criteria to be enrolled in the study:

3. Adult male or female patients 18 years or older with a confirmed diagnosis of symptomatic MM either currently or at the time of initial diagnosis, according to standard criteria (see Section 14.1 and Section 14.5), and relapsed and/or refractory disease after 1 to 3 lines of prior therapy. A patient is considered to have refractory disease if disease progression occurred during the treatment period or within 60 days of receiving the last dose of a given therapy. A line of therapy is defined as 1 or more cycles of a single-agent or combination therapy or a sequence of planned treatments such as induction therapy followed by autologous stem cell transplantation (ASCT) and then maintenance therapy.
4. No evidence of graft-versus-host disease for patients who have undergone prior allogeneic stem cell transplantation.

In addition, all patients (NDMM and RRMM) must meet all of the remaining criteria:

5. Patients must have measurable disease defined by at least 1 of the following 3 measurements:

    - Serum M-protein ≥ 1 g/dL (≥ 10 g/L).
    - Urine M-protein ≥ 200 mg/24 hours.
    - Serum free light chain assay: involved free light chain level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum free light chain ratio is abnormal.

6. Patients must meet all of the following clinical laboratory criteria:

- Absolute neutrophil count (ANC) ≥ 1000/mm^3 and platelet count ≥ 75,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to administration of the study drug.

- Total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN).

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN.

- Calculated creatinine clearance (CrCL) ≥ 30 mL/min (see Section 14.2).

7. Eastern Cooperative Oncology Group performance status of 0, 1, or 2 (see Section 14.3).

8. Female patients who:

   - Are postmenopausal for at least 1 year before the screening visit, or

   - Are surgically sterile, or

   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, or

   - Agree to practice true abstinence over the period previously described, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.), and

   - Adhere to any treatment-specific pregnancy prevention guidelines for cyclophosphamide[32, 33] and dexamethasone[34, 35, 36]

   Male patients, even if surgically sterilized (ie, status postvasectomy), who:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or

   - Agree to practice true abstinence over the period previously described, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for

the female partner] and withdrawal are not acceptable methods of contraception.), and

- Adhere to any treatment-specific pregnancy prevention guidelines for cyclophosphamide[32, 33] and dexamethasone[34, 35, 36]

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

10. Suitable venous access for the study-required blood sampling.

11. Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Prior treatment for multiple myeloma with either standard of care treatment or investigational regimen (for patients with NDMM only).

   NOTE: Prior treatment with corticosteroids (maximum dose of corticosteroids should not exceed the equivalent of 160 mg of dexamethasone over 14 days [see Section 14.4 for a list of steroid equivalent doses]). Localized radiation is permitted as long as it is below a therapeutic level and administered at least 14 days prior to the first dose of study treatment.

2. Diagnosis of smoldering MM, Waldenström's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.

3. Central nervous system involvement.

4. Diagnosed or treated for another malignancy within 2 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

5. Peripheral neuropathy Grade 1 with pain or Grade 2 or higher peripheral neuropathy of any cause on clinical examination during the Screening period.

6. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of study drug, including difficulty swallowing.

7. Infection requiring IV antibiotic therapy or other serious infection within 14 days before the first dose of study drug.

8. Ongoing or active infection, known human immunodeficiency virus (HIV) positive, active hepatitis B or C infection

9. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment.

10. Known allergy to any of the study medications, their analogues, or excipients in the various formulations.

11. Major surgery within 14 days before the first dose of study drug. (Note: kyphoplasty or vertebroplasty is not considered major surgery.)

12. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.

13. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

14. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

15. Treatment with any investigational products for reasons other than MM within 30 days before the first dose of study drug.

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. The study drug regimen will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity as necessary and doses of the appropriate study drug should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of dose.

All doses must be taken as outlined in the Schedule of Events. Dosing should be performed on schedule, but occasional changes in patient scheduling are allowable (± 3 days) for holidays and vacations, except during Cycle 1 for all patients enrolled in the safety lead-in cohort. After the safety lead-in is completed within a treatment arm, an occasional change in the dosing schedule (± 1 week) may be allowable for other administrative reasons after consultation with the Millennium project clinician (or designee). Eligible patients may take MLN9708 in combination with Cd at home as directed. Refer to the Study Manual for additional instructions regarding study drug administration.

6.1.1 MLN9708 Administration

Patients With NDMM (Arms A and B)

During induction, oral MLN9708 will be given weekly at a dose of 4.0 mg on Days 1, 8, and 15 of a 28-day cycle.

At the end of 13 cycles of treatment, the maintenance phase will start. If the patient is still on study (has achieved at least stable disease with an acceptable toxicity profile), MLN9708 will be continued as a single agent, weekly on Days 1, 8, and 15 of a 28-day cycle at the same dose being given at the end of induction therapy. Under certain circumstances the maintenance dose may be increased up to but not exceeding the starting dose of the induction phase if the investigator and Millennium project clinician (or designee) both agree that it would be beneficial for the patient.

Patients With RRMM (Arm C)

For patients with RRMM, oral MLN9708 will be given weekly on Days 1, 8, and 15 of 28-day cycle at the planned dose of 4.0 mg until disease progression or unacceptable toxicity occurs.

All Patients (Arms A, B, and C)

For all 3 treatment arms, the study drug should be taken at approximately the same time each day, on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. Patients should be instructed to swallow MLN9708 capsules whole with water and not to chew, break, or open the capsules. Each dose of MLN9708 will be taken orally with approximately 8 ounces (ie, 240 mL) total of water consumed.

Missed doses on Days 1 and 8 can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. The missed dose on Day 15 can be taken only up to 72 hours after the planned dose (no later than on Day 18). A double dose should not be taken to make up for a missed dose. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

Patients should be monitored for toxicity as necessary, and doses of MLN9708 should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and/or adjustments of MLN9708 dose. Following agreement between the investigator and the sponsor, and after completing 3 cycles of treatment, eligible patients may take MLN9708 at home as directed; however, all patients will be required to report to the clinic for Day 1 of each cycle for scheduled assessments (see the Schedule of Events).

6.1.2 Cyclophosphamide Administration

Patients With NDMM (Arms A and B)

During induction, cyclophosphamide will be given weekly as a single, oral dose of 300 mg/m^2 (Arm A) OR 400 mg/m^2 (Arm B) and rounded to the nearest 50 mg, on Days 1, 8, and 15 of a 28-day cycle.

At the end of 13 cycles of treatment, the maintenance phase will start. If the patient is still on study, cyclophosphamide will be discontinued.

Intrapatient Dose Escalation of Cyclophosphamide for Arm A

Intrapatient dose escalation is not planned; however, if during the continuous monitoring of the study data, clear evidence of antitumor activity is observed in Arm B (cyclophosphamide 400 mg/m^2) with an overall acceptable safety/tolerability profile, patients in Arm A (cyclophosphamide 300 mg/m^2) who have tolerated treatment with cyclophosphamide well at the initially assigned dose may be allowed to increase their dose of cyclophosphamide to 400 mg/m^2 in subsequent cycles of treatment following sponsor and investigator review of the available observed data. Patients in whom an increase in the dose of cyclophosphamide is being considered must have completed at least 2 cycles of treatment at their initially assigned dose. Hematology laboratory samples will be obtained weekly for the next 3 cycles once the dose has been increased.

Patients With RRMM (Arm C)

For patients with RRMM, cyclophosphamide will be given weekly on Days 1, 8, and 15 of a 28-day cycle as a single, oral dose of 300 mg/m^2 and rounded to the nearest 50 mg. An alternative dose schedule of cyclophosphamide may be explored for Arm C if the planned dose is not tolerated.

All Patients (Arms A, B, and C)

For all 3 treatment arms, it is recommended that cyclophosphamide be taken in the morning and at approximately the same time each dosing day. Cyclophosphamide should be taken with solid food or milk. Patients should be instructed to drink plenty of fluids and to urinate frequently during treatment with cyclophosphamide. Patients should be instructed to swallow cyclophosphamide capsules whole with water and not to chew, break, or open the capsules.

Missed doses can be taken within 48 hours from the planned dose. If more than 48 hours have elapsed, the missed dose should be skipped and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Body surface area will be calculated using a standard formula on Cycle 1, Day 1 and on Day 1 of subsequent cycles. If the patient experiences a > 5% change in body weight from the weight used for the most recent BSA calculation, the BSA should be recalculated to determine the dose of cyclophosphamide.

6.1.3 Dexamethasone Administration

Patients With NDMM (Arms A and B)

During induction, dexamethasone will be given as a weekly oral dose of 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle. Patients older than 75 years of age at the time of randomization will receive a reduced dose of dexamethasone 20 mg on the same weekly schedule.

At the end of 13 cycles of treatment, maintenance phase will start. If the patient is still on study, dexamethasone will be discontinued.

Patients With RRMM (Arm C)

For patients with RRMM, dexamethasone will be given as a weekly oral dose of 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle. Patients older than 75 years of age at the time of enrollment will receive the reduced dose of dexamethasone 20 mg on the same weekly schedule.

All Patients (Arms A, B, and C)

For all 3 treatment arms, it is recommended that dexamethasone be taken in the morning and at approximately the same time each dosing day. Dexamethasone should be taken with solid food or milk.

Missed doses can be taken within 48 hours from the planned dose. If more than 48 hours have elapsed, the missed dose should be skipped, and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

6.2 Safety Lead-in

A safety evaluation will be performed after at least 6 safety lead-in evaluable patients have had the opportunity to complete at least 1 cycle of treatment in each of the 3 treatment arms (Arms A, B, and C). Toxicities observed in the first 6 safety lead-in evaluable patients from each of the 3 treatment arms will be used to determine the safety and overall tolerability of the regimen in the 2 patient populations (patients with NDMM assigned to Arm A or Arm B and patients with RRMM enrolled in Arm C) and the feasibility of continued recruitment to the study.

6.2.1 Safety Lead-in Evaluable Patients

Patients who do not receive all doses of MLN9708 or cyclophosphamide during Cycle 1 per the Schedule of Events for reasons other than an AE will be replaced for safety evaluation. Patients who receive all doses of MLN9708 and cyclophosphamide but, for unforeseen circumstances, recovery of toxicity is not available and safety in Cycle 1 cannot be fully evaluated, may be replaced. Toxicity leading to dose modification in Cycle 2 and beyond will be considered when determining continuous enrollment in the treatment arm.

6.2.2 Rules for Continuous Study Enrollment

For each of the 3 treatment arms, a tolerable dose will require first-cycle DLTs (Section 6.2.1) in no more than 1 of 6 safety lead-in evaluable patients in that treatment arm.

For patients with NDMM, when 2 of 6 safety lead-in patients experience DLTs (Section 6.2.1) in 1 treatment arm and no more than 1 of 6 DLT-evaluable patients experience DLTs in the other arms, depending on the overall safety profile and the type of AEs/DLTs observed in the treatment arms, the decision will be made to either stop enrollment in that treatment arm or expand that treatment arm with 6 additional patients. A tolerable dose will then require first-cycle DLTs in no more than 3 of 12 safety lead-in evaluable patients in the expanding treatment arm to proceed with enrollment.

Enrollment in any of the 3 treatment arms (NDMM and RRMM) will be held until the 6th patient has had the opportunity to complete Cycle 1, if a DLT occurs in 1 of the first 5 patients enrolled in that arm. Accrual to a treatment arm will also be stopped if any of the first 5 patients experience AEs, which may not qualify as DLTs per protocol-defined criteria, but the project clinician believes that it is in the interest of patient safety to hold enrollment until all 6 patients complete Cycle 1. If the first 5 patients complete Cycle 1 without any DLTs being observed, enrollment may continue in that treatment arm and will not need to be held until the 6th patient completes Cycle 1, provided that the regimen is being tolerated and no safety concerns are identified. Enrollment in each treatment arm will occur independently, so that accrual of patients to any of the 3 treatment arms can proceed even if enrollment is being held in another treatment arm. In addition, patients previously enrolled in the treatment arm in which accrual is being held will have the opportunity to continue to receive the study drug regimen as long as it is being well tolerated and no safety concerns are identified in those patients. Randomization is required only when patients are being enrolled in Arms A and B concurrently.

After the safety lead-in evaluation, if 1 of the treatment arms for patients with NDMM is stopped, enrollment in the other arm will continue. If the decision is made to stop both treatment arms (Arms A and B), enrollment in the entire study, including accrual of patients to treatment Arm C may be stopped or alternative dosing levels for all 3 treatment arms may be evaluated following discussion between the sponsor and the investigators. If after the safety lead-in evaluation, accrual to Arm C is stopped, enrollment in the other 2 treatment arms may continue and alternate dose schedules may be explored for Arm C, following discussion between the sponsor and investigators.

Expansion of a safety lead-in cohort is permissible if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of the combination.

6.2.2.1 Evaluation of Toxicity: DLT Criteria

Toxicity will be evaluated according to the NCI CTCAE version 4.03.[31] These criteria are provided in the Study Manual. The following AEs that are considered by the investigator to be even possibly related to the MLN9708 in combination with Cd will be considered as DLTs (Cycle 1 only):

1. Grade 3 neutropenia with fever and/or infection, where fever is defined as a temperature > 38.3°C.

2. Grade 4 neutropenia (ANC < 500/mm^3) lasting at least 7 consecutive days.

3. Grade 3 thrombocytopenia with clinically significant bleeding, defined as a blood loss of > 100 cc or the requirement for a red blood cell transfusion.

4. Grade 4 thrombocytopenia (platelets < 25,000/mm^3) lasting at least 7 consecutive days or associated with bleeding.

5. A platelet count < 10,000/mm^3.

6. Grade 3 or higher nausea and/or emesis despite the use of optimal antiemetic prophylaxis. Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs a 5-hydroxytryptamine 3 serotonin receptor (5-HT_3) antagonist given in standard doses and according to standard schedules.

7. Grade 3 or higher diarrhea that occurs despite maximal supportive therapy.

8. Any other Grade 3 or higher nonhematologic toxicity with the following exceptions:

   - Grade 3 arthralgia/myalgia.
   - Brief (< 1 week) Grade 3 fatigue.

9. A delay of more than 2 weeks in the subsequent cycle of treatment because of a lack of adequate recovery of combination study drug-related hematological or nonhematologic toxicities.

10. Other combination study drug-related nonhematologic toxicities Grade 2 or higher that, in the opinion of the investigator, require dose reduction on either MLN9708 or cyclophosphamide or discontinuation of the study drug regimen during Cycle 1.

6.3 Dose Modification Guidelines

Patients will be evaluated weekly for the first 3 cycles and regularly thereafter while on treatment for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE version 4.03.[31] Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Reduction of 1 agent and not the other is appropriate if toxicity is related primarily to 1 of the 3 agents. Before beginning the next cycle of treatment, refer to the guidelines in Section 6.3.1. Further clarification can be obtained in consultation with the Millennium project clinician (or designee). If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines. The same dose modification guidelines will apply during the maintenance phase for patients with NDMM (Arms A and B) who are receiving MLN9708, unless otherwise noted.

6.3.1 Criteria for Toxicity Recovery Before Beginning the Next Cycle and Midcycle of Treatment

If a patient fails to meet the criteria outlined in Table 6-1 for the beginning of the next cycle of treatment, initiation of the next cycle should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. If the start of the next cycle requires a delay of more than 2 weeks because of incomplete recovery from treatment-related toxicity, see Section 6.3.3 for recommended dose reductions. The maximum delay before treatment should be discontinued will be 3 weeks, unless there is evidence for clinical benefit upon agreement by the investigator and Millennium project clinician (or designee).

Table 6-1 Criteria for Hematological and Nonhematological Recovery

	To Start a New Cycle (Day 1)	To Redose Within a Cycle (Days 8 and 15)
ANC	ANC must be ≥ 1,000/mm^3	ANC must be ≥ 750/mm^3
Platelet	Platelet count must be ≥ 75,000/mm^3	Platelet count must be ≥ 50,000/mm^3
Nonhematological	All other nonhematologic toxicities (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition	Neuropathy must be ≤ Grade 1 (with no pain) Other nonhematologic toxicities should be < Grade 3. Refer to Table 6-5.

Abbreviation: ANC = absolute neutrophil count.

6.3.2 Criteria for Selection and Timing of Dose Modification (Delays, Reductions, and Discontinuations)

During the induction phase for patients with NDMM and during treatment for patients with RRMM, the decision regarding which study drug requires dose reduction will be dependent upon the toxicity, its onset, and time course. Alternative dose modifications may be recommended after discussion with the investigator and Millennium project clinician (or designee) to maximize exposure of study treatment while protecting patient safety given that there may be overlapping dose-limiting toxicities (eg, thrombocytopenia, neutropenia, nausea/vomiting, diarrhea).

If any drug dose was held during the previous cycle and was restarted with a 1-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose will be initiated on Day 1 of the following cycle. If any drug dose was held for the remainder of the previous cycle or if the new cycle is held due to known hematologic toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a 1-level dose reduction. The maximum delay before treatment should be discontinued will be 3 weeks, unless there is evidence for clinical benefit upon agreement by the investigator and Millennium project clinician (or designee).

For patients with NDMM, the dose adjustments for MLN9708 during the maintenance period follow the same criteria as during the induction phase; however, dose reduction should be favored over the use of granulocyte colony stimulating factor (G-CSF). In the very specific case where a patient experiences toxicities despite 2 dose reductions of MLN9708, an alternative dose schedule (ie, dosing on Days 1 and 15 on a 28-day cycle) may be recommended after discussion between the investigator and Millennium project

clinician (or designee) to maximize exposure to study treatment while protecting patient safety.

During Study Conduct

In the event of nondrug-related severe renal impairment (CrCL < 30 mL/min) or moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and AST/ALT > 3 × ULN) occurring at any time during study conduct, dose may be modified upon discussion between sponsor and investigator.

6.3.3 Permitted Dose Level Reductions

Throughout the study, no more than 2 dose reductions are permitted for each drug unless there is evidence for clinical benefit upon agreement by the investigator and Millennium project clinician (or designee). Table 6-2 outlines the permitted dose reductions for MLN9708, cyclophosphamide, and dexamethasone for the 3 treatment arms.

Table 6-2 Permitted Dose Level Reductions for MLN9708, Cyclophosphamide, and Dexamethasone

		Dose Level Reduction		
	Starting Dose	**-1**	**-2**	**-3**
MLN9708	4.0 mg	3.0 mg	2.3 mg	Discontinued
Cyclophosphamide				
Arm A and Arm C	300 mg/m^2	200 mg/m^2	100 mg/m^2	Discontinued
Arm B	400 mg/m^2	300 mg/m^2	200 mg/m^2	Discontinued
Dexamethasone				
< 75 years	40 mg	20 mg	8 mg	Discontinued
≥ 75 years	20 mg	8 mg	Discontinued	Discontinued

6.3.4 Dose Adjustments for Hematologic Toxicity: MLN9708 and Cyclophosphamide

Dose adjustments to MLN9708 and cyclophosphamide for thrombocytopenia are presented in Table 6-3.

Table 6-3 Dose Adjustments for Thrombocytopenia

Platelet Count NCI CTCAE Grade	**Action on Drug During Cycle**	**Further Considerations**
Platelets < 50,000-25,000/mm^3 without clinically significant bleeding	• Hold study drug regimen. Check CBC weekly at minimum. Resume treatment at current dose level. See Table 6-1.	The maximum delay before treatment should be discontinued is 3 weeks.
Grade 3 (< 50,000-25,000/mm^3) with clinically significant bleeding OR **Grade 4** (< 25,000/mm^3) OR **Delay of > 2 weeks** in the start of a subsequent cycle due to lack of platelet recovery (count < 75,000/mm^3) as defined in Section 6.3.1	• Hold study drug regimen. Check CBC weekly at minimum. • Dose adjustment at subsequent cycles per Table 6-2: *First occurrence:* Decrease **MLN9708** by 1 dose level *Second occurrence:* Decrease **cyclophosphamide** by 1 dose level *Third occurrence:* Decrease **MLN9708** by 1 dose level *Fourth occurrence:* Decrease **cyclophosphamide** by 1 dose level	

Abbreviations: CBC = complete blood count; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Dose adjustments to MLN9708 and cyclophosphamide for neutropenia are presented in Table 6-4.

Table 6-4 Dose Adjustments for Neutropenia

Neutrophil Count NCI CTCAE Grade	Action on Drug During Cycle	Further Considerations
ANC < 750 - 500/mm^3 without fever	• Hold treatment regimen. Check CBC weekly at minimum. See Table 6-1. • Resume treatment regimen at current dose level. See Table 6-2. • Introduction of G-CSF prophylaxis per ASCO guidelines may be considered.[a]	The maximum delay before treatment should be discontinued is 3 weeks.
Grade 3 with fever (ANC < 1,000 - 500/mm^3 and temperature > 38.3°C) OR **Grade 4** (ANC < 500/mm^3) OR **Delay of > 2 weeks** in the start of a subsequent cycle due to lack of neutrophil recovery (ANC < 1,000) as defined in Section 6.3.1	• Hold treatment regimen. Check CBC weekly at minimum. • Introduction of G-CSF prophylaxis as per ASCO guidelines may be considered at any time as sole and unique adjustment if neutropenia is the only toxicity for which an adjustment is required (G-CSF is not allowed at Cycle 1 for safety lead-in patients).[a] • If G-CSF is not an option or no longer an option, dose adjustment must follow subsequent sequences per Table 6-2: *First occurrence:* Decrease **cyclophosphamide** by 1 dose level *Second occurrence:* Decrease **MLN9708** by 1 dose level *Third occurrence:* Decrease **cyclophosphamide** by 1 dose level *Fourth occurrence:* Decrease **MLN9708** by 1 dose level	

Abbreviations: ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; CBC = complete blood count; G-CSF = granulocyte colony stimulating factor.

a Only short-acting G-CSF may be used (ie, pegylated G-CSF and longer-acting G-CSF are prohibited).

6.3.5 Dose Adjustments for Nonhematologic Toxicity: MLN9708 and Cyclophosphamide

Dose adjustments for nonhematologic toxicities attributed to MLN9708 are presented in Table 6-5.

Table 6-5 Dose Adjustments for Nonhematologic Toxicities Attributed to MLN9708

Toxicity	Criteria	Action on Drug During Cycle	Further Considerations
Peripheral Neuropathy	Grade 1 peripheral neuropathy	No action	Grade 1 signs and symptoms: asymptomatic, without pain or loss of function, clinical or diagnostic observations only[31]
	Grade 1 peripheral neuropathy with pain or Grade 2 peripheral neuropathy	Hold MLN9708 until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs and symptoms: moderate symptoms, limiting instrumental activities of daily living (ADL)[31]
	Grade 2 peripheral neuropathy with pain or Grade 3 peripheral neuropathy	• Hold MLN9708 until resolution to Grade ≤ 1 without pain or baseline • Reduce MLN9708 to next lower dose upon recovery per Table 6-2	Grade 3 signs and symptoms: severe symptoms, limiting self care ADL, assistive device indicated[31]
	Grade 4 peripheral neuropathy	Discontinue MLN9708	
Grade 2 Rash	Symptomatic recommendations per Section 6.7. The investigator and Millennium project clinician (or designee) may discuss considerations for dose modifications and symptom management.		
All Other Grade ≥ 3 Nonhematologic Toxicities	Hold MLN9708 until resolution to Grade < 1 or baseline. Reduce MLN9708 by 1 dose level as outlined in Table 6-2. The maximum delay before treatment should be discontinued is 3 weeks. Note: A dose level reduction will be made either based on within-cycle criteria or for a subsequent cycle criteria, but not for both for a same cycle.		
Grade 4 Nonhematologic Toxicities (except alopecia)	Consider permanently discontinuing MLN9708, unless there is evidence for clinical benefit upon agreement by the investigator and Millennium project clinician (or designee).		

Dose adjustments for nonhematologic toxicities attributed to cyclophosphamide are presented in Table 6-6.

The investigator and Millennium project clinician (or designee) may discuss considerations for dose modifications (see package insert/Summary of Product Characteristics [SmPC]).

Table 6-6 Dose Adjustments for Nonhematologic Toxicities Attributed to Cyclophosphamide

Toxicity	Criteria	Action on Drug During Cycle[a]	Further Considerations
Any Nonhematologic Toxicity	**Grade 3** **OR** **Delay of > 2 weeks** in the start of a subsequent cycle due to lack of nonhematologic toxicities recovery > Grade 1 or not to the patient as defined in Section 6.3.1	• Hold cyclophosphamide until resolution to Grade < 1or baseline • Reduce cyclophosphamide by 1 dose level per Table 6-2	The maximum delay before treatment should be discontinued is 3 weeks.
	Grade 4	• Discontinue cyclophosphamide according to the early stopping rule (see Section 8.1.11)	

a Alternative dose reductions may be discussed between the investigator and the sponsor.

6.3.6 Dexamethasone-Related Treatment Modification

Treatment modifications due to dexamethasone-related AEs are outlined in Table 6-7.[34]

The investigator and Millennium project clinician (or designee) may discuss considerations for dose modifications (see US package insert/SmPC). Alternative dose modifications may be recommended after discussion with the investigator and Millennium project clinician/designee in order to maximize exposure of study treatment while protecting patient safety.

Table 6-7 Dexamethasone–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events

Adverse Event (Severity)		Action on Dexamethasone[a]
Gastrointestinal	Dyspepsia, gastric, or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, decrease dexamethasone by 1 dose level.
	Grade ≥ 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease 1 dose level of current dose along with concurrent therapy with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.

Table 6-7 Dexamethasone–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events

Adverse Event (Severity)		Action on Dexamethasone[a]
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema Grade > 2 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed and decrease dexamethasone by 1 dose level. If edema persists despite these measures, decrease dose another level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurological	Confusion or mood alteration Grade > 2	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite these measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness Grade > 2 (interfering with function and/or interfering with activities of daily living)	Decrease dexamethasone dose by 1 dose level. If weakness persists despite these measures, decrease dose by 1 dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia Grade ≥ 3	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite these measures, decrease dose by 1 dose level until levels are satisfactory.

a Alternative dose reductions may be discussed between the investigator and the sponsor.

6.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted in this study. (A DDI with a strong inhibitor would increase the MLN2238 exposure and could lead to a higher probability of an AE.):

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: Unlike with inhibitors, if there were to be a DDI with an inducer, MLN2238 exposure would be less; therefore, there would be a reduced chance of an AE. However,

there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off MLN9708):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba

The following procedures are prohibited during the study.

- Any antineoplastic treatment with activity against MM, other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day

6.5 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Myeloid growth factors (eg, G-CSF, granulocyte macrophage-colony stimulating factor [GM-CSF]) are not allowed during Cycle 1 for the safety lead-in patients, but may be considered according to standard clinical practice in Cycle 2 and beyond during the induction phase for patients in Arms A and B, and in Cycle 2 and beyond during the treatment period for patients in Arm C. Prophylactic antibiotics are not allowed during Cycle 1 for the safety lead-in patients, but may be considered according to standard clinical practice in Cycle 2 and beyond during the induction phase for patients in Arms A and B, and during the treatment period for patients in Arm C. No prophylactic antibiotics should be administered during the maintenance phase for patients in Arms A and B.
- Erythropoietin.
- Patients should be transfused with red blood cells and platelets as clinically indicated (except as noted previously regarding eligibility).
- Antiviral therapy such as acyclovir is allowed.

- Concomitant treatment with bisphosphonates will be permitted.

- Supportive measures consistent with optimal patient care may be given throughout the study.

6.6 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

It is not known what effects MLN9708 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or

- Surgically sterile, or

- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, or

- Agree to practice true abstinence over the period previously described, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.), and

- Adhere to any treatment-specific pregnancy prevention guidelines for cyclophosphamide[32, 33] and dexamethasone[34, 35, 36]

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or

- Agree to practice true abstinence for the period described previously, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.), and

- Adhere to any treatment-specific pregnancy prevention guidelines for cyclophosphamide[32, 33] and dexamethasone[34, 35, 36]

6.7 Management of Clinical Events

Please refer to the appropriate US Package Insert or SmPC for information relating to AEs attributed to cyclophosphamide and dexamethasone.

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated.

Erythematous Rash With or Without Pruritus

As with VELCADE, rash with or without pruritus has been reported with MLN9708, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominantly on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1or Grade 2.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require IV antihistamines or corticosteroids. Administration of MLN9708 (and/or other causative agent if given in combination) should

be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare risk is Stevens Johnson syndrome, a severe, life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

Nausea and/or Vomiting

Standard antiemetics including 5-HT_3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol; however, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Hypotension

Symptomatic hypotension and orthostatic hypotension have been reported with MLN9708. Blood pressure should be closely monitored while the patient is on study treatment, and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypotension or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. MLN9708 administration should be modified per dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 6.3.4). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura, a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. Thrombotic thrombocytopenic purpura should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. MLN9708 administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Section 6.3.4). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

Fluid Deficit

Dehydration should be avoided since MLN9708 may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with MLN9708, commonly in the setting of the previously noted GI toxicities and dehydration. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration (see Section 6.6).

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES), which ultimately resolved, has been reported with MLN9708. This condition is characterized by headache, seizures, and visual loss, and abrupt increase in blood pressure. Diagnosis may be confirmed by a radiologic procedure. If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

Transverse myelitis has been reported in a patient who was receiving MLN9708. It is not known whether MLN9708 causes transverse myelitis. However, because it was reported in a patient who was receiving MLN9708, the possibility that MLN9708 may have contributed to transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

6.8 Blinding and Unblinding

This is an open-label study; no blinding methods will be employed.

6.9 Description of Investigational Agents

MLN9708 Capsules

The MLN9708 drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg capsules as the active boronic acid.

The 3 different dose strengths are differentiated by both capsule size and color as described in Table 6-8:

Table 6-8 MLN9708 Capsules

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 3	Ivory
3.0 mg	Size 4	Light gray
2.3 mg	Size 4	Flesh

For additional details, please see the MLN9708 IB and Pharmacy Manual.

6.9.1 MLN9708 Preparation, Reconstitution, and Dispensation

For blistered material, the capsules are packaged in cold-form foil-foil blisters in a child-resistant carton.

6.9.2 MLN9708 Packaging and Labeling

The study drug MLN9708 capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations. The formulation consists of 2.3-, 3.0-, and 4.0-mg capsules for oral administration.

The capsules are individually packaged using cold-form foil-foil blisters that are in a child-resistant carton. There are 3 capsules in each wallet/carton.

6.9.3 MLN9708 Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN9708 should remain in the blister and carton provided until use or until it is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). All excursions should be brought to the sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

After completing 3 cycles of treatment, patients may be allowed to self administer this medication at home. Patients are to be instructed on proper storage, accountability, and administration of MLN9708, including that MLN9708 is to be taken as intact capsules.

MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and carton and refrigerated as noted previously until the point of use. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C). Patients should be instructed to return their empty cartons to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns to the clinic. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because MLN9708 is an anticancer drug, as with other potentially toxic compounds, caution should be exercised when handling the study drug. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during clean-up and during return of broken capsules and powder to minimize skin contact. The area should be ventilated and the site washed with soap and water after material pick up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of

contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Please refer to the Pharmacy Manual for additional instructions.

6.9.4 Dexamethasone - Noninvestigational Medicinal Agent

Dexamethasone is a marketed agent. Dexamethasone may be supplied by the sponsor or sourced locally by the clinical sites when arrangements have been made and agreed to by Millennium and the clinical site and when regulations allow for clinical site sourcing, appropriate labeling, and compliance with local and regional regulations. Additional details are provided in the package insert/SmPC.

6.9.5 Cyclophosphamide - Noninvestigational Medicinal Agent

Cyclophosphamide is a marketed agent. Cyclophosphamide may be supplied by the sponsor or sourced locally by the clinical sites when arrangements have been made and agreed to by Millennium and the clinical site and when regulations allow for clinical site sourcing, appropriate labeling, and compliance with local and regional regulations. Additional details are provided in the package insert/SmPC.

6.10 Other Protocol-Specified Materials

No other drugs or ancillary material are supplied for use in this study.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the Millennium project clinician (or designee) for this study, the central laboratory, any additional clinical laboratories or vendors may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

After written informed consent has been obtained, patients with NDMM will be randomized 1:1 to either Arm A or Arm B. Patients with RRMM will be assigned to Arm C. A centralized interactive web response system (IWRS) will be used for randomization and enrollment of all patients. If a patient with NDMM discontinues from the study, the randomization code for that patient will not be reused. No patient will be allowed to re-enter the study after discontinuing from the study.

7.4 Study Procedures

Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, EOT, and Follow-Up (PFS). Tests and procedures should be performed on schedule, but occasional changes may be allowed (± 3 days) for holidays, vacations, and other administrative reasons. If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessments is completed prior to dosing. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the permission of the Millennium project clinician or designee.

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient, including diagnosis (see Section 14.1) and International Staging System (ISS) staging (see Section 14.5) of MM. The history should include a review of all current medications and the patient's current smoking status.

7.4.4 Assessment of Comorbid Condition(s) – Arms A and B

During the Screening period, an assessment of comorbid condition(s) is to be conducted for patients with NDMM only.

7.4.5 Physical Examination

A physical examination will be completed per standard of care at the time specified in the Schedule of Events. A symptom-directed physical examination will also be conducted at the time points specified in the Schedule of Events. A neurologic examination is to be conducted to assess both MM-related clinical findings and TEAEs; note timing in the Schedule of Events.

7.4.6 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance scale (see Section 14.3) at the time points specified in the Schedule of Events.

7.4.7 Vital Signs, Body Weight, Height, and Body Surface Area

Measurement of vital signs, including temperature, blood pressure, heart rate, respiratory rate, and weight will be obtained at the time points specified in the Schedule of Events. Height will be measured at the screening visit only.

For purposes of cyclophosphamide dosing, BSA will be calculated using a standard formula on Cycle 1, Day 1 and at subsequent visits if the patient experiences a > 5% change in body weight from the weight used for the most recent BSA calculation. The application of institutional standards to allow for dosing according to the current weight is acceptable.

7.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening, within 3 days prior to dosing, and at EOT. The results from these tests must be available and negative before the first dose of the study drug regimen is administered.

The Cycle 1, Day 1 pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the first dose. If the Cycle 1, Day 1 serum pregnancy results are not be available before dosing, a urine pregnancy test may be performed.

Pregnancy tests may also be repeated during the study at the request of IEC/IRBs or if required by local regulations.

7.4.9 Electrocardiogram

A 12-lead ECG will be conducted at screening and at the times outlined in the Schedule of Events. It may be repeated as clinically indicated during the study at the discretion of the investigator. ECG data to be obtained include PR interval, QRS interval, QT interval, QTc interval, and waveforms.

7.4.10 Concomitant Medications and Procedures

See Section 6.4 for a list of prohibited concomitant medications and therapies and Section 6.5 for a list of allowed concomitant medications and therapies.

7.4.11 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 9 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

Note that in this study, PN will be captured in the same manner as all other adverse events during the induction and maintenance phases for patients in Arms A and B and during the treatment period for patients in Arm C, with the exception that downgrading of PN events must be reported until 1) resolution, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after treatment discontinuation, whichever occurs first. If the patient exhibits PN at EOT, then PN will be followed during the PFS follow-up period (see Section 8.1.10.1 and Section 9.1.5).

7.4.12 Enrollment

A patient is considered to be enrolled in the study when the patient is assigned to 1 of the 3 treatment arms in the study.

Procedures for completion of the enrollment information are described in the Study Manual.

7.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by a central laboratory. For dosing decisions, local hematology and chemistry laboratory results may be used; however, samples must still be sent to the central laboratory for evaluation. Blood samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events.

Local laboratory evaluations may be done more frequently at the investigator's discretion, ie for acute management of TEAEs. Handling and shipment of central clinical laboratory samples are outlined in the Study Manual.

Clinical Chemistry, Hematology, and Urinalysis

Blood and urine samples for analysis of the following clinical chemistry and hematological parameters will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (absolute neutrophil count [ANC])

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO2)
- Magnesium
- β2-microglobulin (β2) analysis (Screening only)

Urinalysis

- Turbidity and Color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Occult Blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes
- Microscopic assessment

7.4.14 Quality of Life Assessment (European Organization for Research and Treatment of Cancer)

The QOL assessments (EORTC QLQ-C30; see Section 14.6) will be completed by the patient as specified in the Schedule of Events. The EORTC QLQ-30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The time recall period for this instrument is 1 week (the week immediately preceding the assessment).

These are reliable and valid measures of health-related QOL in patients with cancer and takes about 15 minutes to complete. The instruments consist of a total of 50 items and have been validated and used in many countries.

These QOL assessments must be completed before other assessments are performed or any drug in the study drug regimen is administered.

7.4.15 Skeletal Survey

[redacted]

7.4.16 Skeletal-Related Events

[redacted]

7.4.17 Bone Marrow Aspiration

Local Laboratory Evaluations

Disease Assessment

A bone marrow aspirate (BMA) will be obtained at screening for disease assessment and at any time a bone marrow aspirate sample is obtained to assess CR or to investigate suspected PD. This evaluation will be performed locally. A standard BMA drawn prior to consent is acceptable provided this is collected within 42 days of the first dose.

Determination of the κ/λ ratio by immunohistochemistry or immunofluorescence should be performed to assess for sCR when a CR has been documented. A bone marrow biopsy can additionally be performed per local standards for disease assessments.

Cytogenetics

If a sufficient sample is available, cytogenetic evaluation should be performed at screening using fluorescence in situ hybridization (FISH) and/or conventional cytogenetics (karyotype). Examples of cytogenetic markers that may be evaluated are deletion 17p, t(4:14), t(14:16), t(14:20), del 13/13q and del 1q20. All cytogenetic evaluations will be performed locally according to local standards.

Central Laboratory Evaluations

Minimal Residual Disease (MRD)

[redacted]

7.4.18 Blood Sample for Genotyping

[redacted]

7.4.19 Quantification of M-Protein

A blood sample and urine sample will be obtained at screening and at the time points specified in the Schedule of Events.

7.4.20 Quantification of Immunoglobulins

A blood sample for quantification of immunoglobulins (IgM, IgG, IgA, IgD, and IgE) will be obtained at screening and at times outlined in the Schedule of Events.

7.4.21 Serum Free Light Chain Assay

A blood sample for serum free light chain assay will be obtained at screening and at the times outlined in the Schedule of Events.

7.4.22 Immunofixation of Serum and Urine

Serum and urine samples will be obtained for serum and urine immunofixation tests at screening and at the times outlined in the Schedule of Events.

7.4.23 Radiographic Disease Assessments

For patients with documented extramedullary disease, other assessments and scans, such as a CT, PET-CT, or MRI scan, may be required to better delineate the sites and measurements of extramedullary disease. Follow-up scans should use the same imaging modality used at screening and at the time points specified in the Schedule of Events, until disease progression.

All follow-up scans should use the same imaging modality used at screening.

Radiographs will be analyzed locally and reports maintained with the patient record for review during monitoring visits.

7.4.24 Disease Response Assessment

Patients will be assessed for disease response according to the IMWG criteria (see Section 14.7).[23]

Response assessments should be performed at the times outlined in the Schedule of Events. Response categories are as follows:

Table 7-1 Response Assessment

Complete response	CR
Subcategory: stringent complete response	*sCR*
Very good partial response	VGPR
Partial response	PR
Stable disease	SD
Progressive disease	PD

CR should be confirmed with follow-up assessments of serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), immunofixation of blood and urine, and serum free light chains as outlined in Section 14.7. One bone marrow assessment has to occur to document CR; no second bone marrow confirmation is needed.

Please note that to determine a response of sCR, bone marrow, immunohistochemistry or immunofluorescence for κ/λ ratio, and serum free light chain assay should be performed for all patients suspected to be in CR to meet this requirement of this response category.

At any point during treatment, patients for whom disease progression is suspected will have response assessments repeated to confirm the assessment (local laboratory assessment is permitted).

7.4.25 Health Care Utilization Assessments

Health care utilization data will also be collected for all patients as specified in the Schedule of Events. Examples of data to be collected are the number, duration, and type of medical care encounters, such as inpatient admissions, outpatient visits, the accompanying reason for the visit (eg, medication, procedure, an AE), and homecare. In addition, the number is also captured of missed work days or other activities for the patient and patient's caregiver.

7.4.26 Follow-up Assessments (Progression-Free Survival)

Patients who stop treatment for any reason other than PD will continue to have progression-free follow-up visits. See the Schedule of Events for appropriate assessments. The PFS follow-up visits should occur every 8 weeks from EOT until the occurrence of progressive disease or death, or the patient withdraws consent for further follow-up.

If the patient exhibits PN at end of treatment, then PN will be followed during the PFS follow-up period in clinic every 4 weeks. See the Schedule of Events for further details.

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow up. In addition, new primary malignancies that occur during the follow-up periods, irrespective of causality to study regimen, must be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee through death or termination of the study by the sponsor.

Refer to Section 9 for details regarding definitions, documentation, and reporting of SAEs.

7.5 Completion of Treatment

Patients will be considered to have completed the treatment if they meet any of the following criteria:

- Have received at least 13 cycles of treatment
- Progressive disease/death after the completion of Cycle 1

7.6 Completion of Study

Patients will be considered to have completed the study if they are followed until documented progressive disease/death or until the sponsor terminates the study.

7.7 Discontinuation of Treatment With Study Drug, and Patient Replacement

For patients who did not complete treatment as defined in Section 7.5, treatment with study drug must be discontinued for pregnancy. Treatment may be discontinued permanently if any of the following criteria are met:

- Adverse event (including SAE)
- Protocol violation
- Progressive disease
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up

- Other

Once study drug has been discontinued, all study procedures outlined for the End of Treatment visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the electronic case report form (eCRF).

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these will remain in the study for posttreatment assessments as outlined in the Schedule of Events until disease progression occurs.

7.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by subject
- Other

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety.

7.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. The clinical team and the clinical research associate will review treatment compliance during investigational visits and at the completion of the study.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

8.1.1 Determination of Sample Size

The total sample size for the study will be approximately 148 patients. Approximately 70 patients with NDMM will be randomized 1:1 to Arm A or Arm B and approximately 78 patients with RRMM will be enrolled in Arm C.

For patients with NDMM (Arms A and B), the sample size is calculated by using 1 group Chi-square test for each arm separately based on the CR + VGPR rate following a MLN9708 combined treatment regimen. With 31 response-evaluable patients per treatment arm, there will be 80% power to test a null hypothesis CR + VGPR rate of 27% and an alternative hypothesis CR + VGPR rate of 45% at 1-sided significant level of $\alpha = 0.10$. Therefore, assuming 10% of patients are not response evaluable, approximately 35 patients each (70 total) will be enrolled in these 2 treatment arms.

For patients with RRMM (Arm C), the sample size is calculated by using 1 group Chi-square test for each arm separately based on the ORR rate following a MLN9708 combined treatment regimen. With 71 response-evaluable patients in Arm C, there will be 80% power to test a null hypothesis ORR rate of 60% and an alternative hypothesis ORR rate of 72% at 1-sided significant level of $\alpha = 0.10$. Therefore, assuming 10% of patients are not response evaluable, approximately 78 patients will be enrolled in Arm C in this study.

8.1.2 Randomization and Stratification

This study will use a central (ie, not center-specific) randomization ratio of 1:1 to assign patients to Arm A or Arm B. Randomization is not required if accrual to either Arm A or Arm B is stopped. No randomization will be used for patients in Arm C but an IWRS will be used for enrollment.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- **Safety Population**: Patients who receive at least 1 dose of any study drug. The safety population will be used for safety analyses. It will also be used for the analyses of TTP, PFS, QOL, and health care utlization data.

- **DLT-Evaluable Population:** Patients in the safety lead-in cohort who receive all doses of MLN9708 and at least 80% of the cyclophosphamide dose during Cycle 1 per the Schedule of Events, or experience a DLT in Cycle 1. Patients must take all doses in Cycle 1 as outlined in the Schedule of Events if patients do not experience DLTs. None of the doses can be delayed during Cycle 1 due to patient scheduling.

- **Response-Evaluable Population**: The response-evaluable population is defined as patients who receive at least 2 of the 3 MLN9708 doses during Cycle 1, have measurable disease at baseline, and at least 1 postbaseline response assessment. The response-evaluable population will be used for the analyses of response rates, time to response, and DOR.

- **Pharmacokinetic Analysis Population**: All patients who have sufficient dosing data and MLN9708 concentration-time data to permit calculation of MLN9708 PK parameters.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations.

For QOL in EORTC QLQ-C30, if a multi-item subscale has a missing item, then the average of the remaining items will be used as the Scale score, as long as at least half the items in that Scale are present. Example: for fatigue, if Item 12 is missing, the average score of Items 10 and 18 will be used.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for each treatment arm and by the total of Arm A + Arm B, including gender, age, race, weight, height, BSA, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

The IMWG response criteria will be used in this study (see Section 14.7).

8.1.6.1 Primary Efficacy

For patients with NDMM (Arms A and B), the primary endpoint is the CR + VGPR rate during the induction phase. For patients with RRMM (Arm C), the primary endpoint is ORR.

The primary efficacy analysis will be based on the response-evaluable population (patients enrolled in the safety lead-in portion are included). Estimates of the CR + VGPR rates for Arms A and B, and ORR for Arm C will be presented with 2-sided 95% exact binomial confidence intervals (CIs).

8.1.6.2 Secondary Efficacy

The secondary efficacy endpoints include ORR (Arms A and B only), CR + VGPR (Arm C only), CR, VGPR, PR, time to response, DOR, TTP, PFS, and the change from baseline in QOL.

Time to response is defined as the time from the date of enrollment to the date of the first documentation of a confirmed response in a patient who responded during the induction phase.

DOR is defined as the time from the date of first documentation of a confirmed response to the date of first documented PD.

TTP is defined as the time from the date of enrollment to the date of first documentation of PD.

PFS is defined as the time from the date of enrollment to the date of first documented PD or death.

Time to event data will be summarized by 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs and percentage of censored observations.

The response rates, time to response, and DOR will be analyzed for the response-evaluable population. Time to response may also be measured in the population of patients with a confirmed response. Time to progression and PFS will be analyzed based on the safety population. The response rates will be analyzed similarly to the primary endpoint. Time to response, DOR, TTP, and PFS will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates. If appropriate, the association between responses and time to event parameters, such as the difference of PFS among patients with or without sCR,

might be examined. The efficacy results will be summarized for each treatment arm and for the total of Arms A and B.

8.1.6.3 Exploratory Efficacy Endpoints and Analysis

[redacted]

Minimal Residual Disease Analysis

[redacted]

8.1.7 Analyses of Patient-Reported Outcomes

Analyses of patient-reported outcomes will be performed using the safety population and summarized for each treatment arm and by the total of Arm A + Arm B.

QOL will be assessed using the EORTC QLQ-C30. QOL assessments will be analyzed using the safety population to determine if response to therapy is accompanied by measurable improvement in QOL. Descriptive statistics will be presented for change from baseline in QOL assessment over time. Analyses will be performed on summary scores as well as individual items.

8.1.8 Analysis of Health Care Utilization Data

Analyses of health care utilization data will be performed using safety population and summarized for each treatment arm and by the total of Arm A + Arm B in descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities by patient and caregiver.

8.1.9 Pharmacokinetics/Biomarkers

Pharmacokinetic Analysis

[redacted]

Safety Lead-in Cohort

Individual and mean plasma concentration data will be plotted over time. A summary table will be presented for the plasma concentration data.

Pharmacokinetic parameters will be estimated using noncompartmental analysis methods. The plasma PK parameters calculated for individual plasma MLN2238 concentration-time data will include, but are not limited to: C_{max}, T_{max}, and AUC.

Pharmacokinetic parameters will be summarized using descriptive statistics.

All Patients

Pharmacokinetic data collected for all patients including patients in the safety lead-in cohort of the study will be used to perform population PK analysis using a nonlinear mixed effects modeling approach and will assess the effect of various demographic covariates on PK including data from other studies of MLN9708, if possible.

Biomarkers

[redacted]

8.1.10 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population and summarized for each treatment arm and by the total of Arm A + Arm B.

Treatment-emergent AEs that occur after administration of the first dose of study drug through 30 days after the last dose of study drug will be tabulated.

Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs

- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients)
- Serious adverse events

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

For the safety lead-in phase, the incidence of DLTs will be listed.

Development of new or worsening of existing SREs (eg, new fractures [excluding vertebral compression or rib fractures], irradiation of or surgery on bone, or spinal cord compression) from baseline through the development of PD will be summarized and presented.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the MLN9708 safety profile.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN9708.

8.1.10.1 Peripheral Neuropathy Events

Peripheral neuropathy event is defined as the treatment-emergent adverse event in the high-level term of peripheral neuropathies NEC according to MedDRA.

[redacted]

8.1.10.2 Drug Exposure of MLN9708, Cyclophosphamide, and Dexamethasone

Treatment duration, number of treatment cycles, number of doses, the total doses received and dose intensity of MLN9708, cyclophosphamide, and dexamethasone will be summarized for each treatment arm and for the total of Arm A + Arm B.

8.1.11 Interim Analysis

Safety Lead-in Evaluation

A safety lead-in evaluation will be performed after at least 6 safety lead-in evaluable patients in each treatment arm have had the opportunity to complete 1 cycle of therapy. No formal statistical analyses are planned for this safety lead-in evaluation.

Continuous Monitoring and Early Stopping Rule

No formal interim analysis is planned. However, both safety and efficacy will be continuously monitored on the basis of prespecified stopping rules. Grade 4 or higher nonhematological toxicities will be monitored for each arm starting from the first 12 enrolled patients and then every 6 additional enrolled patients based on a Bayesian monitoring strategy.[37] If the stopping bounds of ≥ 4/12, ≥ 6/18, ≥ 7/24, and ≥ 8/30 for Arms A and B (patients with NDMM), or the stopping bounds of ≥ 4/12, ≥ 6/18,≥ 7/24, ≥ 8/30, ≥ 9/36, ≥ 11/42, ≥ 12/48, ≥ 13/54, ≥ 14/60, ≥ 15/66, and ≥ 16/72 for Arm C (patients with RRMM) have been achieved, accrual to the study will be suspended to allow for investigation. If the stopping rule is met, there is at least 80% probability that the true toxicity rate will be greater than 18%. After consideration by the study team, a decision will be made as to whether accrual can be resumed.

The efficacy will be monitored by the Bayesian Predictive Probability method[38] starting from the first 12 response-evaluable patients after 6 cycles of treatment and then every 6 additional response-evaluable patients for Arms A and B or every 12 additional response-evaluable patients for Arm C. If the futility stopping bounds (CR + VGPR) of ≤ 2/12, ≤ 4/18, ≤ 7/24, and ≤ 10/30 for Arms A and B, or the stopping bounds (ORR) of ≤ 3/12, ≤ 10/24, ≤ 18/36, ≤ 26/48, and ≤ 36/60 for Arm C have been met, further investigation will be made by the study team to assess if accrual to any of the 3 treatment arms may be terminated due to futility. These futility stopping rules are established to allow no larger than 0.15 overall type I error rate (one-sided) and still maintain power of approximately 80%.

9. ADVERSE EVENTS

9.1 Definitions

9.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

9.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- Is a **congenital anomaly/birth defect**.

- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical 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; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE version 4.03, effective 14 June 2010.[31] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

9.1.4 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 9.1.5 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 9.1) must be reported (see Section 9.1.5 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance & Risk Management or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. Serious adverse event report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

Cognizant
US and Canada
Toll-Free Fax #: [redacted]
E-mail: [redacted]

All other countries (Rest of World)
Fax #: [redacted]0
E-mail: [redacted]

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE version 4.03, effective 14 June 2010.[31] The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

9.1.5 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs.

  Note that in this study, PN will be captured in the same manner as all other adverse events during the induction and maintenance phase for patients in Arms A and B and the treatment period for patients in Arm C, with the exception that downgrading of PN events must be reported until resolution. If the patient exhibits PN at end of treatment, then PN will be followed during the PFS follow-up period until 1) resolution of PN, 2) the start of an alternative antineoplastic treatment, or 3) 6 months after treatment discontinuation, whichever occurs first. Once a patient has entered PFS follow-up, assessment of PN will be done in clinic every 4 weeks for up to 6 months.

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug, but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance & Risk Management or designee. Serious adverse events should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). In addition, new primary malignancies that occur during the follow-up periods must be reported, irrespective of causality to the study drug, from the first dose of study drug through death, until termination of the study by the sponsor, or for a minimum of 3 years after the last dose of the investigational product, whichever comes first.

9.1.6 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on study drug or within 90 days of the patient's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance & Risk Management or designee. The pregnancy must be followed for the final pregnancy outcome. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Millennium Department of Pharmacovigilance & Risk Management or designee immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance & Risk Management or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10. ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

10.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

10.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

Electronic case report forms will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

10.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

10.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

10.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

10.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if

circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

10.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

10.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

10.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact [redacted] (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
call [redacted] at
[redacted]
(US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Cognizant (refer to Section 9.1.4).

10.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

10.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last

marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

11. USE OF INFORMATION

All information regarding MLN9708 supplied by Millennium to the investigator is privileged and [redacted] information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of MLN9708 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

The Millennium project clinician (or designee) will be the lead and corresponding author on abstracts and publications of the data generated from this study; the overall principal investigator or lead enroller will be the last author. Subsequently, individual investigators may publish results from their study center in compliance with their agreements with Millennium. Millennium reserves the right to determine which authors are named on abstracts and publications and also reserves the right to determine the order in which named authors appear.

12. INVESTIGATOR AGREEMENT

I have read Protocol C16020 Amendment 1: An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 With Cyclophosphamide and Dexamethasone In Patients With Newly Diagnosed or Relapsed and/or Refractory Multiple Myeloma Requiring Systemic Treatment

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

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14. APPENDICES

14.1 Multiple Myeloma Diagnostic Criteria

IMWG Criteria for the Diagnosis of Myeloma

Diagnosis	Diagnostic Criteria: All Three Required
Symptomatic multiple myeloma[a]	• Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma • Monoclonal protein present in the serum and/or urine[b] • Myeloma-related organ dysfunction (≥ 1) [C] Calcium elevation in the blood (serum calcium > 10.5 mg/l or upper limit of normal) [R] Renal insufficiency (serum creatinine > 2 mg per 100 mL) [A] Anemia (hemoglobin < 10 g per 100 mL or 2 g <normal) [B] Lytic bone lesions or osteoporosis[d]

Source: International Myeloma Foundation, myeloma.org. Accessed 16 January 2012.

a These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma.

b If no monoclonal protein is detected (non-secretory disease), then ≥ 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.

c A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

d If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then ≥ 30% plasma cells are required in the bone marrow.

14.2 Cockcroft Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140-\text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})} \quad \text{OR} \quad \frac{(140-\text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [μmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85 \times (140-\text{age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})} \quad \text{OR} \quad \frac{0.85 \times (140-\text{age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [μmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[39]

14.3 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[40]

14.4 Steroid Equivalent Doses

Approximately equivalent doses:

Steroid	Glucocorticoid Anti-inflammatory (mg)	Mineralicorticoid (mg)	Half-life (hours)
Cortisone	100	100	8–12
Hydrocortisone	80	80	8–12
Prednisone	20	100	12–36
Prednisolone	20	100	12–36
Methylprednisolone	16	no effect	12–36
Dexamethasone	2	no effect	36–72

Source: Knoben JE, Anderson PO. Handbook of Clinical Drug Data, 6th ed. Drug Intelligence Pub, Inc. 1988.[41]

14.5 International Staging System Criteria and Durie Salmon Criteria

The International Staging System (ISS) or Durie-Salmon criteria may be used for staging, according to local standard practice.

International Staging System

Stage	Criteria
Stage I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
Stage II	Neither Stage I or Stage III[a]
Stage III	Serum β_2-microglobulin ≥ 5.5 mg/L

Source: Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. Journal of Clinical Oncology 2005;23(15):3412-20.[42]

Abbreviations: ISS = International Staging System.

a There are 2 categories for Stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

Durie-Salmon Criteria

Stage	Criteria

I	All the following:
	• Hemoglobin value > 10 g/dL
	• Serum calcium value normal or ≤ 12 mg/dL
	• Bone X-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only
	• Low M component production rate
	  ○ IgG value < 5 g/dL; IgA value < 3 g/dL
	  ○ Bence Jones protein < 4 g/24 h

II	Neither stage I nor stage III

III	1 or more of the following:
	• Hemoglobin value < 8.5 g/dL
	• Serum calcium value > 12 mg/dL
	• Advanced lytic bone lesions (scale 3)
	• High M component production rate
	  ○ IgG value > 7 g/dL; IgA value >5 g/dL
	  ○ Bence Jones protein >12 g/24 h

Source: Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36(3):842-54.[43]

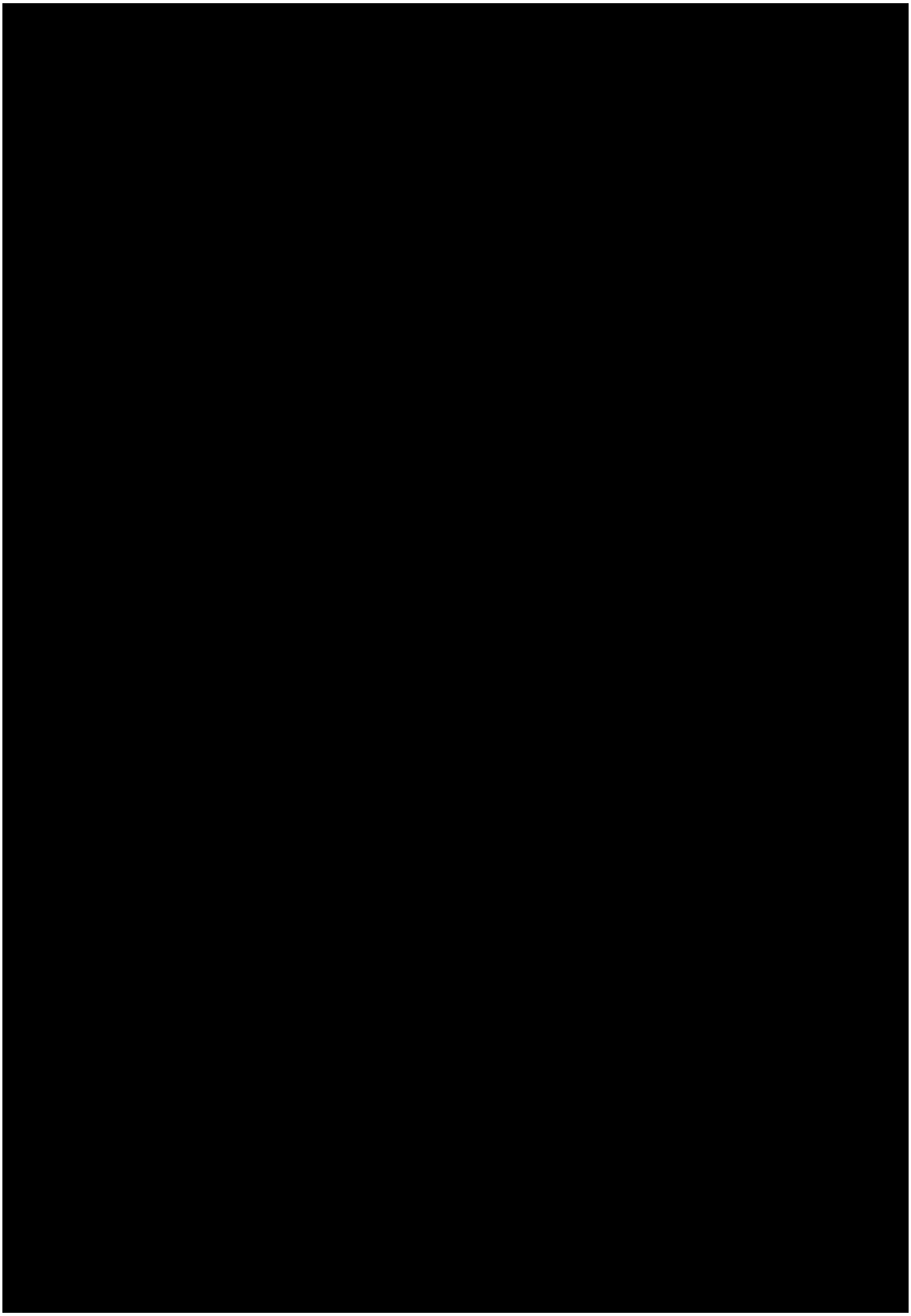
Abbreviations: IgA = immunoglobulin A; IgG = immunoglobulin G.

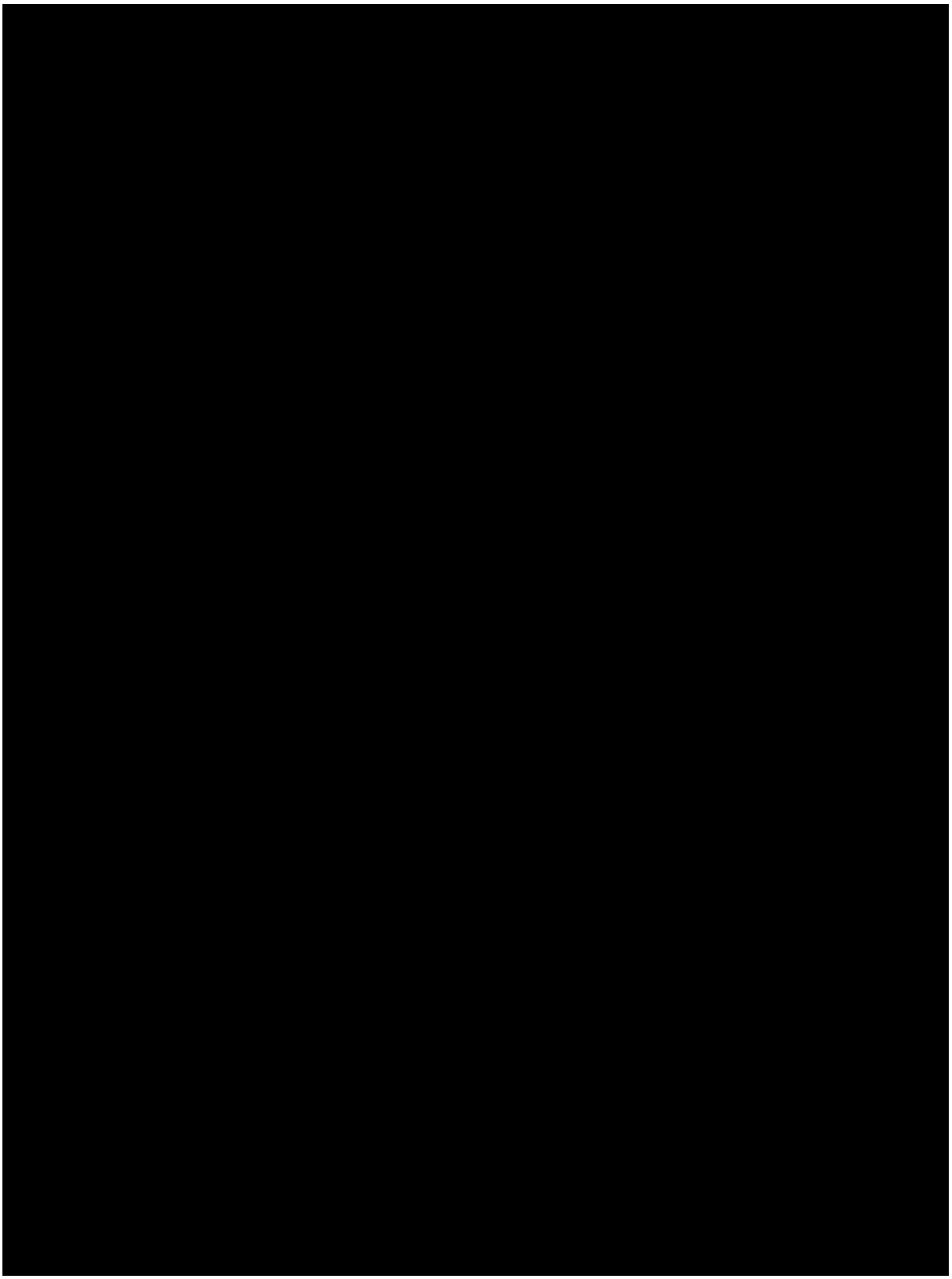
Durie-Salmon subclassifications (either A or B):

A: Relatively normal renal function (serum creatinine value < 2.0 mg/dL).

B: Abnormal renal function (serum creatinine value ≥ 2.0 mg/dL).

14.6 European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (version 3)





14.7 International Myeloma Working Group (IMWG) Response Criteria

Table 1. IMWG uniform response criteria by response subcategory for multiple myeloma

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	Not meeting criteria for CR, VGPR, PR, or PD	Increase of 25% from lowest response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio *and*	≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria		Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or*
< 5% PCs in bone marrow	Absence of clonal PCs by immunohistochemistry		If serum and urine M-protein are not		Urine M-component (absolute increase must
	or 2- to 4-color flow cytometry		measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30%		be ≥ 200 mg/24 h), *and/or*
			In addition to the above criteria, if present at		Only in patients without measurable serum and urine
			baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required		M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
					Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)
					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

Adapted from Durie et al[7] and Kyle et al[13] with permission. All response categories (CR, sCR, VGPR, PR, 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.

PCs indicate plasma cells.

*Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

†Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients 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.

14.8 Amendment 1 Detailed Summary of Changes

THE PRIMARY SECTIONS OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 1 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Revise the protocol title to reflect the added population of patients with RRMM

The primary change occurs on Title Page:

Formerly read:	An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 With Cyclophosphamide and Dexamethasone In Patients With Newly Diagnosed Multiple Myeloma Requiring Systemic Treatment.
Now reads:	An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 With Cyclophosphamide and Dexamethasone In Patients With Newly Diagnosed **or Relapsed and/or Refractory** Multiple Myeloma Requiring Systemic Treatment.

Sections that also contain this change are:

- Protocol Summary
- Section 12, INVESTIGATOR AGREEMENT

Purpose: Revise the Study Overview Diagram to include the patient population with RRMM

The change occurs in Study Overview Diagram:

Summary of change:	A schematic was added of study overview for patients s with RRMM

Purpose: Clarify the description of VELCADE/cyclophosphamide/dexamethasone (VCD) as a therapeutic option for frontline treatment of patients with multiple myeloma

The change occurs in Section 1.1.1, Disease Under Treatment:

Deleted text:	VCD ~~has become a standard of care an~~d is one of several preferred therapeutic options available as frontline therapy for transplant-eligible patients.

Purpose: Update the details of the clinical experience with MLN9708

The change occurs in Section 1.3, Clinical Experience:

Formerly read:	The adverse events (AEs) are consistent with the ~~class-based~~ effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less.
Now reads:	The adverse events (AEs) are consistent with the **known** effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less.

Section 1.4.1, Feasibility of Combination of MLN9708, Cyclophosphamide, and Dexamethasone Therapy also contains this change.

Purpose: Add a brief description of treatment options and prognosis for patients with RRMM

The change occurs in Section 1.1.1, Disease Under Treatment:

Added text: **For patients with relapsed and/or refractory multiple myeloma (RRMM) who experience disease progression after their initial therapy, response to subsequent treatments varies with a decreased likelihood of response and a tendency towards a shorter duration of response (DOR). Ultimately, RRMM becomes refractory to approved therapies, and patients have no alternative treatment options**.

Purpose: Provide a rationale for adding patients with RRMM to the study

The change occurs in Section 1.4, Study Rationale:

Added text: **Relapsed and/or Refractory Disease**

Although multiple therapies are available for patients with RRMM, the frequent relapses that characterize this disease highlight a need for new therapies for patients in whom prior treatments have failed.[18] VCD has been shown to be an effective treatment in patients with RRMM and has a favorable toxicity profile. VCD is recognized by the NCCN as salvage therapy for patients with RRMM with an ORR of 75% to 83%.[19, 20]

The early development program of MLN9708 in patients with RRMM investigated 2 dose schedules commonly used with the first-in-class proteasome inhibitor, VELCADE. In the open-label, dose-escalation, phase 1 studies, C16003 and C16004, MLN9708 was administered on a twice-weekly (Days 1, 4, 8, and 11 of a 21-day cycle) schedule and on a weekly schedule (Days 1, 8, and 15 of a 28-day cycle), respectively. In

both studies, patients had MM that had relapsed following at least 2 lines of therapy that included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, the MTD cohorts were expanded. Patients enrolled in these expansion cohorts had relapsed or refractory disease (refractory was defined as disease progression while on therapy or within 60 days after the last dose of therapy), and included patients who had been previously treated with a proteasome inhibitor such as VELCADE or carfilzomib and considered to be sensitive to a proteasome inhibitor or patients who were proteasome inhibitor naive. Preliminary data suggest that MLN9708 has antitumor activity in heavily pretreated patients with MM, with an ORR of 27% for the MTD expansion cohort in Study C16004. In both studies, durable responses and disease control have been observed with a generally acceptable toxicity profile.

The inclusion of an RRMM treatment arm in this study is proposed on the basis of results of VELCADE in patients with previously treated MM and the emerging activity seen with MLN9708 in patients with previously treated and untreated MM.

Purpose: Revise the description of the study purpose to include patients with RRMM

The change occurs in Section 1.4, Study Rationale:

Formerly read:	The purpose of Study C16020 is to determine the safety, tolerability, and efficacy ~~when~~ MLN9708 ~~is~~ added to a Cd backbone. ~~Extending~~ the duration of the response through prolonged use of single-agent MLN9708 as maintenance therapy following induction will also be evaluated. Patients with stable or responding ~~disease~~ at the end of induction therapy will continue ~~on~~ maintenance treatment.
Now reads:	The purpose of Study C16020 is to determine the safety, tolerability, and efficacy **of oral** MLN9708 when added to a Cd backbone **in patients with NDMM and RRMM**. **For patients with NDMM**, **extending** the duration of the response through prolonged use of single-agent MLN9708 as maintenance therapy following induction will also be evaluated. Patients with **NDMM who are** stable or responding at the end of induction therapy will continue **to receive MLN9708 as** maintenance treatment.

Purpose: Add the RRMM population to the discussion of the rationale for the combination therapy under evaluation in the study

The change occurs in Section 1.4.1, Feasibility of Combination of MLN9708, Cyclophosphamide, and Dexamethasone Therapy:

Formerly read:	Given the similar safety and tolerability profile of MLN9708 compared ~~to~~ VELCADE, adding MLN9708 to a Cd backbone is anticipated to be feasible from a safety perspective.

Now reads: Given the similar safety and tolerability profile of MLN9708 compared **with** VELCADE, adding MLN9708 to a Cd backbone is anticipated to be feasible from a safety perspective **in both the NDMM and RRMM settings**.

Purpose: Add the RRMM population to the discussion of dose intensity schedules for cyclophosphamide

The change occurs in Section 1.4.2, Rationale for the Combination of MLN9708, Cyclophosphamide, and Dexamethasone Dose and Dosing Schedule:

Formerly read: The dose-intensity schedules for cyclophosphamide tested in the myeloma setting are numerous and there is no dosing regimen that can be considered standard.

…

On the basis of available data on weekly cyclophosphamide tested in combination with a proteasome inhibitor in both transplant-eligible and transplant~~-noneligible NDMM~~ patients, weekly cyclophosphamide at a dose of 300 mg/m^2 on Days 1, 8, and 15 on a 28-day cycle was a safe and tolerable dose to consider and was selected for Arm A.

Now reads: The dose-intensity schedules for cyclophosphamide tested in the myeloma setting are numerous and there is no dosing regimen that can be considered standard **in either the frontline or relapsed and/or refractory disease setting**.

… On the basis of available data on weekly cyclophosphamide tested in combination with a proteasome inhibitor in both transplant-eligible and transplant-**ineligible** patients **with NDMM**, weekly cyclophosphamide at a dose of 300 mg/m^2 on Days 1, 8, and 15 on a 28-day cycle was a safe and tolerable dose to consider and was selected for Arm A **and the population with relapsed and/or refractory disease to be enrolled in Arm C**.

…

Although various dose schedules have been used for cyclophosphamide in combination with VELCADE in the relapsed and/or refractory setting, including the 500 mg weekly dose[19] or 50 mg daily dose,[20] a weekly dose of 300 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle is expected to be tolerable in combination with a proteasome inhibitor, based on the toxicity profile observed in patients with NDMM. An alternative dose schedule may be considered for Arm C if the planned dosage is not tolerated.

Purpose: Add the primary study objective for patients with RRMM and delineate the primary objective for the 2 patient populations

The primary change occurs in Section 2.1, Primary Objectives:

Formerly read:

The primary objective is:

- To determine the combined response rate of CR (including stringent CR [sCR]) + VGPR following treatment ~~of~~ oral MLN9708 when added to a ~~standard~~ regimen of cyclophosphamide, and low-dose dexamethasone (Cd) during the induction phase

Now reads:

The primary objective **for patients with newly diagnosed multiple myeloma (NDMM)** is:

- To determine the combined response rate of CR (including stringent CR [sCR]) + VGPR following treatment **with** oral MLN9708 when added to a regimen of cyclophosphamide and low-dose dexamethasone (Cd) during the induction phase

The primary objective for patients with relapsed and/or refractory multiple myeloma (RRMM) is:

- **To determine overall response rate (ORR; CR + VGPR + partial response[PR]) following treatment with oral MLN9708 when added to a regimen of Cd**

The Protocol Summary also contains this change.

Purpose: Add the secondary study objectives for patients with RRMM and delineate the secondary objectives for the 2 patient populations

The primary change occurs in Section 2.2, Secondary Objectives:

Formerly read:

~~T~~he secondary objectives ~~include~~:

- To evaluate the tolerability and toxicity of the combination of oral MLN9708 with Cd ~~in patients with NDMM~~
- To characterize the PK in plasma of oral MLN9708 in combination with Cd ~~in patients with NDMM~~

Now reads:

For patients with NDMM, **t**he secondary objectives **are**:

- To evaluate the tolerability and toxicity of the combination of oral MLN9708 with Cd
- To characterize the PK in plasma of oral MLN9708 in combination with Cd

…

For patients with RRMM, the secondary objectives are:

- **To evaluate the tolerability and toxicity of the combination of oral MLN9708 with Cd**
- **To characterize the PK in plasma of oral MLN9708 in combination with Cd**
- **To determine CR + VGPR, CR, VGPR, and PR**
- **To determine time to response for patients who respond**
- **To determine DOR**
- **To determine TTP**
- **To evaluate PFS**
- **To assess change in global health status, as measured by the patient-reported outcome (PRO) instruments European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30)**

The Protocol Summary also contains this change.

Purpose: Remove the EORTC Multiple Myeloma Module (MY-20) from the assessments to determine changes in global health status

The primary change occurs in Section 2.2, Secondary Objectives:

Deleted text:	To assess change in global health status, as measured by the patient-reported outcome (PRO) instruments European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) ~~and Multiple Myeloma Module (MY-20)~~

Sections that also contain this change are:

- Protocol Summary
- Schedule of Events
- Section 3.2, Secondary Endpoints
- Section 7.4.14, Quality of Life Assessment (European Organization for Research and Treatment of Cancer)
- Section 8.1.7, Analyses of Patient-Reported Outcomes
- Deleted Section 14.7

Purpose: Describe the tertiary/exploratory objectives for the 2 patient populations and add an additional tertiary objective of health care utilization assessments

The primary change occurs in Section 2.3, Exploratory Objectives:

Formerly read: The exploratory objectives ~~include~~:

Now reads: **For patients with NDMM and patients with RRMM**, the exploratory objectives **are**:

[redacted]

The Protocol Summary also contains this change.

Purpose: Align the primary, secondary, and tertiary study endpoints with the primary, secondary, and tertiary study objectives

The change occurs in Section 3.1, Primary Endpoint:

Formerly read: The primary endpoints ~~include~~:

- Combined response rate of CR (including sCR) + VGPR in patients treated with MLN9708 when added to a ~~standard care~~ regimen of Cd ~~during the induction phase~~

3.2 Secondary Endpoints

The secondary endpoints ~~include~~:

…

- ORR (CR + VGPR + PR), CR, VGPR, ~~and~~ PR during the induction phase and throughout the entire study

…

3.3 Exploratory Endpoints

The exploratory endpoints ~~include~~:

- [redacted]

Now reads: **For patients with NDMM**, the primary endpoints **are**:

- Combined response rate of CR (including sCR) + VGPR **during the induction phase** in patients treated with MLN9708 when added to a regimen of Cd

For patients with RRMM, the primary endpoint is:

- **ORR (CR + VGPR +PR) in patients treated with MLN9708 when added to a regimen of Cd**

3.2 Secondary Endpoints

For patients with NDMM, the secondary endpoints **are**:

…

- ORR (CR + VGPR + PR), CR, VGPR, PR, **stable disease (SD), progressive disease (PD)** during the induction phase**; ORR, CR + VGPR, CR, VGPR, PR, SD and PD** and throughout the entire study

…

For patients with RRMM, the secondary endpoints are:

- **All AEs, Grade 3 or higher AEs, AEs resulting in discontinuation, AEs resulting in dose reduction, serious adverse events (SAEs), and assessments of clinical laboratory values**
- **PK parameters including but not limited to single-dose maximum (peak) concentration (C_{max}), T_{max}, and AUC**
- **CR + VGPR, CR, VGPR, PR, SD, PD**
- **Time to response**
- **DOR**
- **TTP**
- **PFS**
- **Comparison of change in global health status between baseline and each postbaseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30**

3.3 Exploratory Endpoints

For patients with NDMM and patients with RRMM, the exploratory endpoints **are**:

- [redacted]

…

- [redacted]

Purpose: Clarify the study design for patients with NDMM and describe the study design for patients with RRMM

The primary change occurs in Section 4.1, Overview of Study Design:

Formerly This ~~will be~~ a phase 2, multicenter, open-label study in patients with NDMM

read: who have not received prior systemic treatment for MM and who are ineligible for high-dose therapy (HDT)-SCT due to age (ie, ≥ 65 years) or comorbid disease(s). It is expected that approximately ~~70~~ patients will be enrolled in this study.

~~Once enrolled~~, patients will be randomized 1:1 to either Arm A or Arm B. Each 28-day treatment cycle ~~is composed~~ of oral MLN9708 (4.0 mg on Days 1, 8, and 15) administered in combination with cyclophosphamide (300 mg/m^2 [Arm A] OR 400 mg/m^2 [Arm B] both on Days 1, 8, and 15) and dexamethasone (40 mg on Days 1, 8, 15, and 22). Patients over 75 years ~~old~~ will receive a reduced dose of dexamethasone ~~(~~20 mg~~)~~. Patients may receive MLN9708 in combination with Cd for an induction phase of approximately 1 year (13 × 28-day cycles) and if at least stable disease ~~(SD)~~ has been reached with an acceptable toxicity profile, patients will be administered, as maintenance, single-agent MLN9708 (at the dose tolerated at the end of induction) on Days 1, 8, and 15 in 28-day treatment cycles until ~~PD/~~death or unacceptable toxicity.

~~A~~ safety lead-in evaluation will be performed after at least 6 patients in each treatment arm have had the opportunity to complete at least 1 cycle of therapy. ~~T~~oxicities observed in the first 6 patients from each arm will be used to determine the safety of the regimen and the feasibility ~~to proceed to continue enrollment~~ to the study.

No formal interim analysis is planned; however, both safety and efficacy will be ~~continuously~~ monitored (see Section 8.1.10) throughout study conduct.

Response will be assessed according to the International Myeloma Working Group (IMWG) criteria ~~for all patients~~ every cycle during the induction phase and every other cycle during maintenance. Radiographic disease assessments are to be performed for patients with documented extramedullary disease. Patients discontinuing study drug ~~prior to PD~~ (ie, for withdrawal of consent, unacceptable toxicity, ~~or initiation of alternative antineoplastic therapy~~) will be followed for PFS until ~~PD/~~death.

…

~~MLN9708 in combination with Cd~~ will be discontinued ~~early if~~ a patient experiences ~~PD~~ or unacceptable study drug related toxicities. Patients may discontinue therapy at any time. Patients will attend the end of treatment (EOT) visit 30 days after receiving their last dose of study drug regimen.

Now reads: This **is** a phase 2, multicenter, open-label study in patients with NDMM who have not received prior systemic treatment for MM and who are ineligible for high-dose therapy (HDT)-SCT due to age (ie, ≥ 65 years) or comorbid disease(s) **and in patients with RRMM who have received 1 to 3 lines of prior therapy and whose disease is not refractory to proteasome inhibitors**. It is expected that approximately **148** patients will be enrolled in this study.

Patients With NDMM: Treatment Arms A and B

Patients **with NDMM** will be randomized 1:1 to either Arm A or Arm B. Each 28-day treatment cycle **consists** of oral MLN9708 (4.0 mg on Days 1, 8, and 15) administered in combination with cyclophosphamide (300 mg/m^2 [Arm A] OR 400 mg/m^2 [Arm B] both on Days 1, 8, and 15) and dexamethasone (40 mg on Days 1, 8, 15, and 22). Patients over 75 years **of age** will receive a reduced dose of dexamethasone 20 mg **on the same weekly schedule**. Patients may receive MLN9708 in combination with Cd for an induction phase of approximately 1 year (13 × 28-day cycles) and if at least stable disease has been reached with an acceptable toxicity profile, patients will be administered, as maintenance, single-agent MLN9708 (at the dose tolerated at the end of induction) on Days 1, 8, and 15 in 28-day treatment cycles until **disease progression**, death, or unacceptable toxicity.

Patients With RRMM: **Treatment Arm** C

Patients with RRMM will receive MLN9708 4.0 mg weekly on Days 1, 8, and 15, in combination with cyclophosphamide 300 mg/m^2 on Days 1, 8, and 15, and dexamethasone 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle (all orally administered). Patients over 75 years of age will receive the reduced dose of dexamethasone 20 mg on the same weekly schedule. Patients with an acceptable toxicity profile will continue treatment until disease progression, death, or unacceptable toxicity.

All Patients: Treatment Arms A, B, and C

For all 3 treatment arms, a safety lead-in evaluation will be performed after at least 6 patients in each treatment arm have had the opportunity to complete at least 1 cycle of therapy. **Dose-limiting** toxicities **(DLTs)** observed in the first 6 patients from each **treatment** arm will be used to determine the safety **and overall tolerability** of the regimen and the feasibility **of continued recruitmen**t to the study.

No formal interim analysis is planned; however, both safety and efficacy will be **continually** monitored (see Section 8.1.11) throughout study conduct.

Response will be assessed according to the International Myeloma Working Group (IMWG) criteria. **For patients with NDMM (Arms A and B), these assessments will be performed at** every cycle during the induction phase and **at** every other cycle during **the** maintenance **phase**. **For patients with RRMM (Arm C), response will be assessed at every cycle during the treatment period**. Radiographic disease assessments are to be performed for patients with documented extramedullary disease. Patients discontinuing study drug **before disease progression** (ie, for withdrawal of consent **or** unacceptable toxicity) will be followed for PFS until **disease progression or** death.

…

The study drug regimen will be discontinued **for** a patient **in any of the**

3 treatment arms who experiences **disease progression** or unacceptable study drug related toxicities. **This includes MLN9708 in combination with Cd during the induction period for patients with NDMM (Arms A and B) or the treatment period for patients with RRMM (Arm C). MLN9708 will also be discontinued for patients with NDMM (Arms A and B) who experience disease progression during the maintenance phase**. Patients may discontinue therapy at any time. Patients will attend the end of treatment (EOT) visit 30 days **(± 7 days)** after receiving their last dose of study drug regimen.

The Protocol Summary also contains these changes.

Purpose: Revise the anticipated number of enrolled patients and investigative sites

The primary change occurs in Section 4.2, Number of Patients:

Formerly read:	~~A~~approximately ~~70~~ patients will be enrolled in this study from approximately ~~20~~ study centers globally.
Now reads:	**It is anticipated that a**pproximately **148** patients, **70 patients with NDMM and 78 patients with RRMM**, will be enrolled in this study from approximately **30** study centers globally.

Sections that also contain this change are:

- Protocol Summary
- Section 8.1.1, Determination of Sample Size

Purpose: Revise the description for anticipated duration of study and timing of the clinical study report

The change occurs in Section 4.3, Duration of Study:

Formerly read:	This includes 24 months of enrollment~~, 12~~ months of ~~induction therapy, and 24 months of maintenance~~ and/or PFS follow-up ~~after the last patient completes induction therapy or until 75% of patients have progressed, whichever occurs first~~. The analyses for the clinical study report (CSR) will be conducted after all ~~patients~~ enrolled ~~in the study~~ have had the opportunity to complete ~~induction therapy~~.
Now reads:	This includes 24 months of enrollment **and up to 36** months of **treatment** and/or PFS follow-up. The analyses for the clinical study report (CSR) will be conducted after all enrolled **patients** have had the opportunity to complete **13 cycles of the study drug regimen**.

The Protocol Summary also contains this change.

Purpose: Add patients with RRMM to the description of study population and clarify the inclusion criteria for the 2 patient populations

The change occurs in Section 5, STUDY POPULATION:

Formerly read: Adult patients ~~age 18 or older~~ with a confirmed diagnosis of symptomatic MM who have received no prior antimyeloma treatment and ~~who~~ are ~~ineligible~~ for HDT-SCT due to age (> 65 years) or comorbidities ~~will be enrolled in this study~~.

Now reads: **Two patient populations will be enrolled in this study**:

- Adult patients with a confirmed diagnosis of symptomatic MM who have received no prior antimyeloma treatment (**NDMM**) and are **not candidates** for HDT-SCT due to age (> 65 years) or comorbidities; **and**
- **Adult patients with a confirmed diagnosis of symptomatic MM and relapsed and/or refractory disease (RRMM) after 1 to 3 lines of prior therapy and whose disease is not refractory to proteasome inhibitors**

Section 5.1, Inclusion Criteria, also contains this change.

Purpose: Describe the inclusion criteria that pertain to both patient populations (NDMM and RRMM)

The change occurs in Section 5.1, Inclusion Criteria:

Formerly read: Patients must meet the following clinical laboratory criteria:

- Absolute neutrophil count (ANC) $\geq 1000/mm^3$ and platelet count $\geq 75{,}000/mm^3$. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug ~~dosing.~~

Now reads: **In addition, all patients (NDMM and RRMM) must meet all of the remaining criteria**:

…

Patients must meet **all of** the following clinical laboratory criteria:

- Absolute neutrophil count (ANC) $\geq 1000/mm^3$ and platelet count $\geq 75{,}000/mm^3$. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to **administration of the** study drug.

Purpose: Add the pregnancy prevention guidelines for cyclophosphamide and dexamethasone

The primary change occurs in Section 5.1, Inclusion Criteria:

Added text:

- Agree to practice true abstinence **over the period previously described**, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.), **and**
- **Adhere to any treatment-specific pregnancy prevention guidelines for cyclophosphamide**[32, 33] **and dexamethasone**[34, 35, 36]

Section 6.6, Precautions and Restrictions also contains this change.

Purpose: Clarify the exclusion criteria for the 2 patient populations

The change occurs in Section 5.2, Exclusion Criteria:

Formerly read:

Patients meeting any of the following exclusion criteria are not to be ~~randomized to treatment~~:

1. Prior treatment for multiple myeloma with either standard of care treatment or investigational regimen.

…

5. Peripheral neuropathy Grade 1 with pain or ≥ Grade 2 of any cause on clinical examination during the Screening period.

Now reads:

Patients meeting any of the following exclusion criteria are not to be **enrolled in the study**:

1. Prior treatment for multiple myeloma with either standard of care treatment or investigational regimen (**for patients with NDMM only**).

…

5. Peripheral neuropathy Grade 1 with pain or Grade 2 **or higher peripheral neuropathy** of any cause on clinical examination during the Screening period.

Purpose: Revise and update the guidelines for study drug administration

The change occurs in Section 6.1, Study Drug Administration:

Added text: **Dosing should be performed on schedule, but occasional changes in patient scheduling are allowable (± 3 days) for holidays and vacations, except during Cycle 1 for all patients enrolled in the safety lead-in cohort. After the safety lead-in is completed within a treatment arm, an occasional change in the dosing schedule (± 1 week) may be allowable for other administrative reasons after consultation with the Millennium project clinician (or designee)**.

Purpose: Describe and clarify the MLN9708 administration guidelines for the 2 patient populations

The primary change occurs in Section 6.1.1, MLN9708 Administration:

Formerly read:

During induction, oral MLN9708 will be given weekly at a dose of 4.0 mg on Days 1, 8, and 15 of a 28-day cycle.

At the end of 13 cycles of treatment, maintenance phase will start. If the patient is still on study (has achieved at least ~~SD~~ with an acceptable toxicity profile), MLN9708 will be continued as a single agent, weekly ~~(~~Days 1, 8, and 15~~) in~~ a 28-day cycle at the same dose ~~tolerated~~ at the end of induction therapy. Under certain circumstances the maintenance dose may be increased up to but not exceeding the starting dose of the induction phase if the investigator and Millennium project clinician (or designee) both agree that it would be beneficial for the patient.

The study drug should be taken at approximately the same time each day, on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. Patients should be instructed to swallow MLN9708 capsules whole with water and not to chew, break, or open the capsules. Each dose of MLN9708 will be taken orally with approximately 8 ounces (ie, 240 mL) total of water consumed.

Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away.

Now reads:

Patients With NDMM (Arms A and B):

During induction, oral MLN9708 will be given weekly at a dose of 4.0 mg on Days 1, 8, and 15 of a 28-day cycle.

At the end of 13 cycles of treatment, **the** maintenance phase will start. If the patient is still on study (has achieved at least **stable disease** with an acceptable toxicity profile), MLN9708 will be continued as a single agent, weekly **on** Days 1, 8, and 15 **of** a 28-day cycle at the same dose **being given** at the end of induction therapy. Under certain circumstances the maintenance dose may be increased up to but not exceeding the starting dose of the induction phase if the

investigator and Millennium project clinician (or designee) both agree that it would be beneficial for the patient.

Patients With RRMM (Arm C):

For patients with RRMM, oral MLN9708 will be given weekly on Days 1, 8, and 15 of 28-day cycle at the dose of 4.0 mg until disease progression or unacceptable toxicity occurs.

All Patients (Arms A, B, and C)

For all 3 treatment arms, the study drug should be taken at approximately the same time each day, on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. Patients should be instructed to swallow MLN9708 capsules whole with water and not to chew, break, or open the capsules. Each dose of MLN9708 will be taken orally with approximately 8 ounces (ie, 240 mL) total of water consumed.

Missed doses **on Days 1 and 8** can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. **The missed dose on Day 15 can be taken only up to 72 hours after the planned dose (no later than on Day 18)**.

The Protocol Summary also contains this change.

Purpose: Describe and clarify the cyclophosphamide administration guidelines for the 2 patient populations

The change occurs in Section 6.1.2, Cyclophosphamide Administration:

Formerly read:

During induction, cyclophosphamide will be given weekly as a single, oral dose of 300 mg/m^2 (Arm A) OR 400 mg/m^2 (Arm B) and rounded to the nearest 50 mg, on Days 1, 8, and 15 of a 28-day cycle.

At the end of 13 cycles of treatment, the maintenance phase will start. If the patient is still on study, cyclophosphamide will be discontinued.

It is recommended that cyclophosphamide be taken in the morning and at approximately the same time each dosing day. Cyclophosphamide should be taken ~~at least 1 hour after MLN9708~~ with food or milk. Patients should be instructed to drink plenty of fluids and to urinate frequently during treatment with cyclophosphamide. Patients should be instructed to swallow cyclophosphamide capsules whole with water and not to chew, break, or open the capsules.

Missed doses can be taken within 48 hours from the ~~last~~ dose. If more than 48 hours ~~has~~ elapsed, the missed dose should be skipped and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

~~BSA~~ will be calculated using a standard formula on Cycle 1, Day 1 and on Day 1 of subsequent cycles if the patient experiences a > 5% change in body weight from the weight used for the most recent BSA calculation.

~~**Intrapatient Dose Escalation of Cyclophosphamide**~~

~~Intrapatient dose escalation is not planned; however, if during,~~ the ~~continuous monitoring of the study, clear evidence of antitumor activity is observed in Arm B (~~cyclophosphamide ~~400 mg/m^2) with an overall acceptable safety/tolerability profile, patients in Arm A (cyclophosphamide 300 mg/m^2) who have tolerated treatment with cyclophosphamide well at the initially assigned dose may be allowed to increase their dose of cyclophosphamide to 400 mg/m^2 in subsequent cycles of treatment following sponsor and investigator review of the available observed data. Patients in whom an increase in the dose of cyclophosphamide is being considered must have completed at least 2 cycles of treatment at their initially assigned dose. Hematology laboratory samples will be drawn weekly for the following 3 cycles once escalation has occurred.~~

Now reads: **Patients with NDMM (Arms A and B)**

During induction, cyclophosphamide will be given weekly as a single, oral dose of 300 mg/m^2 (Arm A) OR 400 mg/m^2 (Arm B) and rounded to the nearest 50 mg, on Days 1, 8, and 15 of a 28-day cycle.

At the end of 13 cycles of treatment, the maintenance phase will start. If the patient is still on study, cyclophosphamide will be discontinued.

Intrapatient Dose Escalation of Cyclophosphamide for Arm A

Intrapatient dose escalation is not planned; however, if during the continuous monitoring of the study data, clear evidence of antitumor activity is observed in Arm B (cyclophosphamide 400 mg/m^2) with an overall acceptable safety/tolerability profile, patients in Arm A (cyclophosphamide 300 mg/m^2) who have tolerated treatment with cyclophosphamide well at the initially assigned dose may be allowed to increase their dose of cyclophosphamide to 400 mg/m^2 in subsequent cycles of treatment following sponsor and investigator review of the available observed data. Patients in whom an increase in the dose of cyclophosphamide is being considered must have completed at least 2 cycles of treatment at their initially assigned dose. Hematology laboratory samples will be obtained weekly for the next 3 cycles once the dose has been increased.

Patients with RRMM (Arm C)

For patients with RRMM, cyclophosphamide will be given weekly on Days 1, 8, and 15 of a 28-day cycle as a single, oral dose of 300 mg/m^2 and rounded to the nearest 50 mg. An alternative dose schedule of cyclophosphamide may be explored for Arm C if the planned dose is not tolerated.

All Patients: Treatment Arms A, B, and C

For all 3 treatment arms, it is recommended that cyclophosphamide be taken in the morning and at approximately the same time each dosing day. Cyclophosphamide should be taken with **solid** food or milk. Patients should be instructed to drink plenty of fluids and to urinate frequently during treatment with cyclophosphamide. Patients should be instructed to swallow cyclophosphamide capsules whole with water and not to chew, break, or open the capsules.

Missed doses can be taken within 48 hours from the **planned** dose. If more than 48 hours **have** elapsed, the missed dose should be skipped and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Body surface area will be calculated using a standard formula on Cycle 1, Day 1 and on Day 1 of subsequent cycles. **I**f the patient experiences a > 5% change in body weight from the weight used for the most recent BSA calculation, the **BSA should be recalculated to determine the dose of** cyclophosphamide.

Purpose: Describe and clarify the dexamethasone administration guidelines for the 2 patient populations

The change occurs in Section 6.1.3, Dexamethasone Administration:

Formerly read:

During induction, dexamethasone will be given as a weekly oral dose of 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle. Patients ~~over~~ 75 years ~~old~~ will receive a reduced dose of dexamethasone ~~(~~20 mg~~,~~ same schedule~~)~~.

At the end of 13 cycles of treatment, maintenance phase will start. If the patient is still on study, dexamethasone will be discontinued.

~~I~~t is recommended that dexamethasone be taken in the morning and at approximately the same time each dosing day. Dexamethasone should be taken ~~at least 1 hour after MLN9708~~ with food or milk.

Missed doses can be taken within 48 hours from the ~~last~~ dose. If more than 48 hours ~~has~~ elapsed, the missed dose should be skipped, and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Now reads:

Patients With NDMM (Arms A and B)

During induction, dexamethasone will be given as a weekly oral dose of 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle. Patients **older than** 75 years **of age at the time of randomization** will receive a reduced dose of

dexamethasone 20 mg **on the** same **weekly** schedule.

At the end of 13 cycles of treatment, maintenance phase will start. If the patient is still on study, dexamethasone will be discontinued.

Patients With RRMM (Arm C)

For patients with RRMM, dexamethasone will be given as a weekly oral dose of 40 mg on Days 1, 8, 15, and 22 of a 28-day cycle. Patients older than 75 years of age at the time of enrollment will receive the reduced dose of dexamethasone 20 mg on the same weekly schedule.

All Patients (Arms A, B, and C)

For all 3 treatment arms, it is recommended that dexamethasone be taken in the morning and at approximately the same time each dosing day. Dexamethasone should be taken with **solid** food or milk.

Missed doses can be taken within 48 hours from the **planned** dose. If more than 48 hours **have** elapsed, the missed dose should be skipped, and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Purpose: Clarify the study enrollment guidelines for the 3 treatment arms

The change occurs in Section 6.2, Safety Lead-in:

Formerly read:

6.2 Safety Lead-in

A safety evaluation will be performed after at least 6 safety lead-in evaluable patients have had the opportunity to complete at least 1 cycle of treatment in each ~~arm~~. Toxicities observed in the first 6 safety lead-in evaluable patients from each ~~arm~~ will be used to determine the safety and overall tolerability of the regimen and the feasibility of continued recruitment to the study.

…

6.2.2 Rules for Continuous Study Enrollment

~~A~~ tolerable dose will require first-cycle DLTs (Section 6.~~3~~.1) in no more than 1 of 6 safety lead-in evaluable patients ~~enrolled at a specific dose level~~.

When 2 of 6 safety lead-in patients experience DLTs (~~Section 6.3.1~~) in 1 treatment arm and no more than 1 of 6 DLT-evaluable patients experience DLTs in the other arm, depending on the overall safety profile and the type of AEs/DLTs observed in ~~both~~ treatment arms, the decision will be made to either stop enrollment in that treatment arm or expand that treatment arm with 6 additional patients. A tolerable dose will then require first-cycle DLTs in no more than 3 of 12 safety lead-in evaluable patients in the expanding treatment arm to proceed with enrollment.

~~The enrollment in each treatment arm will be held after the 6th~~ ~~safety lead-in~~

~~evaluable patient has been enrolled, (or the 12th lead-in patient in the case of expansion) and has had the opportunity to complete Cycle 1. After the safety lead-in evaluation, if a treatment arm is stopped, enrollment in the other arm will continue.~~

If the decision is made to stop both treatment arms, enrollment in the entire study ~~will either stop~~ or alternative dosing levels may be evaluated following discussion between the sponsor and the investigators.

Now reads: 6.2 Safety Lead-in

A safety evaluation will be performed after at least 6 safety lead-in evaluable patients have had the opportunity to complete at least 1 cycle of treatment in each **of the 3 treatment arms (Arms A, B, and C)**. Toxicities observed in the first 6 safety lead-in evaluable patients from each **of the 3 treatment arms** will be used to determine the safety and overall tolerability of the regimen **in the 2 patient populations** (**patients with NDMM assigned to Arm A or Arm B and patients with RRMM enrolled in Arm C**) and the feasibility of continued recruitment to the study.

…

6.2.2 Rules for Continuous Study Enrollment

For each of the 3 treatment arms, a tolerable dose will require first-cycle DLTs (Section 6.2.1) in no more than 1 of 6 safety lead-in evaluable patients **in that treatment arm**.

For patients with NDMM, when 2 of 6 safety lead-in patients experience DLTs (Section 6.2.1) in 1 treatment arm and no more than 1 of 6 DLT-evaluable patients experience DLTs in the other arm**s**, depending on the overall safety profile and the type of AEs/DLTs observed in **the** treatment arms, the decision will be made to either stop enrollment in that treatment arm or expand that treatment arm with 6 additional patients. A tolerable dose will then require first-cycle DLTs in no more than 3 of 12 safety lead-in evaluable patients in the expanding treatment arm to proceed with enrollment.

Enrollment in any of the 3 treatment arms (NDMM and RRMM) will be held until the 6th patient has had the opportunity to complete Cycle 1, if a DLT occurs in 1 of the first 5 patients enrolled in that arm. Accrual to a treatment arm will also be stopped if any of the first 5 patients experience AEs, which may not qualify as DLTs per protocol-defined criteria, but the project clinician believes that it is in the interest of patient safety to hold enrollment until all 6 patients complete Cycle 1. If the first 5 patients complete Cycle 1 without any DLTs being observed, enrollment may continue in that treatment arm and will not need to be held until the 6th patient completes Cycle 1, provided that the regimen is being tolerated and no safety concerns are identified. Enrollment in each treatment arm will occur independently, so that accrual of patients to any of the 3 treatment arms can proceed even if enrollment is being

held in another treatment arm. In addition, patients previously enrolled in the treatment arm in which accrual is being held will have the opportunity to continue to receive the study drug regimen as long as it is being well tolerated and no safety concerns are identified in those patients. Randomization is required only when patients are being enrolled in Arms A and B concurrently.

After the safety lead-in evaluation, if 1 of the treatment arms for patients with NDMM is stopped, enrollment in the other arm will continue. If the decision is made to stop both treatment arms **(Arms A and B)**, enrollment in the entire study**, including accrual of patients to treatment Arm C may be stopped** or alternative dosing levels **for all 3 treatment arms** may be evaluated following discussion between the sponsor and the investigators. **If after the safety lead-in evaluation, accrual to Arm C is stopped, enrollment in the other 2 treatment arms may continue and alternate dose schedules may be explored for Arm C, following discussion between the sponsor and investigators**.

Purpose: Describe and/or clarify the dose modification guidelines for the 3 treatment arms.

The change occurs in Section 6.3, Dose Modification Guidelines:

Formerly read:	The same dose modification guidelines will apply ~~to~~ maintenance ~~cycles~~ unless otherwise noted.
Now reads:	The same dose modification guidelines will apply **during the** maintenance **phase for patients with NDMM (Arms A and B) who are receiving MLN9708**, unless otherwise noted

Sections that also contain this change are:

- Section 6.3.2, Criteria for Selection and Timing of Dose Modification (Delays, Reductions, and Discontinuations)
- Section 6.3.3, Permitted Dose Level Reductions
- Section 6.3.4, Dose Adjustments for Hematologic Toxicity: MLN9708 and Cyclophosphamide, Table 6-4, Dose Adjustments for Neutropenia

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Purpose: Clarify the permitted medications and procedures for patients in the 3 treatment arms

The change occurs in Section 6.5, Permitted Concomitant Medications and Procedures:

Formerly read:	Myeloid growth factors (eg, G-CSF, granulocyte macrophage-colony stimulating factor [GM-CSF]) are not allowed during Cycle 1 for the safety lead-in patients ~~in Arm A and Arm B~~, but may be considered according to standard clinical practice in Cycle 2 and beyond during the induction phase. Prophylactic antibiotics are not allowed during Cycle 1 for the safety lead-in patients ~~in Arm A and Arm B~~, but may be considered according to standard

clinical practice in Cycle 2 and beyond during the induction phase. No prophylactic antibiotics should be administered during maintenance.

Now reads: Myeloid growth factors (eg, G-CSF, granulocyte macrophage-colony stimulating factor [GM-CSF]) are not allowed during Cycle 1 for the safety lead-in patients, but may be considered according to standard clinical practice in Cycle 2 and beyond during the induction phase **for patients in Arms A and B**, **and in Cycle 2 and beyond during the treatment period for patients in Arm C**. Prophylactic antibiotics are not allowed during Cycle 1 for the safety lead-in patients, but may be considered according to standard clinical practice in Cycle 2 and beyond during the induction phase **for patients in Arms A and B, and during the treatment period for patients in Arm C**. No prophylactic antibiotics should be administered during maintenance **for patients in Arms A and B**.

Purpose: Revise and update the subheading pertaining to infection and add transverse myelitis to the discussion of clinical events for MLN9708

The change occurs in Section 6.7, Management of Clinical Events

Added text: Prophylaxis Against Risk of **Reactivation of Herpes** Infection

Transverse Myelitis

Transverse myelitis has been reported in a patient who was receiving MLN9708. It is not known whether MLN9708 causes transverse myelitis. However, because it was reported in a patient who was receiving MLN9708, the possibility that MLN9708 may have contributed to transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

Purpose: Revise the description of capsule sizes and capsule colors for MLN9708 to align with the certificate of analysis provided by the manufacturer

The change occurs in Section 6.9, Description of Investigational Agents, Table 6-8, MLN9708 Capsules:

Formerly read:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size ~~4~~	Ivory
3.0 mg	Size ~~3~~	Light gray
2.3 mg	Size ~~2~~	~~Light pink~~

Now reads:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size **3**	Ivory
3.0 mg	Size **4**	Light gray
2.3 mg	Size **4**	**Flesh**

Purpose: Clarify MLN9708 preparation, reconstitution, and dispensation guidelines

The change occurs in Section 6.9.1, MLN9708 Preparation, Reconstitution, and Dispensation:

Deleted text: ~~MLN9708 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling MLN9708 capsules~~.

Purpose: Clarify the storage, handling, and accountability requirements for MLN9708

The change occurs in Section 6.9.3, MLN9708 Storage, Handling, and Accountability:

Formerly read:

MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and carton and refrigerated as noted previously until the point of use. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. ~~Patients who are receiving take-home medication should be given only 1 cycle of medication at a time~~. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) ~~for the duration of each cycle~~. Patients should be instructed to return their empty cartons to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns ~~for their next cycle of take home medication~~. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because MLN9708 is an ~~investigational agent, it~~ should be ~~handled with due care~~.

Now reads:

MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and carton and refrigerated as noted previously until the point of use. Comprehensive instructions should be provided to the patient to ensure compliance with dosing procedures. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C). Patients should be instructed to return their empty cartons to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns **to the clinic**. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because MLN9708 is an **anticancer drug, as with other potentially toxic compounds, caution** should be **exercised when handling the study drug**.

Purpose: Clarify and/or define treatment assignments for the 3 treatment arms

The change occurs in Section 7.3, Treatment Group Assignments:

Formerly read:	After written informed consent has been obtained, patients will be randomized ~~in a~~ 1:1 ~~ratio~~ to either Arm A or Arm B. A centralized ~~randomization using~~ interactive ~~voice~~ response system (I~~V~~RS) will be used. If a patient discontinues from the study, ~~that~~ randomization code ~~will not be reused, and the~~ patient will not be allowed to re-enter the study.
Now reads:	After written informed consent has been obtained, patients **with NDMM** will be randomized 1:1 to either Arm A or Arm B. **Patients with RRMM will be assigned to Arm C**. A centralized interactive **web** response system (I**W**RS) will be used **for randomization and enrollment of all patients**. If a patient **with NDMM** discontinues from the study, **the** randomization code **for that** patient will not be **reused**. **No patient will not be** allowed to re-enter the study **after discontinuing from the study**.

Purpose: Clarify timing for performing study procedures

The change occurs in Section 7.4, Study Procedures:

Formerly read:	Tests and procedures should be performed on schedule, but occasional changes may be allowed (± ~~2~~ days) for holidays, vacations, and other administrative reasons.
Now reads:	Tests and procedures should be performed on schedule, but occasional changes may be allowed (± **3** days) for holidays, vacations, and other administrative reasons.

The Schedule of Events also contains this change.

Purpose: Clarify that assessment of comorbid conditions pertains to patients with NDMM only (Arms A and B)

The change occurs in Section 7.4.4, Assessment of Comorbid Condition(s) – Arms A and B:

Added text:	Assessment of Comorbid Condition(s) **– Arms A and B** During the Screening period, an assessment of comorbid condition(s) is to be conducted **for patients with NDMM only**.

Purpose: Clarify the guidelines for monitoring of peripheral neuropathy (PN) and PN-related events for the 2 patient populations

The primary change occurs in Section 7.4.11, Adverse Events:

Formerly read:	Note that in this study, PN will be captured in the same manner as all other adverse events during the induction and maintenance ~~periods~~, with the exception that downgrading of PN events must be reported until 1) resolution, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after treatment discontinuation, whichever occurs first.
Now reads:	Note that in this study, PN will be captured in the same manner as all other adverse events during the induction and maintenance **phases for patients in Arms A and B and the treatment period for patients in Arm C**, with the exception that downgrading of PN events must be reported until 1) resolution, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after treatment discontinuation, whichever occurs first.

Section 9.1.5, Monitoring of Adverse Events and Period of Observation, also contains this change.

Purpose: Revise the definition of enrollment in the study for the 3 treatment arms

The change occurs in Section 7.4.12, Enrollment:

Formerly read:	A patient is considered to be enrolled in the study when the patient ~~has been randomized~~ to ~~study~~ treatment.
Now reads:	A patient is considered to be enrolled in the study when the patient **is assigned** to **1 of the 3** treatment **arms in the study**.

Purpose: Clarify the guidelines for clinical laboratory evaluations

The change occurs in Section 7.4.13, Clinical Laboratory Evaluations:

Formerly read:	Clinical laboratory evaluations will be performed by a central laboratory. ~~For patients eligible for take home dosing, labs may be collected locally with the exception of Day 1 of each cycle~~. For dosing decisions, local hematology and chemistry laboratory results may be used.
Now reads:	Clinical laboratory evaluations will be performed by a central laboratory. For dosing decisions, local hematology and chemistry laboratory results may be used**; however, samples must still be sent to the central laboratory for evaluation**.

Purpose: Clarify the procedure for performing the skeletal survey at screening

The change occurs in Section 7.4.15, Skeletal Survey:

Formerly read:	A complete skeletal survey, using ~~roentgenography~~, will be performed at screening (within 8 weeks prior to ~~randomization~~), once annually, and if at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions.
Now reads:	A complete skeletal survey, using **conventional X-ray**, will be performed at screening (within 8 weeks prior to **enrollment**), once annually, and if at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions.

Purpose: Clarify that the blood sample for genotyping is optional and not required for study enrollment

The change occurs in Section 7.4.18, Blood Sample for Genotyping:

Added text:	**This blood sample is optional and is not required for enrollment in the study**.

Purpose: Revise and clarify disease response assessments for the 3 treatment arms

The change occurs in Section 7.4.24, Disease Response Assessment:

Formerly read:	Response assessments should ~~occur~~ at the times outlined in the Schedule of Events. … At any point during treatment ~~(induction or maintenance)~~, patients suspected ~~of having~~ ~~PD~~ will have response assessments repeated to confirm ~~disease progression (ie, 2 sets of response assessments at least 1 week apart;~~ local laboratory assessment is permitted).
Now reads:	Response assessments should **be performed** at the times outlined in the Schedule of Events. … At any point during treatment, patients **for whom disease progression is** suspected will have response assessments repeated to confirm **the assessment (**local laboratory assessment is permitted).

Purpose: Add description of health care utilization assessments

The change occurs in Section 7.4.25, Health Care Utilization Assessments:

Added text: **Health care utilization data will also be collected for all patients as specified in the Schedule of Events. Examples of data to be collected are the number, duration, and type of medical care encounters, such as inpatient admissions, outpatient visits, the accompanying reason for the visit (eg, medication, procedure, an AE), and homecare. In addition, the number is also captured of missed work days or other activities for the patient and patient's caregiver**.

Purpose: Clarify follow-up assessments for progression-free survival and SAE reporting during follow-up

The change occurs in Section 7.4.26, Follow-up Assessments (Progression-Free Survival):

Formerly read: The PFS follow-up visits should occur every 8 weeks from EOT until the occurrence of ~~PD/~~death, the patient withdraws consent for further follow-up, ~~or the initiation of alternative antineoplastic therapy~~. ~~All subsequent antineoplastic therapies will be recorded, regardless if they are initiated before or after PD.~~

…

In addition, new primary malignancies that occur during the follow-up periods, irrespective of causality to study regimen, must be reported to the Millennium Department of Pharmacovigilance or designee.

Now reads: The PFS follow-up visits should occur every 8 weeks from EOT until the occurrence of **progressive disease or** death, **or** the patient withdraws consent for further follow-up.

…

In addition, new primary malignancies that occur during the follow-up periods, irrespective of causality to study regimen, must be reported to the Millennium Department of Pharmacovigilance **& Risk Management** or designee **through death or termination of the study by the sponsor**.

Purpose: Describe and/or clarify the statistical considerations to determine sample size for the 2 patient populations (NDMM and RRMM)

The change occurs in Section 8.1.1, Determination of Sample Size:

Formerly read: The sample size ~~in~~ is calculated using 1 group Chi-square test for each arm separately based on the CR + VGPR rate following a MLN9708 combined treatment regimen. With 31 response-evaluable patients, there will be 80% power to test a null hypothesis CR + VGPR rate of 27% and an alternative hypothesis CR + VGPR rate of 45% at 1-sided significant level of $\alpha = 0.10$. Therefore, assuming 10% of patients are not response evaluable, approximately 35 patients ~~per arm~~ (70 total) will be enrolled in ~~this study.~~

Now reads: **The total sample size for the study will be approximately 148 patients. Approximately 70 patients with NDMM will be randomized 1:1 to Arm A or Arm B and approximately 78 patients with RRMM will be enrolled in Arm C**.

For patients with NDMM (Arms A and B), the sample size is calculated **by** using 1 group Chi-square test for each arm separately based on the CR + VGPR rate following a MLN9708 combined treatment regimen. With 31 response-evaluable patients **per treatment arm**, there will be 80% power to test a null hypothesis CR + VGPR rate of 27% and an alternative hypothesis CR + VGPR rate of 45% at 1-sided significant level of $\alpha = 0.10$. Therefore, assuming 10% of patients are not response evaluable, approximately 35 patients **each** (70 total) will be enrolled in **these 2 treatment arms**.

For patients with RRMM (Arm C), the sample size is calculated by using 1 group Chi-square test for each arm separately based on the ORR rate following a MLN9708 combined treatment regimen. **With 71 response-evaluable patients in Arm C, there will be 80% power to test a null hypothesis ORR rate of 60% and an alternative hypothesis ORR rate of 72% at 1-sided significant level of $\alpha = 0.10$**. **Therefore, assuming 10% of patients are not response evaluable, approximately 78 patients will be enrolled in Arm C in this study**.

Purpose: Revise and clarify the randomization or enrollment process for the 3 treatment arms

The change occurs in Section 8.1.2, Randomization and Stratification:

Formerly read:	This study will use a central (ie, not center-specific) randomization ratio of 1:1 to Arm A or Arm B.
Now reads:	This study will use a central (ie, not center-specific) randomization ratio of 1:1 to assign patients to Arm A or Arm B. **Randomization is not required if accrual to either Arm A or Arm B is stopped**. **No randomization will be used for patients in Arm C but an IWRS will be used for enrollment**.

Purpose: Revise the description of analysis populations

The change occurs in Section 8.1.3, Populations for Analysis:

Formerly read:	• Safety Population: Patients who receive at least 1 dose of any study drug. The safety population will be used for safety analyses. ~~The safety population~~ will be used for the analyses of TTP and ~~PFS~~. • DLT-Evaluable Population: Patients in the safety lead-in cohort who receive all doses of MLN9708 and cyclophosphamide during Cycle 1 per the Schedule of Events, or experience a DLT in Cycle 1.
Now reads:	• Safety Population: Patients who receive at least 1 dose of any study drug. The safety population will be used for safety analyses. **It** will **also** be used for the analyses of TTP, **PFS, QOL**, and **health care utilization data**. • DLT-Evaluable Population: Patients in the safety lead-in cohort who receive all doses of MLN9708 and **at least 80% of the** cyclophosphamide **dose** during Cycle 1 per the Schedule of Events, or experience a DLT in Cycle 1.

Purpose: Revise the proposed pooling of the study data and presentation of study results for the 3 treatment arms

The primary change occurs in Section 8.1.5, Demographic and Baseline Characteristics:

Formerly read:	Demographic and baseline characteristics will be summarized ~~by~~ treatment arm and by total, including gender, age, race, weight, height, BSA, primary diagnosis, and other parameters as appropriate.
Now reads:	Demographic and baseline characteristics will be summarized **for each** treatment arm and by **the** total **of Arms A and B**, including gender, age, race, weight, height, BSA, primary diagnosis, and other parameters as appropriate.

Sections that also contain this change are:

- Section 8.1.6.2, Secondary Efficacy
- Section 8.1.7, Analyses of Patient-Reported Outcomes
- Section 8.1.8, Analysis of Health Care Utilization Data
- Section 8.1.10, Safety Analysis
- Section 8.1.10.1, Peripheral Neuropathy Events
- Section 8.1.10.2, Drug Exposure of MLN9708, Cyclophosphamide, and Dexamethasone.

Purpose: Add text to clearly delineate the primary efficacy endpoint for the 2 patient populations

The change occurs in Section 8.1.6.1, Primary Efficacy:

Added text:	**For patients with NDMM (Arms A and B)**, the primary endpoint is the CR + VGPR rate during the induction phase. **For patients with RRMM (Arm C), the primary endpoint is ORR**. The primary efficacy analysis will be based on the response-evaluable population (patients enrolled in the safety lead-in portion are included). Estimates of the CR + VGPR rates **for Arms A and B**, **and ORR for Arm C** will be presented with 2-sided 95% exact binomial confidence intervals (CIs).

Purpose: Revise and update the description of secondary study endpoints

The change occurs in Section 8.1.6.2, Secondary Efficacy:

Formerly read:	The secondary efficacy ~~parameters~~ include ~~the~~ ORR (CR + VGPR~~ + PR~~), CR, VGPR, PR, time to response, DOR, TTP, PFS, and the change from baseline in QOL.
Now reads:	The secondary efficacy **endpoints** include ORR (**Arms A and B only**), CR + VGPR **(Arm C only**), CR, VGPR, PR, time to response, DOR, TTP, PFS, and the change from baseline in QOL.

Purpose: Describe the analysis of health care utilization data

The change occurs in Section 8.1.8, Analysis of Health Care Utilization Data:

Added text:	**Analyses of health care utilization data will be performed using the safety population and summarized for each treatment arm and by the total of Arm A + Arm B in descriptive statistics of medical encounters (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities by patient and caregiver.**

Purpose: Revise and update the description of safety analysis

The primary change occurs in Section 8.1.10, Safety Analysis:

Formerly read:	Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population~~.~~ ~~Exposure to study drug and reasons for discontinuation will be tabulated~~.
Now reads:	Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population **and summarized for each treatment arm and by the total of Arm A + Arm B**.

Purpose: Revise the description of assessments pertaining to drug exposure

The change occurs in Section 8.1.10.2, Drug Exposure of MLN9708, Cyclophosphamide, and Dexamethasone:

Formerly read:	~~The total doses received~~, number of treatment cycles, number of doses, and dose intensity of MLN9708, cyclophosphamide, and dexamethasone will be ~~presented and~~ summarized.
Now reads:	**Treatment duration**, number of treatment cycles, number of doses, **the total doses received** and dose intensity of MLN9708, cyclophosphamide, and dexamethasone will be summarized **for each treatment arm and for the total of Arms A and B**.

Purpose: Revise and update stopping rules for patients in the 3 treatment arms

The change occurs in Section 8.1.11, Interim Analysis:

Formerly read:	No formal interim analysis is planned. However, both safety and efficacy will be continuously monitored. Grade 4 or ~~greater~~ nonhematological toxicities will be monitored for each arm starting from the first 12 enrolled patients and then every 6 additional enrolled patients based on a Bayesian monitoring strategy.[37] If the stopping bounds of ≥ 4/12, ≥ 6/18, ≥ 7/24, and ≥ 8/30 have been achieved, accrual to the study will be suspended to allow for investigation. ~~After consideration by the study team, a decision will be made as to whether accrual can be resumed.~~ If the stopping rule is met, there is at least 80% probability that the true toxicity rate will be greater than 18%. ~~Similarly~~, the efficacy will be monitored ~~for each arm starting from the first 12 response evaluable patients after 6 cycles of treatment and then every 6 additional response evaluable patients~~ by the Bayesian Predictive Probability method. If the futility stopping bounds (CR + VGPR) of ≤ 2/12, ≤ 4/18, ≤ 7/24, and

≤ 10/30 have been met, further investigation will be made by the study team to assess if ~~either arm~~ may be terminated due to futility.

Now reads:

No formal interim analysis is planned. However, both safety and efficacy will be continuously monitored **on the basis of prespecified stopping rules**. Grade 4 or **higher** nonhematological toxicities will be monitored for each arm starting from the first 12 enrolled patients and then every 6 additional enrolled patients based on a Bayesian monitoring strategy.[37] If the stopping bounds of ≥ 4/12, ≥ 6/18, ≥ 7/24, and ≥ 8/30 **for Arms A and B (patients with NDMM), or the stopping bounds of ≥ 4/12, ≥ 6/18,≥ 7/24, ≥ 8/30, ≥ 9/36, ≥ 11/42, ≥ 12/48, ≥ 13/54, ≥ 14/60, ≥ 15/66, and ≥ 16/72 for Arm C (patients with RRMM)** have been achieved, accrual to the study will be suspended to allow for investigation. If the stopping rule is met, there is at least 80% probability that the true toxicity rate will be greater than 18%. **After consideration by the study team, a decision will be made as to whether accrual can be resumed**.

The efficacy will be monitored by the Bayesian Predictive Probability method **starting from the first 12 response-evaluable patients after 6 cycles of treatment and then every 6 additional response evaluable patients for Arms A and B or every 12 additional response-evaluable patients for Arm C**. If the futility stopping bounds (CR + VGPR) of ≤ 2/12, ≤ 4/18, ≤ 7/24, and ≤ 10/30 **for Arms A and B, or the stopping bounds (ORR) of ≤ 3/12, ≤ 10/24, ≤ 18/36, ≤ 26/48, and ≤ 36/60 for Arm C** have been met, further investigation will be made by the study team to assess if **accrual to any of the 3 treatment arms** may be terminated due to futility. **These futility stopping rules are established to allow no larger than 0.15 overall type I error rate (one-sided) and still maintain power of approximately 80%**.

Purpose: Update the SAE Reporting contact information to align with the sponsor's current guidelines and practices

The primary change occurs in Section 9.1.4, Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Formerly read:

SAE Reporting Contact Information

[redacted] ~~(North & South America):~~

~~24-hour helpline:~~ [redacted]

~~Fax:~~ [redacted]

[redacted] ~~(all other countries)~~:

~~24-hour helpline:~~ [redacted]

~~Fax:~~ [redacted]

Now reads:	SAE Reporting Contact Information **Cognizant** **US and Canada**: **Toll-Free Fax #:** [redacted] **E-mail:** [redacted] **All other countries (Rest of World)**: **Fax #:** [redacted] **E-mail:** [redacted]

Section 10.11, Product Complaints, also contains this change.

Purpose: Revise and update reporting requirements for new malignancies

The change occurs in Section 9.1.5, Monitoring of Adverse Events and Period of Observation:

Formerly read:	In addition, ~~all cases of~~ new primary ~~malignancy~~ ~~will~~ be ~~immediately~~ reported to the Millennium Department of Pharmacovigilance & Risk Management or designee, in compliance with regional governing regulations.
Now reads:	In addition, new primary **malignancies that occur during the follow-up periods must** be reported, **irrespective of causality to the study drug**, **from the first dose of study drug through death**, **until termination of the study by the sponsor**, **or for a minimum of** 3 **years after the last dose of the investigational product**, **whichever comes first**.

Purpose: Add a Schedule of Events for patients enrolled in Arm C (patients with RRMM)

The change occurs in the Schedule of Events: Arm C (RRMM)

Summary of change:	Two tables were added: Schedule of Events: Arm C (RRMM) and Study Drug Regimen Administration: Arm C (RRMM).

Purpose: Revise and update footnotes in the Schedule of Events to clarify study procedures

The change occurs in the Schedule of Events: Arms A and B (NDMM)

Formerly read:	Tests and procedures should be performed on schedule, but occasional changes may be allowed (± ~~2~~ days) for holidays, vacations, and other administrative reasons. … a Evaluations during the Screening period are to be conducted within 28 days before randomization, unless otherwise noted.

b During induction and maintenance, there will be a ± ~~2~~-day window for study visits unless otherwise noted.

…

~~g~~ Body surface area (BSA) will be ~~recalculated during induction for dosing purposes if a subject~~ experiences a > 5% change in weight from the weight used ~~in~~ the most recent BSA calculation.

…

o To be performed prior to dosing during induction, every other cycle during maintenance starting with Cycle 14, at EOT, and during PFS follow-up.

Now reads:

Tests and procedures should be performed on schedule, but occasional changes may be allowed (± **3** days) for holidays, vacations, and other administrative reasons.

…

a Evaluations during the Screening period are to be conducted within 28 days before randomization, unless otherwise noted. **The date of randomization or enrollment should be within 7 days of Cycle 1, Day 1 (C1D1)**.

b During induction and maintenance, there will be a ± **3**-day window for study visits unless otherwise noted.

…

g To assess MM-related symptoms and TEAEs.

h Body surface area (BSA) will be **calculated at C1D1 and at any subsequent visit that the patient** experiences a > 5% change in weight from the weight used **for** the most recent BSA calculation.

…

n Patient-reported outcomes assessments and health care utilization assessments should be completed before any other study procedures are performed and before the study drug regimen is administered.

…

q To be performed prior to dosing during induction, every other cycle during maintenance starting with Cycle 14, at EOT, and during PFS follow-up. **Note: The collection of these samples is required to be repeated at C1D1 only if the collection during screening was done > 14 days before the first dose of the study drug regimen**. **Serum-only patients will have 24-hour urine collected for UPEP and urine immunofixation at screening, noted complete response (CR) or progressive disease (PD), and at EOT. All other patients should have the M-component quantification by UPEP and urine immunofixation performed prior to dosing in every cycle in induction and every other cycle during the maintenance phase starting with Cycle 14, at EOT, and during PFS follow-up**.

Purpose: Add health care utilization assessments to the Schedule of Events (NDMM)

The change occurs in Schedule of Events: Arms A and B (NDMM)

Summary of change:	**A row for Health Care Utilization Assessment** was added to the Schedule of Events.

Purpose: Revise table title for the PK sampling schedule to include all 3 treatment arms

The change occurs in the Schedule of Events, Pharmacokinetic Sampling Schedule for All Patients in Safety Lead-In:

Added text:	Pharmacokinetic Sampling Schedule for **All** Patients in Safety Lead-In (**Arms A, B, C**)

Purpose: Revise and update the timing of predose PK assessments

The change occurs in Pharmacokinetic Sampling Schedule for All Patients in Safety Lead-In (Arms A, B, C), footnote a:

Formerly read:	a Predose PK assessments should occur within ~~1 hour~~ ~~of~~ dosing.
Now reads:	a Predose PK assessments should occur within **2 hours before** dosing

Purpose: Correct typographical errors, punctuation, grammar, and formatting

These changes are not listed individually.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical VP Approval	[redacted] 18:46
[redacted]	Clinical Approval	[redacted] 19:11