Title: A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral Ixazomib Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

NCT Number: NCT01564537

Protocol Approve Date: 08 January 2021

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

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CLINICAL STUDY PROTOCOL C16010 AMENDMENT 8

MLN9708

A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

Protocol Number:	C16010
Indication:	Relapsed and/or Refractory Multiple Myeloma
Phase:	3
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2011-005496-17
Therapeutic Area:	Oncology

Protocol History

Original	21 February 2012
Amendment 1	14 September 2012
Amendment 2 *(For use in China only)*	27 November 2013
Amendment 3	08 July 2014
Amendment 4 *(For use in China only)*	27 August 2014
Amendment 5 *(For use in China only)*	23 December 2015
Amendment 6	12 December 2016
Amendment 7 *(For use in China only)*	20 December 2016
Amendment 8 (substantial)	08 January 2021

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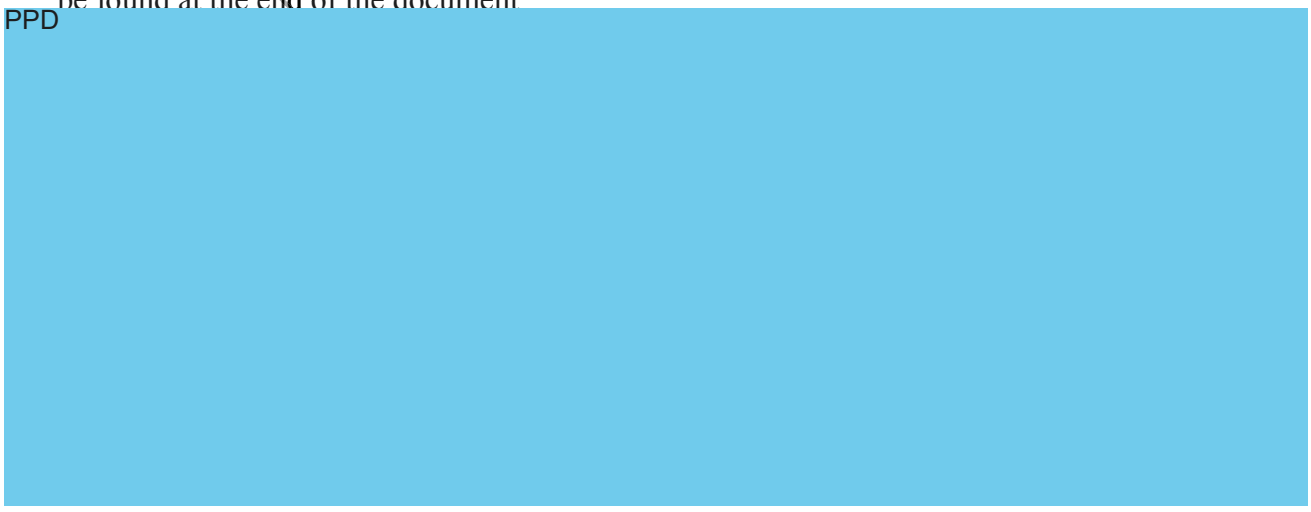
PPD



Rationale for Amendment 8

This document describes the changes to the protocol incorporating Amendment 8. The primary rationale for this amendment is to modify the study procedures and assessments for patients still on study at the time of the final analysis. The final analysis data cutoff has been conducted and as such, the study is considered complete for statistical analysis purposes. All patients will be unblinded. Only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Because no further formal statistical analyses will be performed, only assessments contributing to long-term safety monitoring are required. Most study assessments besides safety are discontinued to ease the burden of protocol-mandated assessments on patients.

Patients still on treatment at the time of the final analysis:

Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an End of Treatment (EOT) visit and transition onto an alternative supply of (eg, commercially available) ixazomib (MLN9708) and/or LenDex, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care.

Patients who are receiving ixazomib plus lenalidomide and dexamethasone (LenDex) will continue to receive ixazomib plus LenDex. Patients who are receiving placebo plus LenDex will receive LenDex only; the placebo capsule will no longer be administered and patients receiving placebo will not be crossed over to ixazomib in this study.

Upon implementation of Amendment 8, data collection requirements will be limited to collection of adverse events (AEs), serious adverse events (SAEs), laboratory assessments of safety, physical examinations, and concomitant medications. Quality of life, health care utilization, EQ-5D, and pain assessments are discontinued. Survival data will no longer be collected because the analysis of overall survival (OS) will be complete at the time of the final analysis. Other study assessments are no longer required, as noted in the new Schedule of Events (the previous, full Schedule of Events is now moved to Section 15.12 for reference only).

Patients in the OS Follow-Up Period at the time of the final analysis:

Upon implementation of Amendment 8, patients will no longer be followed in the OS Follow-Up Period. The EQ-5D and skeletal-related event assessments are discontinued. Survival data will no longer be collected because the analysis of OS will be complete at the time of the final analysis.

Descriptions of how to manage study procedures during unavoidable circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic, have additionally been added.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific descriptions of text changes and location of the changes, see Section 15.21.

Purposes for Amendment 8

The purposes of this amendment are to:

1. Clarify the study objectives as of Amendment 8.
2. Clarify the study endpoints as of Amendment 8.
3. Clarify that the final analysis data cutoff has been conducted and the study is considered complete for statistical analysis purposes.
4. Add language to clarify ongoing treatment of patients—patients still receiving study treatment will stay on their assigned study regimen. Patients should be moved off study and onto an alternative supply of (eg, commercially available) ixazomib and/or LenDex, or onto another standard of care treatment.
5. Discontinue all remaining efficacy assessments (eg, OS, Quality of Life) and clarify ongoing safety laboratory evaluations.
6. Discontinue the OS follow-up period.
7. Revise information regarding the interim analyses.
8. Update language about the management of clinical events in patients receiving ixazomib.
9. Clarify the procedures for storage, handling, and accountability.
10. Add flexibility in study conduct in unavoidable circumstances (eg, the COVID-19 pandemic).
11. Add language requiring all patients to reconsent.
12. Clarify the definition of Completion of Treatment.
13. Clarify the definition of Completion of Study.
14. Update the procedures for SAE reporting.
15. Add information about alternative monitoring approaches, such as remote source data verification, in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.

For specific examples of changes in text and where the changes are located, see Section 15.21.

PROTOCOL SUMMARY

Study Title: A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

Study Phase: 3

Number of Patients: Approximately 703

Study Objectives

Note that the primary objective and corresponding endpoint have been met. Upon implementation of Amendment 8, the objective is to continue to collect long-term safety data from patients who are continuing on ixazomib (MLN9708) and LenDex or LenDex (note the placebo capsule will be discontinued) because of continuing clinical benefit. Data collection for all other study objectives and endpoints will be complete at the time of the final analysis and no further formal analyses will be conducted. The original lists of objectives are retained below for reference only.

Primary Objective:

- To determine whether the addition of oral MLN9708 to the background therapy of lenalidomide and dexamethasone improves progression-free survival (PFS) in patients with relapsed and/or refractory multiple myeloma (RRMM)

Key Secondary Objectives:

- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves overall survival (OS)
- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves the OS in high-risk patients carrying deletion del(17)

Other Secondary Objectives:

- To determine overall response rate (ORR), including partial response (PR), very good partial response (VGPR), and complete response (CR)
- To determine CR + VGPR
- To determine duration of response (DOR)
- To determine time to progression (TTP)
- To determine the safety of the addition of MLN9708 to lenalidomide and dexamethasone
- To determine pain response rate, as assessed by the BPI-SF and analgesic use
- To assess change in global health status, functioning, and symptoms as measured by the patient-reported outcome (PRO) instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and MY-20 module
- To determine the PFS and OS in high-risk cytogenetic patient groups such as translocations t(4;14), t(14;16), +1q, del(13), or del(17)
- To evaluate the potential relationship between response or resistance to MLN9708 treatment and proteasome and NFKB-related genes, such as PSMB1 and TRAF-3 in blood samples
- To collect PK data to contribute to population PK analyses

CCI

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[redacted]

Overview of Study Design:

This is a phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of MLN9708 versus placebo in patients with relapsed and/or refractory multiple myeloma (MM) who are treated with lenalidomide and dexamethasone as their standard therapy. The patient population will consist of adult men and women who have a confirmed diagnosis of MM, who have received 1 to 3 prior lines of therapy, and who meet other outlined eligibility criteria.

Following the Screening period, patients who will be enrolled and treated with lenalidomide plus dexamethasone will be randomized to receive a study drug in a double-blind fashion, either MLN9708 or placebo. Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms, stratified by: 1 versus 2 or 3 prior therapies, proteasome-inhibitor (PI) exposed versus PI naïve, and International Staging System (ISS) stage at screening of 1 or 2 versus stage 3.

Patients will receive study drug (MLN9708 4.0 mg or matching placebo capsule) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients may continue to receive treatment until progressive disease or unacceptable toxicity, whichever comes first. Dose modifications may be made based on toxicities. Patients with a low creatinine clearance ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) will receive a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

Treatment periods will be defined as 28-day cycles. Patients will be seen at regular treatment cycle intervals while they are participating in the study: twice a treatment cycle for the first 3 cycles, then once a treatment cycle for the remainder of their participation in the active treatment and, if applicable, the PFS and OS follow-up phases of the study. As of Amendment 6, however, the primary endpoint has been met. As such, the PFS follow-up phase has been discontinued for patients currently receiving study therapy.

An independent review committee (IRC) will review all cases of disease response and progression. Response will be assessed according to the International Myeloma Working Group (IMWG) criteria for all patients every 4 weeks until disease progression. As of Amendment 6, however, because PFS follow-up is now completed for this study, for all patients still receiving study therapy, all central and investigator assessments of response and progression for protocol purposes are discontinued—IRC review will no longer be performed, and IRC response will no longer be assessed.

All patients will continue to be followed for survival after progression. Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

The final analysis data cutoff has been conducted and as such, the study is considered complete for statistical analysis purposes. All patients will be unblinded. Only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Because no further formal statistical analyses will be performed, only assessments contributing to long-term safety monitoring are required. Most study assessments besides safety are discontinued to ease the burden of protocol-mandated assessments on patients.

Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib and/or LenDex, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care.

Patients who are receiving ixazomib plus LenDex will continue to receive ixazomib plus LenDex. Patients who are receiving placebo plus LenDex will receive LenDex only; the placebo capsule will no longer be administered and patients receiving placebo will not be crossed over to ixazomib in this study. Upon implementation of Amendment 8, data collection requirements will be limited to collection of AEs, SAEs, and concomitant medications. Quality of life, health utilization, EQ-5D, and pain assessments are discontinued. Survival data will no longer be collected because the analysis of OS will be complete at the time of the final analysis. Other study assessments are no longer required, as noted in the new Schedule of Events. Patients will not be followed for the OS follow-up period because OS data are no longer being collected.

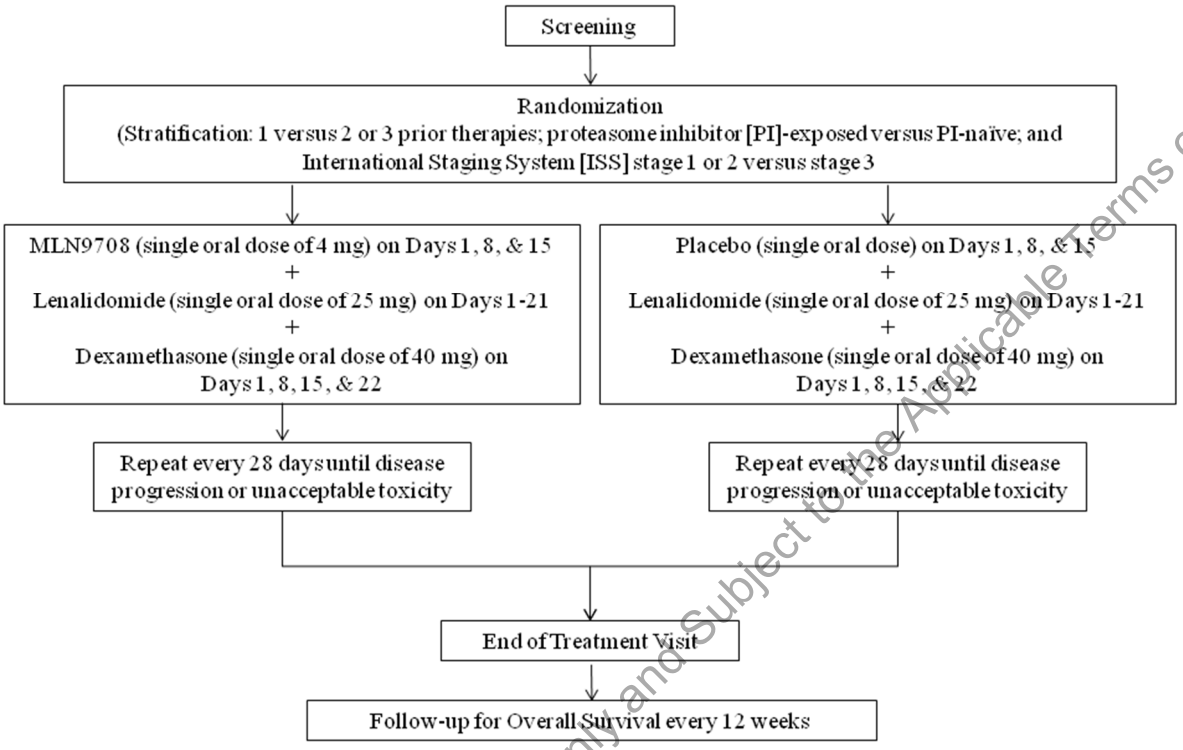
Study Population:

Adult patients with a confirmed diagnosis of symptomatic MM and relapsed and/or refractory disease will be enrolled in this study.

Duration of Study:

The duration of the study, including enrollment, treatment, and follow-up, will be approximately 81 months.

STUDY OVERVIEW DIAGRAM



NOTE: Upon implementation of Protocol Amendment 8, patients receiving placebo + LenDex will no longer receive the placebo capsule. In addition, follow-up for OS will no longer occur. The full Study Overview Diagram is retained for reference.

SCHEDULE OF EVENTS—AMENDMENT 8

The final analysis data cutoff has been conducted and as such, the study is considered complete for statistical analysis purposes. Upon implementation of Amendment 8, the investigator will unblind all patients remaining on study treatment and will follow the new Schedule of Events.

Only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Because no further formal statistical analyses will be performed, only assessments contributing to long-term safety monitoring are required. Most study assessments besides safety are discontinued to ease the burden of protocol-mandated assessments on patients. Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib (MLN9708) and/or LenDex, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care.

Patients who are receiving ixazomib plus LenDex will continue to receive ixazomib plus LenDex. Patients who are receiving placebo plus LenDex will receive LenDex only; the placebo capsule will no longer be administered and patients receiving placebo will not be crossed over to ixazomib in this study. Upon implementation of Amendment 8, data collection requirements will be limited to collection of AEs, SAEs, and concomitant medications. Quality of life, health care utilization, EQ-5D, and pain assessments are discontinued. Survival data will no longer be collected because the analysis of OS will be complete at the time of the final analysis. Other study assessments are no longer required, as noted in the new Schedule of Events. Patients will not be followed for the OS follow-up period because OS data are no longer being collected.

Study Procedures	**Treatment Period 28-Day Cycles**	**End of Treatment[b]**
Cycle	**Cycle X[a] and Beyond**	
Day	**1**	
Window	**± 1 week**	**+ 1 week**
Informed Consent (Reconsent)	X[c]	
Complete Physical Examination		X[d]
Symptom-Directed Physical Exam	X[d, e]	
Pregnancy Test [f]	X	X
Hematology	X[e, g]	X[g]
Clinical Chemistry	X[e, g]	X[g]
Adverse Event Reporting	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 [h]	
Serious Adverse Event Reporting	**Serious adverse 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 [h]	
New Primary Malignancy Assessment	Continuous from the start of study drug administration until death or termination of the study by the sponsor	
Concomitant Medications/Procedures	Recorded from the first dose of study drug through 30 days after last dose of study drug[i]	
Study Drug Administration		
MLN9708[j]	Days 1, 8, and 15 of each cycle	
Lenalidomide	Continuous Days 1-21 of each cycle	
Dexamethasone	Days 1, 8, 15 and 22 of each cycle	

AE=adverse event; eCRF=electronic case report form; GCP=Good Clinical Practice; IMiDs=immunomodulatory drugs; IEC=independent ethics committee; IRB=institutional review board; SAE=serious adverse event.

a Follow this Schedule of Events at the start of the next full treatment cycle upon implementation of Amendment 8.

b Patients who do not continue treatment must complete the End of Treatment assessments, which should occur 30 days (+1 week) after the last dose of study drug or prior to the initiation of subsequent antineoplastic therapy, whichever comes first.

c Before dosing on Day 1 of the next full treatment cycle upon implementation of Amendment 8, patients must be reconsented. Reconsenting should be done in person. Remote reconsenting is permitted as long as the process adheres to site, sponsor, IRB/EC, regulatory, and GCP standards and local regulations.

d Patients should be assessed and treated according to standard of care. Collect and record only clinically significant findings as AEs in the eCRF.

e Alternative methods for administering study procedures/assessments may be considered when it is not possible for the patient to come to the study site due to extenuating circumstances (eg, due to the COVID-19 pandemic). Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having lab assessment performed at a facility closer to the patient's home, etc.) If any of the following study procedures/assessments is missed because a site visit is done remotely, the study procedure/assessment is waived: complete physical examination,

symptom-directed physical examination, hematology, clinical chemistry, concomitant medications/procedures.

f Treatment with IMiDs requires pregnancy testing in female patients of child-bearing age prior to each cycle. A serum pregnancy test will be performed at the local laboratory for all women of childbearing potential.

g All central laboratory assessments are discontinued. Patients should be assessed and treated according to standard of care using local laboratory evaluations. Abnormal hematology and chemistry data are to be collected and recorded in the eCRF only to the extent that they are needed to document or support an AE. Laboratory assessments to inform dosing decisions and routinely monitor patients do not need to be recorded in the eCRF.

h Patients should be assessed and treated per standard of care. All AEs/SAEs will be recorded in the eCRF according to the criteria outlined in Section 10. Patient safety outside the protocol assessments should be monitored during the time between on-site visits at the investigator's discretion, per standard of care. At minimum, there will be a phone call with an investigator within the specified-visit window timeframe, which will include an assessment of AEs/SAEs.

i Concomitant medications are to be collected and recorded in the eCRF only to the extent that they are needed to document an AE.

j Only for patients who were receiving MLN9708 in combination with LenDex. Patients who received placebo in combination with LenDex will receive LenDex but will no longer be administered the placebo capsule.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATF-3	Activating Transcription Factor-3
AUC	area under the plasma concentration versus time curve
BPI-SF	Brief Pain Inventory – Short Form
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL	clearance, IV dosing
C_{max}	single-dose maximum (peak) concentration
CMH	Cochran-Mantel-Haenszel
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CYP	cytochrome P_{450}
Del	deletion
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of Treatment (visit)

Abbreviation	Term
EQ-5D	EuroQol 5-Dimensional Health Questionnaire
EU	European Union
FCBP	female of childbearing potential
FDA	United States Food and Drug Administration
GADD34	Growth Arrest DNA Damage 34
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GVHD	graft-versus-host disease
HIV	human immunodeficiency virus
HU	health utilization
IA	interim analysis
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMiD	immunomodulatory drugs
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IMWG	International Myeloma Working Group
IRB	institutional review board
IRC	independent review committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference

Abbreviation	Term
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MP	melphalan and prednisone
MR	minor response
MRI	magnetic resonance imaging
MRP2	multidrug resistance associated protein
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
NFKB	nuclear factor kappa-light chain enhancer of activated B cells
NSAID	nonsteroidal anti-inflammatory drugs
OME	oral morphine equivalent
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
PET-CT	positron emission tomography - computed tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI	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
PRO	patient-reported outcome
PSMB1	Proteasome subunit beta type-1
PTCL	peripheral T-cell lymphoma
QALY	quality-adjusted life year
QD	*quaque die*; each day; once daily
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RP2D	recommended phase 2 dose

Abbreviation	Term
RRAL	Relapsed or refractory Primary systemic light chain (AL) amyloidosis
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SmPC	Summary of Product Characteristics
SPEP	serum protein electrophoresis
SRE	skeletal-related event
SQ	subcutaneous
T	translocation
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
TRAF	Tumor necrosis factor receptor-associated factor
TSH	thyroid stimulating hormone
TTP	time to progression
UK	United Kingdom
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
US	United States
VGPR	very good partial response
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Multiple myeloma (MM) is a clonal disease of plasma cells that is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and sometimes results 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.[1-3] Although less common in Asian countries, MM is a growing health problem with an incidence that is approaching western countries and a larger population base.[4,5] In the United States, approximately 20,000 cases of MM are diagnosed each year and 10,650 deaths per year are due to the disease (approximately 2% of all cancer deaths).

Although MM is uniformly fatal, survival has dramatically improved over the last 2 decades because of newer and more effective treatment options. Between 1990 and 2007, the cancer death rate for people with MM in the United States decreased by approximately 9% for males and 13% for females due to introduction of stem cell transplant and novel agents VELCADE®, thalidomide, and lenalidomide.[6] In addition, 5-year survival improved from 25% in 1975 to 39% in 2006 because of the development of more effective treatments.[7] Most patients receive multiple therapies over the course of their disease; however, responses are transient despite the marked improvement in treatment options.

Multiple myeloma is sensitive to a number of cytotoxic drugs such as alkylating agents, anthracyclines, and corticosteroids for initial treatment and for relapsed disease. The last several years have witnessed the introduction of several agents such as VELCADE, thalidomide, and lenalidomide that have improved response, and contributed to the improved 5-year survival. VELCADE, the first proteasome inhibitor, has proven effective in the frontline setting including improvements in overall survival, has shown marked response in the relapsed setting, and is an effective agent in the pretransplant setting.

Despite the increase in the number of therapeutic options, the disease remains incurable and there is a need for new and better agents. Patients who relapse after their initial therapy demonstrate variable response to subsequent treatments with decreasing likelihood and duration of response (DOR). Patients ultimately become refractory to approved therapies

and have no alternative treatment options. In an effort to further target the proteasome with improved activity in MM and other cancers, Millennium has developed MLN9708, a small molecule 20S proteasome inhibitor.

1.1.2 MLN9708, Millennium's Next-Generation Proteasome Inhibitor

VELCADE (bortezomib), the first-in-class, small-molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc (Millennium), validated the proteasome as a therapeutic target. Recognizing that proteasome inhibition is an effective anticancer therapeutic approach, Millennium has developed MLN9708 with the aim of improving the pharmacology of the agent, building on the efficacy seen with VELCADE in MM and other hematologic malignancies, and improving safety and convenience of drug administration.

Like VELCADE, MLN9708 is a modified peptide boronic acid analog. MLN9708 is the citrate ester of the biologically active dipeptide boronic acid, MLN2238. MLN9708 was formulated to improve the chemical properties of MLN2238 for clinical delivery. MLN9708 rapidly hydrolyzes to MLN2238 upon contact with either plasma or aqueous solutions. MLN2238 is the active form that potently, reversibly, and selectively inhibits the proteasome. In contrast to VELCADE, MLN2238 demonstrates a faster dissociation rate from the proteasome that may result in enhanced tumor penetration, exhibits antitumor activity in a broader range of tumor xenografts, and has more prolonged tissue penetration.

MLN2238 preferentially binds the β5 site of the 20S proteasome; at higher concentrations, it also inhibits the activity of the β1 and β2 sites. MLN2238 was selective for the proteasome over a panel of several proteases (IC_{50} values between 20 and100 μM), 103 kinases (IC_{50} values > 10 μM), and receptors (IC_{50} values > 10 μM). MLN2238 and bortezomib have different β5 proteasome dissociation terminal disposition half-lives ($t_{1/2}$), reflecting differences in their on-off binding kinetics (the β5 proteasome dissociation [$t_{1/2}$] for MLN2238 and bortezomib are 18 and 110 minutes, respectively). Based on these favorable characteristics, MLN2238 is anticipated to be effective against MM.

1.2 Preclinical Experience

1.2.1 Nonclinical Pharmacology: In Vivo Studies

Antitumor activity was observed with MLN2238 in 4 xenograft models: CWR22 (a human prostate cancer cell line), WSU-DLCL2, OCI-Ly7-7D1-luc, and PHTX-22L (3 human lymphoma cell lines). In contrast, bortezomib demonstrated weaker antitumor activity in

these latter 3 lymphoma models, demonstrating that MLN2238 has improved activity in nonclinical models compared to bortezomib. MLN2238 treatment demonstrated an improved tumor pharmacodynamic response compared to bortezomib in WSU-DLCL2 human diffuse large B cell lymphoma (DLBCL) xenografts. WSU-DLCL2 xenografts from MLN2238-treated mice displayed greater tumor 20S proteasome inhibition compared to xenografts from bortezomib-treated mice and demonstrated increased downstream biological effects, as determined by protein marker expression.

MLN2238-treated xenografts displayed higher and more sustained 20S proteasome inhibition and increased downstream biological effects as determined by Growth Arrest DNA Damage 34 (GADD34) and Activating Transcription Factor-3 (ATF-3 levels). MLN2238 demonstrated both an improved efficacy profile and pharmacodynamic response compared to bortezomib.

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

1.3 Clinical Experience

Like VELCADE, MLN9708 is a modified peptide boronic acid analog. MLN9708 is the first investigational oral proteasome inhibitor in clinical trials in humans with safety, tolerability, PK, pharmacodynamics, and disease response assessed in each study. As of 12 October 2011, 247 patients have been treated with MLN9708 across 7 enrolling sponsor-led phase 1 or phase 1/2 studies with a twice-weekly and a weekly dosing schedule being evaluated. Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle and, in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. Details of these trials can be found in ClinicalTrials.gov, the current version of the IB, and the sections to follow.

In addition to the trials noted above and this study, there are currently 3 planned trials, each of which will use the oral formulation of MLN9708:

- Study C16008, oral (PO) twice-weekly administration in combination with lenalidomide and low-dose dexamethasone every 21 days in adult patients with newly diagnosed multiple myeloma (NDMM)

- Study C16009, PO administration on Days 1 and 15 of the first 28-day cycle to assess drug-drug interactions with ketoconazole, relative bioavailability, and food effect in patients with advanced solid tumor malignances, lymphoma, or Waldenstroms macroglobulinemia; PO administration in subsequent cycles on Days 1, 8, and 15 of a 28-day cycle

These studies are in the process of Investigational Review Board (IRB) and Ethics Committee reviews, but have not yet begun to enroll patients. (For additional information, please refer to ClinicalTrials.gov.)

Study C16011 is a phase 3 trial of weekly oral MLN9708 in combination with dexamethasone compared with physician's choice of treatment from a list of defined chemotherapy options, which are dexamethasone alone or dexamethasone combined with melphalan, cyclophosphamide, thalidomide, or lenalidomide in patients with relapsed or refractory systemic immunoglobulin light chain (AL) amyloidosis.

Clinical Trial Experience Using the Oral Formulation of MLN9708

In the 5 studies actively enrolling patients to investigate oral MLN9708 in patients with differing plasma cell dyscrasias (multiple myeloma and AL amyloidosis), a total of 115 patients have been treated thus far with different doses of MLN9708, as noted in Table 1-1.

Table 1-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 56	PO, twice weekly (TW), single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash,thrombocytopenia
C16004 RRMM N = 32	PO, weekly (W), single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting
C16005 NDMM N = 15	PO weekly, combination with LenDex	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switching to fixed dosing in phase 2, relevant to 2.23 mg/m^2)
C16006 NDMM N = 6	PO twice weekly (Arm A) and weekly (Arm B), combination with melphalan and prednisone	Arm A[a]: 3-mg fixed dose, TW: 3.7mg fixed dose Arm B[a]: 3-mg fixed dose, W: 4-mg fixed dose
C16007 RR-AL N = 6	PO, weekly, single agent	4-5.5-mg fixed dose[a] W

Abbreviations: RRAL = Relapsed or refractory Primary systemic light chain (AL) amyloidosis ; BSA = body surface area; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; NDMM = newly diagnosed multiple myeloma; PO = orally; RRMM = relapsed and/or refractory multiple myeloma; TW = twice weekly; W = weekly; RP2D= recommended phase 2 dose.

a Approximate BSA and flat dosing equivalence: 3 mg~ equivalent to 1.68-mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23-mg/m^2 BSA dosing; and 5.5 mg~ equivalent to 2.97-mg/m^2 BSA dosing.

The emerging safety profile indicates that oral MLN9708 is generally well tolerated with manageable and reversible treatment-emergent adverse events (TEAEs) or adverse reactions. As noted in Table 1-1, the maximum tolerated dose (MTD) has been established in 1 trial administering MLN9708 twice-weekly (Study C16003, relapsed/refractory multiple myeloma [RRMM]) and in 2 trials administering MLN9708 weekly as a single agent and in combination with lenalidomide and dexamethasone (LenDex) (Study C16004, RRMM and Study C16005, NDMM, respectively) with dose escalation continuing in 2 other enrolling studies (Study C16006, NDMM and C16007, relapsed/refractory amyloidosis [RRAL]). The potential risks reported with oral MLN9708 use, pooled from the enrolling 5 phase 1 and phase 1/2 clinical studies (N = 115) are shown in Table 1-2. As of 12 October 2011, no patient treated with the oral formulation of MLN9708 has reported Grade 3 peripheral neuropathy (PN); while 16% (18 patients) have reported Grade 1 or 2 PN with 12 of these patients reporting baseline Grade 1 neuropathy at study entry.

Table 1-2 MLN9708 Potential Risks (Pooled PO Formulation), as of 12 October 2011

Adverse Drug Reactions	Thrombocytopenia Skin rash (Includes terms: erythematous, generalized, pruritic, macular, macula-papular, papular) Nausea, vomiting, diarrhea Fatigue
Potential Risks Reported (> 10%) Due to MLN9708 or Disease Under Study	Fever Anorexia, constipation, dehydration Anemia, neutropenia Headache Upper respiratory infection, cough Dizziness Peripheral neuropathy Arthralgia

Relapsed and/or Refractory Multiple Myeloma

As of 12 October 2011, 2 ongoing phase 1 clinical trials were investigating oral MLN9708 in RRMM: Study C16003 and Study C16004. Both studies have completed the phase 1 portion of the study and patients are enrolling into defined expansion cohorts: relapsed and refractory multiple myeloma, VELCADE relapsed, proteasome inhibitor naïve, or carfilzomib exposed.

Study C16003 Single-agent; Twice-Weekly MLN9708

Study C16003 has enrolled 56 patients. These patients are heavily pretreated as evidenced by a median number of 4 (range 1–28) prior lines of therapy with 47% refractory to the last line of therapy.[8] Patients have received a median of 3.5 cycles of therapy (range 1-23). Six patients have achieved at least a partial response (PR) (1 complete response [CR] and 5 PRs); additionally 1 patient and 28 patients achieved minor response (MR) and durable disease stabilization for up to 12.9 months, respectively.[8]

In Study C16003, 1 of 3 patients experienced a protocol-defined dose-limiting toxicity (DLT) (Grade 3 rash) at a dose of 2.23 mg/m^2. An additional patient at this dose experienced Grade 4 thrombocytopenia (platelet count of 10,000/mm^3). After a discussion with the participating investigators, an intermediate yet lower dose was evaluated as allowed in the C16003 protocol and supported by available pharmacokinetic (PK) data to further characterize dose-related toxicities. Six patients were treated at the intermediate dose of

2.0 mg/m^2, a dose approximately half way between the 2 existing dose levels of 2.23 mg/m^2 and 1.68 mg/m^2 (a dose without any DLTs). Given that no patient (0/6) experienced a DLT, the MTD of PO MLN9708 administered twice weekly was determined to be 2.0 mg/m^2.[8]

A summary of the safety profile of patients treated in Study C16003 is outlined in Table 1-3. Overall, 98% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/2 in 10% of patients; with all of these patients reporting baseline Grade 1 PN at study entry.

Table 1-3 Study C16003: Oral MLN9708, Single Agent Given Twice Weekly, in RRMM Most Common TEAEs as of 12 October 2011 (N = 56)

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (57%) Skin rash (all terms) (50%) Thrombocytopenia (41%) Nausea (34%) Diarrhea (36%) Vomiting and fever (30% each) Cough (25%) Anorexia (23%) Neutropenia (21%)
Drug-Related Grade ≥ 3 in ≥ 2 Patients	Thrombocytopenia (n = 19) Neutropenia (n = 8) Fatigue (n = 5) Rash (all terms) (n = 5)

Fifteen patients have experienced drug-related serious adverse events (SAEs) involving thrombocytopenia, anemia, neutropenia, febrile neutropenia, nausea, vomiting, abdominal pain, chest pain (noncardiac), orthostatic hypotension, hypotension, hypophosphatemia, hyperuricemia, febrile neutropenia, fever, chills, rash, pneumonia, hypoxia, pulmonary hypertension, fall, headache, fatigue, or dehydration. Five patients discontinued therapy due to a TEAE; 3 patients due to events considered at least possibly related to MLN9708 (thrombocytopenia, pulmonary hypertension, and pruritic rash) and 2 patients due to events related to disease progression (spinal cord compression and bone pain). There have been 2 on-study deaths reported as not related to study drug.[8]

Study C16004 Single-agent; Weekly MLN9708

As of 12 October 2011, 28 patients have been enrolled in the dose escalation phase of Study C16004, in which MLN9708 is administered weekly. These patients are heavily pretreated as evidenced by a median number of 5 (range 2–15) prior lines of therapy with 59%

refractory to the last line of therapy.[9] Patients have received a median of 2 cycles of therapy (range 1-11). Two patients have achieved objective response: 1 achieved a VGPR and 1 achieved a PR. Additionally 6 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 2 patients remain on treatment; discontinuation was mainly due to progressive disease (PD) (69%).[9]

In Study C16004, 2 of 3 patients experienced protocol-defined DLT (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m^2. As per protocol, subsequent patients were treated at 1 dose level below (2.97 mg/m^2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral MLN9708 was determined to be 2.97 mg/m^2. This dose cohort is currently being expanded to further evaluate the safety and activity of MLN9708.[9]

A summary of the safety profile of patients treated in Study C16004 (28 patients in the dose escalation phase and 4 in the extension phase) is outlined in Table 1-4. Overall, 97% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/2 in 3 patients; with all patients reporting baseline Grade 1 PN at study entry.

Table 1-4 Study C16004: Oral MLN9708, Single Agent Given Weekly, Most Common TEAE as of 12 October 2011 (N = 32)

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (50%) Thrombocytopenia (34%) Nausea (38%) Diarrhea (31%) Vomiting (28%)
Drug-Related Grade ≥ 3 in ≥ 2 Patients	Thrombocytopenia (n = 4; 1 Grade 4 and 3 Grade 3) Neutropenia and diarrhea (n = 3 each)

There have been 2 drug-related SAEs involving diarrhea, dehydration, and dizziness. Six patients discontinued therapy due to a TEAE considered at least possibly related to MLN9708 (thrombocytopenia, rash, neutropenia, diarrhea, nausea, vomiting, and abdominal pain). There has been 1 on-study death reported which was considered related to disease progression.[9]

Newly Diagnosed Multiple Myeloma

As of 12 Oct 2011, 2 ongoing phase 1/2 clinical trials are investigating oral MLN9708 in NDMM: Study C16005 and Study C16006.

In Study C16005, MLN9708 is given weekly (Days 1, 8, and 15) in combination with lenalidomide (Days 1-21) and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle. Enrollment to the phase 1 portion of the study is complete, with enrollment open to the phase 2 portion. This study has enrolled 15 patients as of the clinical data cut (12 Oct 2011) to 4 dose cohorts. No DLTs were seen at doses up to 2.23 mg/m^2. Three of 3 patients treated at the 3.95 mg/m^2 dose cohort experienced Grade 3 nausea and vomiting despite adequate anti-emetic therapy; 1 of which additionally experienced Grade 2 syncope and in another patient the dose of lenalidomide was compromised such that they received < 80% of the planned doses. As per protocol, subsequent patients were treated at 1 dose level below (2.97 mg/m^2) where 1 of 6 patients experienced a DLT (Grade 3 rash). The MTD of weekly MLN9708 in combination with a 28-day cycle of lenalidomide and dexamethasone was established at 2.97 mg/m^2. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to analyses of efficacy results and toxicity characterization (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Based on this review the RP2D dose was determined to be 2.23 mg/m^2 in this combination schedule. The clinical development of MLN9708 included a population PK analysis evaluating the feasibility of switching from body surface area (BSA)-based dosing to fixed dosing.[10] The results of this analysis support the transition from BSA-based dosing to fixed dosing. Therefore, in Study C16005, all patients treated in the phase 2 portion of the trial will receive oral MLN9708 at a fixed dose of 4.0 mg (the RP2D dose of 2.23 mg/m^2 x the mean patient BSA of 1.86 m^2.[11]

As of 12 October 2011, patients in Study C16005 have completed a median of 5 cycles (range 1-9). To date, all 15 response-evaluable patients have achieved a PR or better to therapy including 4 CRs, 4 VGPRs, and 7 PRs; 14 out of 15 patients achieved ≥ PR after Cycle 1, and all 15 achieved ≥ PR after Cycle 2.[11]

A summary of the safety profile of patients treated in Study C16005 is outlined in Table 1-5. Overall, 100% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1 or 2 in 3 patients.

Table 1-5 Study C16005: Oral MLN9708 Given Weekly in Combination With Lenalidomide and Dexamethasone, Most Common TEAEs as of 12 Oct 2011 (N = 15)

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (60%) Vomiting (53%) Anemia (40%) Diarrhea and nausea (33% each) Insomnia, peripheral edema, and thrombocytopenia (27%)
Drug-Related[a] Grade ≥ 3 in ≥ 2 Patients	Rash and vomiting (n = 2 each)

a Related means to ANY drug in the study drug combination.

There have not been any on-study deaths. One patient discontinued study drug due to an unrelated TEAE. Four patients have experienced drug-related SAEs involving nausea, vomiting, dehydration, dizziness, fainting, orthostatic hypotension, hypotension, deep vein thrombosis (DVT), atrial fibrillation, and muscle weakness.[11]

An additional study, Study C16006, is being conducted in patients with newly diagnosed multiple myeloma, investigating oral MLN9708 in combination with melphalan and prednisone. In this study, oral MLN9708 is being administered in 2 schedules: twice-weekly and weekly. On the twice-weekly schedule, MLN9708 is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29, and 32) with melphalan and prednisone (MP, Days 1-4) in a 42-day cycle. On the weekly schedule, MLN9708 is given weekly (Days 1, 8, and 15) with melphalan and prednisone (Days 1-4) in a 28-day cycle. This study recently started to enroll patients. Six patients, 3 in each treatment group, have been treated as of 12 October 2011; all patients received a fixed starting dose of 3.0 mg with standard dose MP. Early signs of activity were observed. No SAEs, study drug discontinuations due to TEAE, or deaths have been reported to date.

Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

Study C16007 is evaluating single-agent, weekly, oral dosing in patients with relapsed or refractory AL amyloidosis after at least 1 prior therapy. This study is currently enrolling patients in the phase 1 portion of the trial.

As of 12 October 2011, 6 patients have been treated at the first dose level in the dose escalation portion of Study C16007. One of the first 3 patients experienced thrombocytopenia that lasted more than 2 weeks (meeting the definition of a DLT due to the

delay in starting Cycle 2 for 2 weeks). The prolonged thrombocytopenia was thought to be due to the patient's underlying bone marrow reserve, as the platelet count did return to the patient's baseline level but not to levels defined by the protocol. As per protocol, 3 additional patients were treated at this first dose level without additional dose-limiting toxicity (DLT); thus, the dose of MLN9708 will be escalated in the next 3 patients. Early signs of activity were reported, including 3 of 6 patients with partial hematologic response after the first cycle. As of the data cut, best clinical responses include 2 hematologic VGPR, 1 hematologic PR, and stable hematologic disease after 1 cycle of therapy in 3 patients. TEAEs, irrespective of grade or causality, occurring in more than 1 patient include diarrhea and peripheral edema (3 patients each); anemia, fatigue, nausea, and thrombocytopenia (2 patients each). No TEAEs have resulted in study drug discontinuation. No deaths have been reported.

Clinical Trial Experience Using the IV Formulation of MLN9708

There are 2 ongoing studies investigating intravenous (IV) MLN9708 in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively). As of 12 October 2011, a total of 132 patients had been treated in these studies. Refer to the current version of the IB for more information about the potential adverse events of the IV formulation. Dose-limiting toxicities and preliminary observations of response as evidenced by at least a 50% reduction in disease burden have been reported as follows:

C16001 Solid Tumors, Twice-weekly, Single Agent (N = 111):

- DLT: rash, thrombocytopenia, and acute renal failure
- Doses investigated: 0.125 to 2.34 mg/m^2
- MTD: 1.76 mg/m^2
- Objective Response: 1 partial response in a patient with head and neck carcinoma [12]

C16002 Lymphoma, Weekly, Single Agent (N = 21):

- DLT: neutropenia
- Doses investigated: 0.125 to 2.34 mg/m^2 with enrollment currently open at 3.11 mg/m^2

- Objective Response: 3 PR (2 in patients with follicular cell lymphoma and 1 in a patient with peripheral T-cell lymphoma [PTCL]) [13]

Clinical Trial Safety Experience: Pooled IV and Oral Formulation

The potential risks reported with MLN9708 use, pooled from both IV and oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the MLN9708 IB and informed consent form (ICF) documents. The type of TEAE reported is consistent, regardless of the MLN9708 formulation, even though there are some differences in the frequency and severity of the reported events. While the predominant potential toxicities may be severe in some cases, they are largely reversible and can be managed by routine clinical monitoring and standard medical interventions, which may include dose reductions and supportive care. Please refer to the IB for further information.

1.4 Study Rationale

Despite clinical advantages provided by the proteasome inhibitor VELCADE and immunomodulatory (IMiD) agents thalidomide and lenalidomide in both previously untreated and treated patients with MM, the disease remains incurable.[14] Although multiple therapies are available for RRMM patients, the frequent relapses that characterize this disease highlight a need for new therapies for patients in whom prior treatments have failed. This study is designed to determine whether adding MLN9708 to a background therapy of lenalidomide and dexamethasone will improve the clinical outcomes of patients with RRMM.

1.4.1 Rationale for the Combination of MLN9708, Lenalidomide, and Dexamethasone

Clinical data support the combination of a proteasome inhibitor, an IMiD, and a glucocorticosteroid. The combination of bortezomib, lenalidomide, and low-dose dexamethasone, as noted in clinical studies and the National Comprehensive Cancer Network (NCCN) guidelines, illustrates that this combination is very active and well tolerated in the MM population.[15-18] From a clinical perspective, adding proteasome inhibitors to lenalidomide and dexamethasone has demonstrated significant synergistic effects.[8,17]

Recognizing that proteasome inhibition is an effective anticancer therapeutic approach, Millennium developed MLN9708, which is a modified dipeptide boronic acid proteasome inhibitor similar to VELCADE, with the aim of improving the pharmacology of the agent

and improving drug administration, while building on the efficacy seen with VELCADE. Given that MLN9708 has improved binding kinetics and a similar pharmacologic profile compared with VELCADE, it is expected that these differences will translate into similar, if not improved, efficacy and safety profiles.[19] Nonclinical work by Chauhan and colleagues supports clinical evaluation of MLN9708 in combination with lenalidomide and dexamethasone based on their results reporting that MLN2238 combined with lenalidomide or dexamethasone triggers synergistic anti-MM activity.[20]

In terms of safety, the toxicological profile of MLN2238 in nonclinical studies is generally consistent with class-based effects of proteasome inhibition and is similar to what has been reported previously in nonclinical studies with bortezomib. The most common TEAEs, regardless of causality, of single-agent MLN9708 across all dose level cohorts in all phase 1 studies reported to date, as discussed in Section 1.3, were anticipated based on preclinical data and previous experience with bortezomib. Given the available data, the similar nonclinical toxicity profile between MLN2238 and bortezomib, and the toxicities demonstrated in studies with lenalidomide and dexamethasone and the low potential for drug-drug interactions, it is anticipated that any potential for overlapping toxicities with a combination of MLN9708, lenalidomide, and dexamethasone can be monitored in the clinic with routine clinical observations and laboratory tests.

Patients enrolled in both arms of C16010 will receive lenalidomide and dexamethasone, one of several regimens recommended by the International Myeloma Working Group (IMWG) as well as the NCCN. While initial data from ongoing trials are promising regarding the addition of bortezomib to this regimen, longer follow up and data from randomized phase III studies are still needed before bortezomib is broadly incorporated into treatment recommendations.[21]

This study is proposed based on the results of VELCADE in previously treated MM,[22] the emerging activity seen with MLN9708 in the treatment of previously treated and untreated MM (see Section 1.3), and the urgent need for better treatment options for this incurable disease. This study is designed to determine the efficacy and safety of MLN9708 with lenalidomide and dexamethasone, compared with lenalidomide and dexamethasone alone in patients with relapsed and/or refractory MM. The primary purpose of this study is to determine the progression-free survival of patients in the 2 treatment groups.

1.4.2 Rationale for MLN9708, Lenalidomide, and Dexamethasone Dose and Schedule Selection

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 as a single agent and in combination with lenalidomide and dexamethasone. The weekly schedule was well tolerated in in vivo toxicology studies and was predicted to allow dosing on a schedule that produced maximum antitumor activity in mouse models. Study C16004, a phase 1 study in adult patients with RRMM, investigated single-agent MLN9708 in this weekly schedule. The estimated MTD is 2.97 mg/m^2 with DLTs of transient rash, nausea, and vomiting. Given that the weekly schedule of MLN9708 combines well with the established 28-day lenalidomide plus low-dose dexamethasone regimen providing a simple course of therapy for patients, Study C16005, a phase 1/2 study of weekly MLN9708 plus a 28-day cycle of lenalidomide (25 mg on Days 1-21) and dexamethasone (40 mg weekly on Days 1, 8, 15, and 22) was initiated.

In the phase 1 portion of Study C16005, 3 evaluable patients were enrolled in each of the following dose cohorts: Cohort 1 (1.68 mg/m^2), Cohort 2 (2.23 mg/m^2), and Cohort 3 (2.97 mg/m^2), respectively. There were no DLTs noted for any of these patients during Cycle 1. Three evaluable patients were enrolled in Cohort 4 (3.95 mg/m^2). DLTs were noted during Cycle 1 for 3 out of 3 patients in Cohort 4 at the 3.95-mg/m^2 dose level. The DLTs were Grade 3 fainting/passing out, nausea, vomiting, and diarrhea. Per protocol, dosing at the 3.95-mg/m^2 dose level was stopped. Since 6 patients were not enrolled at the previous dose level (2.97 mg/m^2), 3 additional patients were enrolled at this lower dose. One of the additional 3 patients had a DLT of Grade 3 rash during Cycle 1. Therefore, DLTs were noted for 1 out of 6 patients enrolled at the 2.97-mg/m^2 dose level; according to the protocol, 2.97 mg/m^2 was determined as MTD.

The clinical data were evaluated for the available phase 1 data, which included the analyses of efficacy results (response rates: PR, VGPR, and CR) and toxicity characterization (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, dose holding, and treatment discontinuation). Cycle 1 data from 15 evaluable patients were reviewed, as well as the available clinical data supporting tolerance over multiple treatment cycles. AEs that met DLT criteria in Cycle 2 and beyond were considered, and toxicities leading to dose modification in Cycle 2 and beyond were also considered.

Six patients were enrolled at the 2.97-mg/m^2 dose level. All 6 patients received all doses of MLN9708 and dexamethasone during Cycle 1. However, 3 out of 6 patients were not able to

receive all of their lenalidomide doses during Cycle 1 due to Grade 2 or 3 rash. Three patients were enrolled at the 2.23-mg/m^2 dose level. All 3 patients received all doses of MLN9708, dexamethasone, and lenalidomide during Cycles 1 through 3, except 1 patient who did not receive 1 dose of dexamethasone during Cycle 2. After 4 cycles of treatment, the patients enrolled at 2.23 mg/m^2 achieved responses of CR, PR, and VGPR, respectively. All 3 patients achieved PR after Cycle 1, 2 of them achieved VGPR after Cycle 2, and CR after Cycle 4 and Cycle 5. Given that the dose of MLN9708 at 2.97 mg/m^2 significantly compromised the doses of the lenalidomide and dexamethasone background regimen, and that the dose of 2.23 mg/m^2 is very tolerable and clinically active, the clinical team has proposed to use 2.23 mg/m^2 as the dose for the pivotal phase 3 trial. More data will be gained from the phase 2 cohort of the ongoing C16005 study, in which patients will receive MLN9708 at 2.23 mg/m^2.

This recommended starting dose of 2.23 mg/m^2 is translated into a fixed dose of 4.0 mg based on the results from the population PK analysis. At initiation of clinical development of MLN9708, early phase 1 clinical studies empirically used a BSA-based dosing approach that has been traditionally used in the development of cytotoxic anticancer agents. Accordingly, dosing of MLN9708 in individual patients was BSA-scaled (in mg/m^2) in Study C16005 and in 4 ongoing single-agent trials (Studies C16001, C16002, C16003, and C16004). However, it is well known that the clearance of small molecule drugs is typically not a linear function of BSA and the appropriateness of traditional BSA-scaled approaches for dosing anticancer agents has been critically questioned in the recent scientific literature.[23-26]

Therefore, a preliminary population PK analysis was performed for MLN9708 based on the available data from 4 ongoing phase 1 studies to quantitatively assess the contribution of interpatient variability in BSA to the overall interpatient variability in clearance of MLN9708, and thereby evaluate the feasibility of switching from BSA-based dosing to fixed dosing in future clinical development. A population PK model was built using data from both the twice-weekly and once-weekly IV (n = 86) and oral (n = 51) dosing regimens (N = 137). Population PK analysis showed that MLN9708 PK can be well described by a 3-compartment model with linear elimination for IV data and with an additional absorption compartment (first order absorption) for oral data. Covariate analyses indicate that interpatient variability in BSA, and/or body weight did not significantly contribute to the variability in clearance (CL) and volume of distribution (V2) in the central compartment. Clearance and volume of distribution in the central compartment (V2) are the PK parameters that will affect AUC and single-dose maximum (peak) concentration (C_{max}). The lack of a discernable relationship between BSA and MLN9708 clearance based on data in

137 patients over a relatively wide BSA range (1.4-2.6 m^2) indicates that total systemic exposure (AUC) following fixed dosing should be independent of the individual patient's BSA (see Figure 1-1). Therefore, BSA is not expected to affect C_{max} or AUC after IV or oral dosing, and thus fixed dosing is appropriate for both oral and IV routes of administration. The clinical development of MLN9708 has therefore transitioned from use of BSA-based dosing to fixed dosing in all recently initiated phase 1/2 studies (eg, Studies C16007, C16008, and C16009).

Accordingly, the starting dose of MLN9708 in the proposed phase 3 study is a fixed dose of 4.0 mg, based on the recommended dose of 2.23 mg/m^2 (using mean patient BSA of 1.86 m^2 from the 2208 patients with MM in VELCADE clinical trials for conversion to a fixed dose).

Figure 1-1 No Apparent Relationship Between MLN9708 Clearance and BSA

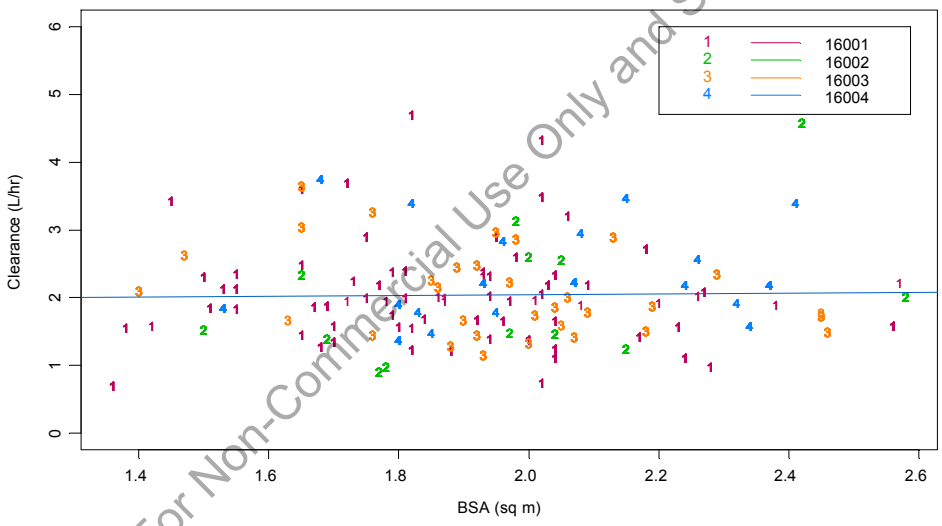

Figure 1-1 provides a plot of individual values of MLN9708 clearance across the range of BSA (1.4-2.6 m2) from 4 phase 1 studies (N = 137). Each color identifies each study and the blue line represents linear regression line.

1.4.3 Rationale for the Molecular Analyses

The heterogeneity of clinical results with myeloma therapeutics is, in large part, related to variation in the molecular subtypes of myeloma and the complex interaction of each tumor with the biology of the host. Several clinical studies have shown that tumor biology can be directly related to the clinical efficacy of either multidrug combinations in myeloma (a validated gene expression model of high-risk MM is defined by deregulated expression of

genes mapping to chromosome 1 [27-29] or to outcome after single-agent VELCADE therapy).[30,31] These studies highlight links between TRAF3, a key regulator of the NFKB pathway, and protein synthesis with clinical sensitivity and resistance respectively to VELCADE. A recent whole genome sequencing study of MM patients reported the presence of mutations in known cancer genes that had either not previously been reported in MM such as BRAF, or that were present at much higher frequency in MM than previously reported (KRAS, NRAS).[32] Similar studies with samples from VELCADE clinical trials highlighted the link between mutations in these pathways and response to proteasome inhibitor.[33]

In this clinical study, a screening tumor sample will be collected from each patient to test the link between clinical outcomes and the presence of specific gene mutations of the RAF/RAS pathway, as well as to test if expression of NFKB or protein synthesis gene signatures are related to the efficacy of the MLN9708-based combination. This hypothesis will be tested in all patients. Additional analyses of tumor molecular characteristics may be done to identify biomarkers linked to clinical outcomes in this study. These tumor analyses may include but are not limited to gene expression, DNA mutations, and/or epigenetic factors. Similar analyses will be done in tumor samples from patients who initially responded to therapy and subsequently relapsed.

Recent data also identify host variation, specifically germline DNA variants in proteasome subunits [34] and the NFKB pathway [35] as important contributors to VELCADE clinical activity. A blood sample will be collected at screening in order to test if specific polymorphisms in proteasome-related genes are associated with MLN9708 efficacy. Variants in NFKB-related genes will also be assessed, as they may relate to the activation of the NFKB pathway in the tumor or in the host microenvironment, impacting the growth, survival, and/or drug resistance of a given patient's myeloma. Additional associations with either the efficacy or safety of MLN9708 may be examined if there is a reasonable approach to identify myeloma patient populations with differential risk to benefit ratios upon treatment with MLN9708.

Circulating proteasome levels have been demonstrated to be an independent prognostic factor in MM patients with increasing circulating proteasome levels correlating with advance disease.[36] Given that MLN9708 directly targets the 20S proteasome, this leads to the possibility that pretreatment circulating proteasome levels may be relevant for prediction of patient response to therapy. Retrospective analysis of baseline proteasome levels from clinical trial samples for patients treated with bortezomib in combination with melphalan

and prednisone demonstrated that circulating proteasome levels were associated with both overall survival (OS) and progression free survival (PFS) only for bortezomib-containing therapy leading to the possibility that high-circulating protesome levels could be both a poor prognostic and also a specific marker of poor outcome with bortezomib. These data point to the potential value of further exploring the relationship between predose circulating proteasome levels and response to MLN9708. In this study, a blood sample will be collected at screening in order to test the levels of circulating proteasome and its association to MLN9708 efficacy.

1.4.4 Rationale for the Combination of MLN9708, Lenalidomide, and Dexamethasone in a High-Risk Patient Population

The clinical outcome of relapsed myeloma is highly variable and can be related to specific cytogenetic subtypes. Abnormalities such as t(11;14), t(6;14), and hyperdiploidy are associated with neutral or favorable prognosis while t(4;14), t(14;16), deletion(17p), and amplification of 1q impart an unfavorable prognosis.[37] Recently Klein et al and Bahlis et al have described the outcome of these subtypes in the context of patients with relapsed or refractory MM treated with lenalidomide and dexamethasone. Both del(17) and amplification 1q21 were associated with significantly worse PFS and OS, and the median OS for the del(17) patients was only 6.7 months.[38] Two recent reports showed that bortezomib-based treatment improves outcome in patients with MM including patients with high-risk chromosomal aberrations).[39,40] Patients with del(17) had a notable benefit. The median PFS time was 26.2 months for the bortezomib arm versus 12 months for the standard arm ($p = 0.024$), while the 3-year OS rate in this subtype improved from 17% to 69% ($p = 0.028$). After multivariate analysis, del(17) was an independent predictor for PFS ($p < 0.0001$) and OS ($p < 0.0001$) only in the bortezomib arm. In light of these observations, this study will assess the outcome of patients with del(17) RRMM to determine if addition of MLN9708 to lenalidomide and dexamethasone improves PFS and OS.

2. STUDY OBJECTIVES

Note that the primary objective and corresponding endpoint have been met. Upon implementation of Amendment 8, the objective is to continue to collect long-term safety data from patients who are continuing on ixazomib (MLN9708) and LenDex or LenDex (note the placebo capsule will be discontinued) because of continuing clinical benefit. Data collection for all other study objectives and endpoints will be complete at the time of the final analysis and no further formal analyses will be conducted. The original lists of objectives are retained below for reference only.

2.1 Primary Objective

The primary objective of this study is:

- To determine whether the addition of oral MLN9708 to the background therapy of lenalidomide and dexamethasone improves PFS in patients with RRMM

2.2 Secondary Objectives

The key secondary objectives are:

- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves OS
- To determine whether the addition of oral MLN9708 to lenalidomide and dexamethasone improves the OS in high-risk patients carrying deletion del(17)

Other secondary objectives include:

- To determine overall response rate (ORR), including PR, VGPR, and CR
- To determine CR + VGPR
- To determine DOR
- To determine time to progression (TTP)
- To determine the safety of the addition of MLN9708 to lenalidomide and dexamethasone
- To determine pain response rate, as assessed by the BPI-SF and analgesic use

- To assess change in global health status as measured by the global heath status, functioning, and symptoms as measured by the patient-reported outcome (PRO) instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and MY-20 module

- To determine the PFS and OS in high-risk cytogenetic patient groups such as translocations t(4;14), t(14;16), +1q, del(13), or del(17)

- To evaluate the potential relationship between response or resistance to MLN9708 treatment and proteasome and NFKB-related genes, such as PSMB1 and TRAF-3, in blood samples

- To collect PK data to contribute to population PK analyses

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[redacted]

3. STUDY ENDPOINTS

Note that the primary endpoint has been met. Upon implementation of Amendment 8, evaluation of the safety profile of MLN9708 and/or LenDex is the only endpoint being assessed. Analysis of all other study endpoints will be complete at the final analysis and no further formal statistical analyses will be performed. However, the complete list of endpoints is retained below for reference.

3.1 Primary Endpoint

The primary endpoint is:

- PFS, defined as the time from the date of randomization to the date of first documentation of disease progression based on central laboratory results and IMWG criteria as evaluated by an independent review committee (IRC), or death due to any cause, whichever occurs first

3.2 Secondary Endpoints

The key secondary endpoints are:

- OS, measured as the time from the date of randomization to the date of death
- OS in high-risk patients carrying del(17)

Other secondary endpoints are:

- Overall response rate (CR + VGPR + PR)
- CR + VGPR rate
- Duration of response, measured as the time from the date of first documentation of response to the date of first documented progression

- Time to progression, measured as the time from randomization to the date of first documented progression
- Eastern Cooperative Oncology Group (ECOG) performance scores, AEs, SAEs, and assessments of clinical laboratory values
- Pain response rate, measured by the proportion of pain responders, as determined by the BPI-SF and analgesic use
- 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 and MY-20
- OS and PFS in high-risk population carrying del(13), del(17), +1q21, t(4;14), or t(14;16)
- Association between response or resistance to MLN9708 treatment and proteasome and NFKB-related genes, such as PSMB1 and TRAF-3
- Plasma concentration-time data to contribute to future population PK analysis

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4. STUDY DESIGN

MLN9708 capsules and placebo capsules will be subsequently referred to as study drug.

4.1 Overview of Study Design

This is a phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of MLN9708 versus placebo in patients with relapsed and/or refractory MM who are treated with lenalidomide and dexamethasone as their standard therapy. The patient population will consist of adult men and women who have a confirmed diagnosis of MM, who have received 1 to 3 prior lines of therapy, and who meet other eligibility criteria (see Section 5). Approximately 703 patients will be enrolled in the study.

The following paragraphs describe the study design before implementation of Amendment 8.

General eligibility criteria may be assessed prior to the formal Screening period if it is part of standard clinical practice. However, per the Schedule of Events, formal screening will occur during the Screening period, which may last for up to 28 days prior to randomization. An MPI/designee clinician will confirm patient eligibility prior to randomization. Determination of disease progression as an entry criterion may be based on patient data obtained during or following the patient's most recent prior antineoplastic therapy.

Following the Screening period, patients who will be enrolled and treated with lenalidomide plus dexamethasone will be randomized to receive a study drug in a double-blind fashion, either MLN9708 or placebo. Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms, stratified by: 1 versus 2 or 3 prior therapies, proteasome-inhibitor exposed versus proteasome-inhibitor naïve, and ISS stage at screening of 1 or 2 versus stage 3.

Patients will receive study drug (MLN9708 4.0 mg or matching placebo capsule) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients may continue to receive treatment until PD or unacceptable toxicity, whichever comes first. Dose modifications may be made based on toxicities. Patients with a low creatinine clearance ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) will receive a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding

to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

Treatment periods will be defined as 28-day cycles. Patients will be seen at regular treatment cycle intervals while they are participating in the study: twice a treatment cycle for the first 3 cycles, then once a treatment cycle for the remainder of their participation in the active treatment and, if applicable, the PFS (every 4 weeks) and OS (every 12 weeks) follow-up phases of the study. As of Amendment 6, the primary endpoint has been met; as such, the PFS follow-up phase no longer applies to patients currently receiving study therapy or to any patients who have discontinued treatment for reasons other than PD. However, all patients will continue to be followed for survival.

Patients will be assessed for disease response and progression by an IRC. Response will be assessed according to the IMWG criteria for all patients every 4 weeks until disease progression. As of Amendment 6, however, because PFS follow-up is now completed for this study, for all patients still receiving study therapy, all central and investigator assessments of response and progression for protocol purposes will be discontinued—IRC review will no longer be performed, and IRC response will no longer be assessed.

All patients will continue to be followed for survival after progression or after discontinuation of treatment for reasons other than progression. Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

Pain evaluation (using the BPI-SF) will include quantified assessments of intensity, frequency and duration, degree of discomfort, location, and likely relationship to MM (versus prior therapy or comorbidities). Time to pain progression will be based on pain assessments using the worst pain item on the BPI-SF rated on a scale from 0 to 10, collected as outlined in the Schedule of Events.

Health-related quality of life (QOL) will also be evaluated through patient self-reported instruments including the EORTC QLQ-C30, MY-20, and the EQ-5D generic health status measure. In addition to assessing selected symptoms, these instruments elucidate the effects of disease on physical, social, psychological/emotional, and cognitive functioning.

ECOG performance score, adverse events (AEs), laboratory values, and vital sign measurements will be collected and assessed to evaluate the safety of therapy throughout the study. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010.

Unscheduled visits may occur between treatment cycles as required. For example, symptomatic pain progression should result in an interim unscheduled visit, as would ongoing Grade 3 or worse AEs.

Patients will attend an End of Treatment (EOT) visit approximately 30 days after receiving their last dose of study drug and will continue to be followed for other follow-up assessments specified in the Schedule of Events. Patients discontinuing study drug prior to disease progression will continue to be assessed for disease progression during the PFS follow-up portion of the study. All patients will now only be followed for survival after treatment termination or progression. Patients will be contacted every 12 weeks until death or termination of the study by the sponsor.

The final analysis data cutoff has been conducted. Upon implementation of Amendment 8, the investigator will unblind all patients remaining on study treatment and will follow the new Schedule of Events presented in this amendment. Only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Because no further formal statistical analyses will be performed, only assessments contributing to long-term safety monitoring are required. Most study assessments besides safety are discontinued to ease the burden of protocol-mandated assessments on patients.

Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib and/or LenDex, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care.

Patients who are receiving ixazomib plus LenDex will continue to receive ixazomib plus LenDex. Patients who are receiving placebo plus LenDex will receive LenDex only; the placebo capsule will no longer be administered and patients receiving placebo will not be crossed over to ixazomib in this study. Upon implementation of Amendment 8, data collection requirements will be limited to collection of AEs, SAEs, local laboratory

assessments of safety, physical examinations, and concomitant medications. Quality of life, health care utilization, EQ-5D, and pain assessments are discontinued. Survival data will no longer be collected because the analysis of OS will be complete at the time of the final analysis. Other study assessments are no longer required, as noted in the new Schedule of Events. Patients will not be followed for the OS follow-up period because OS data are no longer being collected.

Three interim analyses (IAs) have been planned during the study. The first will occur when approximately 262 patients have experienced disease progression or death. This is the first analysis for PFS and the first IA for OS. The second IA will occur when approximately 365 patients have experienced disease progression or death. This is the final analysis for PFS and the second IA for OS. If the test for PFS at the second IA is not statistically significant, the study will be claimed as unsuccessful and no further testing will be conducted. If the test for PFS is significant at either of the first two IAs, OS will be tested; however, the study will not be stopped for OS efficacy or futility due to the predicted small number of death events at the first IA.

As of Amendment 8, the 3 IAs have been performed. The primary analysis (data cutoff date, 30 October 2014) occurred when 286 patients had experienced disease progression or death; at this analysis, the primary endpoint of PFS was met. The next analysis (data cutoff date, 12 July 2015) occurred when 372 patients had experienced disease progression or death. This was the first analysis for OS. A total of 171 deaths had been reported and the threshold for OS statistical significance was not met. Per the study design and statistical analysis plan, the study was to continue, following patients for survival. The third IA (data cutoff date, 25 October 2017) occurred when 333 deaths had been reported. The threshold for statistical significance was not met and the study was to continue to the final analysis. The final analysis occurred in the fourth quarter of 2020.

An independent data monitoring committee (IDMC) will review safety and efficacy data at the IAs. See Section 9.3 for more information.

4.2 Number of Patients

Approximately 703 patients will be enrolled in this study from approximately 150 study centers globally.

4.3 Duration of Study

Patients will be followed up until 486 deaths have been reported. The duration of the study will be approximately 80 months (6 years 8 months), including 20 months for enrollment and 60 months follow-up from the last patient enrolled.

Patients may remain on treatment until the occurrence of PD or unacceptable toxicity. Delayed treatment-related AEs will be followed for 30 days after last dose of study drug. Patients who stop treatment for any reason other than disease progression will continue in PFS follow-up and be seen every 4 weeks until documented disease progression. After disease progression all patients will continue to the overall survival follow-up phase and be contacted every 12 weeks.

Upon implementation of Amendment 8, only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an End of Treatment (EOT) visit and transition onto an alternative supply of (eg, commercially available) ixazomib and/or LenDex, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care.

5. STUDY POPULATION

Adult patients with a confirmed diagnosis of MM and relapsed and/or refractory disease will be enrolled in this study.

5.1 Inclusion Criteria

To be eligible for this study, a prospective patient must meet each of the following main criteria:

1. Male or female patients 18 years of age or older.

2. Multiple myeloma diagnosed according to standard criteria either currently or at the time of initial diagnosis (see Section 15.2 for standard criteria).
   NOTE: The initial diagnosis must be symptomatic MM, although the relapsed disease does not need to be symptomatic.

3. 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.

4. Patients with relapsed and/or refractory MM who have received 1 to 3 prior therapies.

   NOTE: This patient population includes the following 3 categories of patients:

   - Patients who relapsed from their previous treatment(s) but were not refractory to any previous treatment.
   - Patients who were refractory to all lines of previous treatment(s) (ie, patients who have never responded to any therapies received).
   - Patients who were relapsed from at least 1 previous treatment AND additionally were refractory to at least 1 previous treatment. For the purposes of this study,

refractory disease is defined as disease progression on treatment or progression within 60 days after the last dose of a given therapy.

A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered 1 line of therapy.[42] Autologous and allogenic transplants are permitted.

5. Patients must meet the following clinical laboratory criteria:

   - Absolute neutrophil count (ANC) ≥ 1,000/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 randomization.
   - Total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN.
   - Calculated creatinine clearance ≥ 30 mL/min
     NOTE: Patients with a low creatinine clearance ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) will receive a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

6. ECOG performance status of 0, 1, or 2.

7. Patients who received prior allogenic transplant must have no active graft-versus-host disease (GVHD).

8. Female patients who:

   - Are postmenopausal for at least 24 months before the screening visit, OR

- Are surgically sterile, OR

- Females of childbearing potential (FCBP – see Section 6.9 for definition) must:

    1. Have a negative pregnancy test with a sensitivity of at least 25 mIU/mL within 10 to 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide

    2. Either agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. *(Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)* OR begin TWO reliable methods of birth control: 1 highly effective method and 1 additional effective method AT THE SAME TIME, at least 28 days before starting study drug through 90 days after the last dose of study treatment

    3. Agree to ongoing pregnancy testing

    4. Adhere to the guidelines of the RevAssist program (United States [US] participants), RevAid program (Canadian participants), iAccess program (Australian participants), RevMate program (Japanese participants) or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial supplies)

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

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. *(Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)* OR

- Agree to practice effective barrier contraception during the entire study treatment period and 90 days after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy, AND

- Adhere to the guidelines of the RevAssist program (US participants), RevAid program (Canadian participants), iAccess program (Australian participants),

RevMate program (Japanese participants) or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the study Manual (all other participants who are not using commercial supplies)

9. Must be able to take concurrent aspirin 81 to 325 mg daily (or enoxaparin 40 mg subcutaneously daily [or its equivalent] if allergic to aspirin), per published standard or institutional standard of care, as prophylactic anticoagulation.
   NOTE: For patients with prior history of DVT, low molecular weight heparin (LMWH) is mandatory. (See Section 6.10 for thromboembolism prophylaxis.)

10. 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.

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 randomized in the study:

1. Patient was refractory to lenalidomide or proteasome inhibitor-based therapy at any line.

   NOTE: Refractory disease defined as disease progression on treatment or progression within 60 days after the last dose of a given therapy. Patients who progress after 60 days from the last dose of a given therapy will be considered relapsed and are eligible for inclusion in the study.

   Patients who were refractory to thalidomide-based therapy are eligible.

2. Female patients who are breast feeding or pregnant.

3. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the effects of prior chemotherapy (except for alopecia) regardless of the interval since last treatment.

4. Major surgery within 14 days before randomization.

5. Radiotherapy within 14 days before randomization.

6. Central nervous system involvement.

7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before randomization.

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

9. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

10. 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 randomization in the study.

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

12. 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 (eg, peripheral neuropathy that is Grade 1 with pain or Grade 2 or higher of any cause).

13. Psychiatric illness/social situation that would limit compliance with study requirements.

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

15. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal (GI) condition that could interfere with the oral absorption or tolerance of treatment.

16. Diagnosed or treated for another malignancy within 2 years before randomization 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.

6. STUDY TREATMENT

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug 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 treatment drug or study drug should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of MLN9708 dose.

All doses must be taken as outlined in the Schedule of Events. Eligible patients may take study drug at home as directed. Refer to the Study Manual for additional instructions regarding study drug administration.

6.1 Test Article (MLN9708) and Matched Placebo

MLN9708 capsules and placebo capsules will be subsequently referred to as study drug.

MLN9708 active capsules will be supplied as single capsules at 3 different dose strengths, containing 4.0, 3.0, and 2.3 mg of MLN9708. Placebo capsules will be identical in shape, size, and color to the MLN9708 active capsules. Both the active and placebo capsules will be provided by the sponsor.

The final analysis data cutoff has been conducted and as such, the study is considered complete for statistical analysis purposes. Upon implementation of Amendment 8, the investigator will unblind all patients remaining on study treatment Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib and/or LenDex, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care. Patients who are receiving ixazomib plus LenDex will continue to receive ixazomib plus LenDex. Patients who are receiving placebo plus LenDex will

receive LenDex only; the placebo capsule will no longer be administered and patients receiving placebo will not be crossed over to ixazomib in this study.

Study drug will be given as a single, oral dose of 4.0 mg weekly (Days 1, 8, and 15) for 3 weeks, followed by 1 week without study drug in a 28-day cycle. Patients should be instructed to swallow MLN9708/placebo capsules whole with water and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after food. The capsule should be swallowed with a sip of water. A total of approximately 240 mL of water should be taken with the capsules.

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

6.2.1 Lenalidomide Administration

Lenalidomide will be given as a single, daily oral dose of 25 mg for a total of 21 days out of a 28-day cycle. Patients with a low creatinine clearance ≤ 60 mL/min (or ≤ 50 mL/min, according to local label/practice) will receive a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment. If renal function normalizes (ie, creatinine clearance > 60 mL/min or > 50 mL/min, according to local label/practice) and the patient continues to tolerate this treatment, lenalidomide may then be escalated to 25 mg once daily.

Administration of lenalidomide will be at approximately the same time each day. Patients should be instructed to swallow lenalidomide capsules whole with or without food and not to break, chew, or open the capsules.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

6.2.2 Dexamethasone Administration

Dexamethasone will be given as an oral dose of 40 mg/day weekly on Days 1, 8, 15, and 22 of a 28-day cycle.

Dexamethasone should be taken at approximately the same time preferably with food/milk to avoid stomach irritation. If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers it. If enough time has elapsed that it is almost time for the next dose (within 6 hours), 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.

6.3 Dose-Modification Guidelines

The patient will be evaluated for possible toxicities that may have occurred after the previous dose(s) according to the Schedule of Events. Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Each adverse event should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Only 1 dose adjustment per cycle will be performed for a given agent when toxicity is suspected to be related primarily to that agent. Reduction of 1 agent and not the other is appropriate if the toxicity is suspected to be related primarily to 1 of the agents. Dose reduction of multiple agents may be considered after consultation with the Millennium clinician/study clinician designee. Guidelines for dose modification within cycles are provided in Sections 6.4.1 and 6.4.2. Prior to beginning the next cycle of treatment, refer to the guidelines in Section 6.5.

Further clarification can be obtained in consultation with the Millennium clinician/study clinician designee. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines.

Alternative dose modifications may be recommended after discussion with the investigator and MPI clinician/designee in order to maximize exposure of study treatment while protecting patient safety.

6.4 Criteria for Dose Modification (Delays, Reductions, and Discontinuations)

6.4.1 Dose Adjustments for Hematologic and Nonhematologic Toxicity: Study Drug and Lenalidomide

A 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 clinician/study clinician designee to maximize exposure of study treatment while protecting patient safety given that there may be overlapping dose limiting toxicities (eg, thrombocytopenia, neutropenia, rash, and peripheral neuropathy (see Table 6-1, Table 6-2, and Table 6-3 respectively).

Table 6-1 Study Drug and Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Action on Study Drug (MLN9708/Placebo)	Action on Lenalidomide[43]	Action
First fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow complete blood count (CBC) weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if MLN9708 dose was 4 mg, reduce to 3 mg
Third fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if MLN9708 dose was 3 mg, reduce to 2.3 mg Do not reduce below 2.3 mg
Fifth fall to < 30,000/mm^3	Interrupt treatment	Interrupt treatment	Follow CBC weekly
Return to ≥ 30,000/mm^3 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Do not reduce below 5 mg

Table 6-2 Study Drug and Lenalidomide Dose Adjustment for Neutropenia

Absolute Neutrophil Count	Action on Study Drug (MLN9708/Placebo)	Action on Lenalidomide[43]	Action
First fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; add G-CSF
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if MLN9708 dose was 4 mg, reduce to 3 mg
Third fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume and **maintain** dose level lower	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume study drug at next **lower** dose level	Resume and **maintain** dose level	Eg, if MLN9708 dose was 3 mg, reduce to 2.3 mg Do not reduce below 2.3 mg.
Fifth fall to $< 0.5 \times 10^9$/L	Interrupt treatment	Interrupt treatment	Follow CBC weekly; see Section 6.7 for myeloid growth factor recommendations.
Return to $\geq 0.5 \times 10^9$/L within the same cycle	Resume and **maintain** dose level lower	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Do not reduce below 5 mg

Table 6-3 Study Drug and Lenalidomide Dose Adjustment for Rash

CTCAE Grade	Action on Study Drug (MLN9708/Placebo)	Action on Lenalidomide[43]	Action[a]
First occurrence Grade 2 or 3	Maintain dose	Interrupt treatment	Symptomatic recommendations noted in Section 6.10
Return to < Grade 2 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level[43]	Eg, if lenalidomide dose was 25 mg, reduce to 15 mg
Second occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations noted in Section 6.10
Return to < Grade 2 within the same cycle	For Grade 2, resume and **maintain** dose level For Grade 3, resume study drug at next **lower** dose level	For Grade 2, resume and **maintain** dose level For Grade 3, resume and **maintain** dose level	Symptomatic recommendations, including prophylactic treatment, in Section 6.10 Eg, if MLN9708 dose was 4 mg, reduce to 3mg
Third occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations, including prophylactic treatment, noted in Section 6.10
Return to < Grade 2 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 15 mg, reduce to 10 mg
Fourth occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations, including prophylactic treatment, noted in Section 6.10
Return to < Grade 2 within the same cycle	For Grade 2, resume and **maintain** dose level For Grade 3, resume study drug at next **lower** dose level	For Grade 2, resume and **maintain** dose level For Grade 3, resume and **maintain** dose level	Eg, if MLN9708 dose was 3 mg, reduce to 2.3 mg Do not reduce below 2.3 mg
Fifth occurrence Grade 2 or 3	Interrupt treatment	Interrupt treatment	Symptomatic recommendations, including prophylactic treatment, noted in Section 6.10
Return to < Grade 2 within the same cycle	Resume and **maintain** dose level	Resume lenalidomide at next **lower** dose level	Eg, if lenalidomide dose was 10 mg, reduce to 5 mg Do not reduce below 5 mg

In some severe situations, both lenalidomide and study drug may be interrupted if needed, or alternative dose modification management implemented based on discussion between the treating physician and Millennium clinician/study clinician designee. Angioedema and Grade 4 rash have been reported with lenalidomide and should result in lenalidomide discontinuation. **[43]**

a Please refer to Table 6-7 for additional information on lenalidomide (REVLIMID®) treatment modification for rash.

6.4.2 Study Drug Treatment Modification

Dose adjustments are allowed based on clinical and laboratory findings. Sequential dose reductions of study drug from the starting dose of 4.0 mg daily are recommended for toxicity as indicated in Table 6-4. Treatment modifications due to study drug-related AEs are outlined in Table 6-5.

Table 6-4 Dose Reduction Steps for Study Drug

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
4.0 mg	3.0 mg	2.3 mg	Discontinue study drug

Table 6-5 Study Drug Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events

Adverse Event (Severity)	Action on Study Drug/Placebo	Further Considerations
Grade 1 peripheral neuropathy	No action	Grade 1 signs & symptoms: asymptomatic, without pain or loss of function, clinical or diagnostic observations only[39]
Grade 1 peripheral neuropathy with pain or Grade 2	Hold study drug until resolution to Grade ≤ 1 or baseline	Grade 2 signs & symptoms: moderate symptoms, limiting instrumental activities of daily living (ADL) [39]
Grade 2 peripheral neuropathy with pain or Grade 3	Hold study drug until resolution to Grade ≤ 1 or baseline Reduce study drug to next lower dose upon recovery	Grade 3 signs & symptoms: severe symptoms, limiting self care ADL, assistive device indicated[39]
Grade 4 peripheral neuropathy	Discontinue study drug	
Grade 3 nonhematologic toxicity judged to be related to study drug	Hold study drug until resolution to Grade < 1 or baseline	Symptomatic recommendations noted in Section 6.10
If does not recover to < Grade 1 or baseline within 4 weeks	Reduce study drug to next lower dose upon return to < Grade 1 or baseline	
Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 4 weeks	Hold study drug until resolution to Grade < 1 or baseline Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care

Table 6-5 Study Drug Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events

Adverse Event (Severity)	Action on Study Drug/Placebo	Further Considerations
Grade 4 nonhematologic toxicities judged to be related to study drug	Consider permanently discontinuing study drug	Exception, in a case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the MPI/designee clinician
Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.5: ANC < 1,000/mm^3, platelet count < 75,000/mm^3, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition	Hold study drug until resolution per criteria in Section 6.5 Restart study drug and/or lenalidomide at the next lower dose level (based on attribution or previous reductions)	The maximum delay before treatment should be discontinued (except in the case of investigator determined clinical benefit and discussion with the MPI/designee clinician) will be 3 weeks

6.4.3 Lenalidomide Treatment Modification

Dose adjustments are allowed based on clinical and laboratory findings. Sequential dose reductions from the starting dose of 25 mg daily are recommended for toxicity as indicated in Table 6-6. Treatment modifications due to lenalidomide-related AEs are outlined in Table 6-7.

Table 6-6 Dose Reduction Steps for Lenalidomide

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
25 mg QD	15 mg QD	10 mg QD	5 mg QD

Table 6-7 Lenalidomide (REVLIMID®) Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Non-Hematologic Adverse Events[43]

Adverse Event (Severity)	Action on Lenalidomide	Further Considerations
Grade 3/4 toxicities judged to be related to lenalidomide	• Hold lenalidomide treatment, and restart at the next lower dose level when toxicity has resolved to ≤ Grade 2[43]	Do not dose below 5 mg daily
Renal dysfunction	• Dose reduce per lenalidomide package insert/SmPC for impaired renal function	Care should be taken in dose selection/modification in the elderly as they are more likely to have decreased renal function. Monitor renal function regularly
≥ Grade 2 thrombosis/embolism	• Hold lenalidomide and start anticoagulation therapy; restart at investigator's discretion after adequate anticoagulation; maintain dose level	See Section 6.10 for anticoagulation recommendations
Angioedema, Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)	• Permanently discontinue lenalidomide per package insert/SmPC[43]	
Grade 2/3 skin rash	• Hold or discontinue lenalidomide per package insert/ SmPC[43]	
Grade 4 exfoliative or bullous rash	• Permanently discontinue lenalidomide per package insert/SmPC[43]	
Tumor Lysis syndrome	• Dose modify as per lenalidomide package insert/SmPC[43]	Monitor closely and take appropriate medical precautions

6.4.4 Dexamethasone-Related Treatment Modification

Dosage adjustments for dexamethasone are outlined in Table 6-8**.** Treatment modifications due to dexamethasone-related AEs are outlined in Table 6-9.

Table 6-8 Dose Reduction Steps for Dexamethasone

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
40 mg	20 mg	8 mg	Discontinue dexamethasone

Table 6-9 Dexamethasone–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events[44]

Adverse Event (Severity)		Action on Dexamethasone
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.
	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 ± 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.

6.5 Criteria for Toxicity Recovery Before Beginning the Next Cycle of Treatment

The criteria for toxicity recovery before the patient can begin the next cycle of treatment are as follows:

- ANC ≥ 1,000/mm^3
- Platelet count ≥ 75,000/mm^3, or

- Other clinically significant nonhematologic toxicities ≤ Grade 1 or to the patient's baseline condition.

If a patient fails to meet the criteria above for beginning 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.

See Section 6.4 for recommended dose reduction because of incomplete recovery from treatment-related toxicity. The maximum delay before treatment should be discontinued (except in the case of investigator determined clinical benefit and discussion with the MPI/designee clinician) will be 3 weeks.

6.6 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study. Note that the excluded concomitant medication information has been updated to reflect the available in vitro metabolism and clinical drug-drug interaction information as of Amendment 6. Please refer to the IB for additional details.

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: If there were to be a drug-drug interaction with an inducer, MLN2238 exposure would be decreased.)

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

Excluded medicinal products include St. John's wort.

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). Palliative radiotherapy for pain control in a preexisting lesion may be considered after discussion with the sponsor's clinical representative.

- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing

6.7 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care per local standard will be available to patients, as necessary. All blood products and concomitant medications received from first dose of study drug until 30 days after the final dose will be recorded in the CRFs.

The following medications and procedures are permitted during the study:

- Myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Millennium clinician or study clinician designee.

- Erythropoietin will be allowed in this study, but given the potential increased risk of DVT when erythropoietin is administered concurrent with lenalidomide, the use of erythropoietin should be minimized as much as possible.

- Patients should be transfused with red cells and platelets as clinically indicated.

- When digoxin was co-administered with lenalidomide, the digoxin AUC was not significantly different; however, the digoxin C_{max} was increased by 14%. Periodic monitoring of digoxin plasma levels in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication is recommended during administration of lenalidomide.

- Concomitant treatment with bisphosphonates will be permitted.

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

6.8 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.

6.9 Contraception Requirements

It is not known what effects MLN9708 has on human pregnancy or development of the embryo or fetus. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Female patients of childbearing potential (FCBP) and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below. FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has not had menses at any time during the preceding 24 consecutive months).

All females of childbearing potential must either:

- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the patient, for at least 28 days before starting study drug through 90 days after the last dose of study treatment. *(Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)* OR

- Agree to practice 2 reliable methods of contraception, at the same time, for at least 28 days before starting study drug through 90 days after the last dose of study treatment

- The 2 methods of reliable contraception must include 1 highly effective method and 1 additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

  Highly effective methods:

  - Intrauterine device (IUD)

- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Condom
- Diaphragm
- Cervical Cap

- Must also adhere to the guidelines of the RevAssist program (US participants), RevAid program (Canadian participants), iAccess program (Australian participants), RevMate program (Japanese participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial supplies)

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

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. *(Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)* OR
- Agree to use effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy, AND
- Adhere to the guidelines of the RevAssist program (US participants), RevAid program (Canadian participants), iAccess program (Australian participants), RevMate program (Japanese participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial supplies)

6.10 Management of Clinical Events

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. Unless there is a clinical contraindication, prophylactic antiviral therapy is required for all patients while receiving study treatment. Examples of acceptable antiviral therapy include acyclovir (eg, 400 mg given orally, 3 times a day), famciclovir (eg, 125 mg given orally, twice a day), or valacyclovir (eg, 500 mg given orally, twice a day) or standard of care/local practice.

Thromboembolism Prophylaxis

While on lenalidomide, patients should be on routine thromboprophylaxis.[45] Prophylactic therapy with aspirin (81 - 325 mg PO once daily) or LMWH (equivalent to enoxaparin 40 mg subcutaneous [SQ] per day) per published standard or institutional standard of care is required for all patients to prevent thromboembolic complications that may occur with lenalidomide-based regimens in combination with dexamethasone. Thromboprophylaxis according to the American Society of Clinical Oncology (ASCO) guidelines or institutional standard of care is recommended.[46]

Nausea and/or Vomiting

Prophylaxis with standard antiemetics, including serotonin 5-hydroxytryptamine 3 receptor antagonists, is recommended for emesis. Any fluid deficit occurring during treatment should be promptly corrected.

Diarrhea

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. Any fluid deficit occurring during treatment should be promptly corrected.

Erythematous Rash With or Without Pruritus

Rash has been reported with both lenalidomide and MLN9708. The lenalidomide induced rash is characterized as generalized, maculopapular, morbilliform, urticarial, papular, often with pruritus, and is noted as a warning/precaution in the lenalidomide package insert.[43,47,48] Serious skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported. Lenalidomide interruption or

discontinuation should be considered as described in the package insert (PI)/ summary of product characteristics (SmPC).[43]

Rash may range from limited erythematous areas, macular 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 and self-limiting and is typically Grade 1 or 2 in severity. As in many other oncology trials, rash may occur in patients receiving placebo and in patients receiving MLN9708. If rash occurs, consideration should be given to alternate causes of the rash such as concomitant medications, infections, etc; these other causative agents should be discontinued and alterative agents considered if medically necessary.

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 [see Section 15.5]) 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).

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when MLN9708 (or placebo) was given with concomitant medications that are known to cause rash (eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding TEAEs. These severe, potentially life-threatening or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. Study medications should be discontinued in the event of severe, potentially life-threatening rash. Additional information regarding these reactions can be found in the IB.

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. Lenalidomide or study drug administration should be modified as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-1). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura and hemolytic uremic syndrome, are rare, serious blood disorders that cause low levels of platelets and red blood cells and result in blood clots in small blood vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders, including fatal cases, have been reported in patients receiving MLN9708. If TMA is suspected, consider withdrawal of the suspected causative agent and manage 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. Lenalidomide or study drug administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

Fluid Deficit

Dehydration should be avoided since lenalidomide is substantially excreted by kidney, and 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 gastrointestinal toxicities and dehydration. Fluid deficit should be promptly corrected before initiation of study drug and as needed during treatment to avoid dehydration (see Section 6.8).

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with MLN9708. Blood pressure should be closely monitored as per standard of care

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 decreased appetite. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- 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.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported with MLN9708. This condition is usually transient and reversible. It is characterized by headache, seizures, and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI) or computed tomography (CT). 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 with MLN9708. It is not known whether MLN9708 causes transverse myelitis; however, because it happened to a patient 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.

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. If overdose occurs, consider close observation including hospitalization for hemodynamic support. Gastric lavage may be considered if instituted within 1 hour of ingestion of MLN9708 overdose.

6.11 Blinding and Unblinding

To maintain the blind, all study personnel including the investigators, site personnel, study clinicians, and the sponsor will be blinded to the treatment assignments for the duration of the study.

Kit assignments will be obtained through the interactive voice response system (IVRS) according to the procedures outlines in the Study Manual. Information regarding the kit

assignments will be kept securely at Millennium or designee, per its standard operating procedures. Emergency unblinding, if necessary, will be conducted via the IVRS.

Records of the patient number, the date study drug was dispensed, and the kit assignment will be maintained by the study site. If the treatment assignment must be revealed for the safety of the patient or to treat an AE, the investigator will contact the Millennium clinician/ study clinician designee (contact information is in the Study Manual). A decision to break the blind must be reached by the Millennium clinician/study clinician designee and the investigator. The investigator, or designee, may break the blind through the IVRS independent of the Millennium clinician/ study clinician designee only if it is considered to be an emergency by the investigator that requires specific knowledge of the blinded study treatment in order to properly treat the AE/safety issue. If the treatment of the AE/ safety issue is the same regardless of the study drug assignment, the blind should not be broken. The event requiring breaking the blind must be documented in the electronic case report form (eCRF), including the date the blind was broken. In addition, the patient will be discontinued from further study drug administration in this study.

The final analysis data cutoff has been conducted and as such, the study is considered complete for statistical analysis purposes. Upon implementation of Amendment 8, the investigator will unblind all patients remaining on study treatment and will follow the new Schedule of Events presented in this amendment. Only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib and/or LenDex, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care. Patients who are receiving ixazomib plus LenDex will continue to receive ixazomib plus LenDex. Patients who are receiving placebo plus LenDex will receive LenDex only; the placebo capsule will no longer be administered and patients receiving placebo will not be crossed over to ixazomib in this study.

6.12 Description of Investigational Agents

MLN9708 and matching placebo capsules are manufactured by Millennium. The MLN9708 drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg capsules as the active boronic

acid. Three forms of matched placebo will correspond to each dose strength of MLN9708 and will be identical in size, shape, and color to the corresponding MLN9708 capsule.

The 3 different dose strengths are differentiated by both capsule size and color:

Table 6-10 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.

6.13 Preparation, Reconstitution, and Dispensing

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

6.14 Packaging and Labeling

The MLN9708 capsules and placebo capsules will be provided by Millennium. The study drug labels will fulfill all requirements specified by governing regulations. The formulation consists of 4.0-, 3.0-, and 2.3-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.

6.15 Storage, Handling, and Accountability

On receipt at the investigative site, study drug should remain in the blister pack and carton provided until use or dispensation. All excursions that occur at the site storage or during transportation from depot to the site should immediately 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.

Study drug dispensed to the patient should remain in the blister packaging and carton until the point of use. Refer to the Pharmacy Manual or equivalent storage guidelines. In case of extenuating circumstances that prevent a patient from attending the study site (eg, the

COVID-19 pandemic), sites may use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations and with prior approval from the investigator and the sponsor's project clinician/designee. Comprehensive instructions should be provided to the patient in order to ensure compliance with, and understanding of, dosing procedures. Patients who are receiving take-home medication ordinarily should be given only 1 cycle of study drug at a time; more than 1 cycle of medication may be dispensed on a case-by-case basis for holidays, travel, or other circumstances upon discussion with the investigator and sponsor project clinician/designee. (Note: patients in France are only permitted to receive 1 cycle of medication at a time). Should more than 1 cycle of medication be dispensed, the investigator and/or health care provider must review the proper dosing instructions with the patient to avoid the potential for incorrect self-administration or overdose of medication.

Patients should be instructed to store the medication according to the storage conditions that are outlined in the Pharmacy Manual or equivalent storage guidelines. 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 study drug. In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), drug packs and dosing diaries should be returned at the next available on-site clinic visit. 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 agent, 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 contract. 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.

Patients are to be instructed on proper storage, accountability, and administration of study drug, including that study drug is to be taken as intact capsules.

Please refer to the Pharmacy Manual for additional instructions, including, but not limited to, study drug shipping and storage guidelines.

6.15.1 Standard of Care Therapies

6.15.1.1 Lenalidomide

Lenalidomide may be supplied by the site or from commercial sources, depending on regional availability as follows:

- US: Subjects will receive lenalidomide through the RevAssist program
- Canada: Subjects will receive lenalidomide through the RevAid program
- Australia: Subjects will receive lenalidomide through the iAccess program
- Japan: Subjects will receive lenalidomide through the RevMate program
- All other countries: Subjects will receive lenalidomide from the site through supply provided by sponsor

6.15.1.2 Dexamethasone

Dexamethasone may be supplied by the site from commercial sources, depending on regional availability. Additional details are provided in the package insert and Pharmacy Manual.[44]

Dexamethasone tablets should be stored according to the instructions provided in the manufacturer's package insert or on the drug label (if supplied by the sponsor).

6.16 Other Protocol-Specified Materials

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

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 clinician/study clinician designee, the central laboratory, any additional clinical laboratories or vendors participating on the study 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 central recruitment from a vendor, 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, the patient will be assigned an enrollment code (country-, site-, and patient-specific) using IVRS.

Patient eligibility will be confirmed by an MPI/designee clinician before randomization by the investigator into the study, as patients will not be permitted to re-enroll. A centralized randomization using IVRS will be used. Patients will be randomized strictly sequentially at a center as they become eligible for randomization. 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.

7.4 Study Procedures

In acknowledgement of hospital, local, state or national government restrictions, or other site-related factors caused by unavoidable circumstances (eg, the COVID-19 pandemic) that may prevent investigators from conducting the study according to the Schedule of Events at the clinical study site, investigators may continue patients in the study despite departure from the Schedule of Events. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for patients to continue. In evaluating such requests, the investigator/study site staff will give the highest priority to the safety and welfare of the patients. Patients must be willing and able to continue taking study medication and remain compliant with the protocol. For patients that are impacted by these unavoidable circumstances, any procedures not conducted per the study protocol will be documented in the eCRF.

Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having lab assessment performed at a facility closer to the patient's home, etc.) If a patient misses an in-person study visit, the investigator/study team staff will speak directly with the patient by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact with the patient, the study site physician or other qualified site staff should at minimum conduct AE collection and an assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Assessments/procedures that cannot be completed during the protocol-specified window because a site visit is done remotely (eg, complete physical examination, symptom-directed physical examination, hematology, clinical chemistry, concomitant medications/procedures) are waived.

Upon implementation of Amendment 8, patients continuing to derive clinical benefit will be evaluated for safety only during the treatment period and at EOT. The primary endpoint has been met and all other formal statistical analyses will be complete at the time of the final analysis. As such, the PFS and OS follow-up phases are discontinued for patients currently receiving study therapy. Patients in the OS follow-up phase will be discontinued.

Refer to the updated Schedule of Events for the timing of assessments. Tests and procedures should be performed on schedule, but occasional changes are allowable (± 7 days) for holidays, vacations, and other administrative reasons. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing.

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.

Patients remaining on study treatment will need to be reconsented. Reconsenting should be done in person. Remote reconsenting is permitted as long as the process adheres to site, IRB/IEC, and GCP standards and local regulations.

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 (Section 15.2) and current staging (Section 15.4) of MM. The history should include a review of all current medications, prior radiation or antineoplastic therapy, and the patient's current smoking status.

7.4.4 Physical Examination

A complete physical examination and symptom-directed physical exam will be conducted at the time points specified in the Schedule of Events. Symptom-directed examinations should include examination of organ systems related to patient symptoms to document potential AEs, AE severity, and AE resolution.

7.4.5 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance scale (see Section 15.1) at the time points specified in the Schedules of Events in Section 15.12 and Section 15.13. Upon implementation of Amendment 8, ECOG performance status will no longer be collected.

7.4.6 Vital Signs

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

7.4.7 Pregnancy Test

Two pregnancy tests with sensitivity of at least 25 mIU/mL will be performed for all women of childbearing potential prior to initiation of study drug treatment. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug, and as required by the lenalidomide package insert. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on treatment (including breaks in therapy), at discontinuation of study treatment, and at Day 28 after the last dose of study drug. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on study (including breaks in therapy), at discontinuation of treatment, and at Days 14 and 28 after the last dose of treatment. All patients must be counseled about pregnancy precautions, risks of fetal exposure, and other risks in accordance with the RevAssist program (US participants), RevAid program (Canadian participants), iAccess program (Australian participants), RevMate program (Japanese participants), or The Lenalidomide Pregnancy Risk Minimisation Plan as outlined in the Study Manual (all other participants who are not using commercial supplies).

The Cycle 1, Day 1 pregnancy test may be collected up to 24 hours before dosing. The results must be available and negative before the first dose of study drug is administered.

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

7.4.8 Electrocardiogram

A 12-lead ECG will be conducted at screening and at the times outlined in the Schedules of Events in Section 15.12 and Section 15.13. 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.

Upon implementation of Amendment 8, ECG data will no longer be collected.

7.4.9 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 central labs as well. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Days 8, 15 and 22 dosing, where required. Per Amendment 6, centralized clinical laboratory evaluations of safety will be performed only on Day 1 of every cycle. For dosing decisions and for all other safety assessments for the patient, local hematology and chemistry laboratory results may be used; however, samples must still be sent to central labs also. Local laboratory evaluations may be done more frequently at the investigator's discretion, ie for acute management of TEAEs. In general, local laboratory results of safety will not need to be entered into the eCRF. Local laboratory evaluations should be entered into the eCRF only if required to document an AE, dose modification, or other event, and the information entered should be limited to that required to understand the event (eg, for a dose hold for thrombocytopenia, enter the platelet count only). Handling and shipment of central clinical laboratory samples are outlined in the Study Manual.

As the centralized laboratory results may not be available at the initiation of the next cycle, it is not required that these centralized measurements be reviewed before initiating the next treatment cycle unless either of the following applies:

1. The patient has an ongoing toxicity. If the patient has had a toxicity resulting in a dose hold, it is mandatory that safety labs (local or central) are collected AND reviewed before starting the next cycle of treatment.

2. It is required per your local practice or guidelines to have safety labs reviewed before starting the next cycle of treatment.

Upon implementation of Amendment 8, centralized clinical laboratory evaluations of efficacy and safety are no longer required and local laboratories are to be utilized. Local laboratory evaluations should be entered into the eCRF only if required to document or support a TEAE. For dosing decisions and all other safety assessments for the patient, local hematology and chemistry laboratory results should be used and do not need to be entered into the eCRF. Local laboratory evaluations may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs), per the investigator's judgement of standard of care.

7.4.10 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. Blood samples should be collected prior to administration of any study drugs.

Note that as the primary endpoint of PFS has now been met, for all patients still receiving study therapy, all central and investigator assessments of response and progression for protocol purposes are discontinued, including urinalysis assessments and collection of thyroid-stimulating hormone. Upon implementation of Amendment 8, blood samples for analysis of the remaining hematology parameters below will continue to be obtained on Day 1 of each cycle for purposes of dosing decisions and safety assessments only.

Hematology

- Hemoglobin
- Hematocrit
- Platelet Count
- WBC Count with Differential

Serum Chemistry

- BUN
- Creatinine
- Total bilirubin
- Uric Acid
- LDH
- Alkaline phosphatase
- AST
- ALT
- Albumin
- Glucose
- Sodium
- Potassium
- Chloride
- CO_2
- Magnesium
- Calcium
- Phosphate
- Thyroid stimulating hormone (TSH; no longer done as of Amendment 6)

Urinalysis (no longer done as of Amendment 6)

- Appearance and color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes
- Microscopic assessment

7.4.11 Health Utilization Data Collection

During the treatment and the follow-up periods indicated in the Schedules of Events in Section 15.12 and Section 15.13, all medical care encounters since the previous collection will be collected from all patients, regardless of the reason for the medical care encounter. Examples of data to be collected are number and duration of medical care encounters, such as inpatient/outpatient admissions, homecare, and time of work loss.

Upon implementation of Amendment 8, health utilization data will no longer be collected.

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

The QOL assessments (EORTC-QLQ-C30 and MY-20; see Sections 15.9 and 15.10) will be completed by the patient as specified in the Schedules of Events in Section 15.12 and Section 15.13. 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).

The MY-20 multiple myeloma module (20-items) has 4 independent subscales, 2 functional subscales (body image, future perspective), and 2 symptoms scales (disease symptoms and side-effects of treatment). This will be administered subsequent to the EORTC QLQ-C30.

These are reliable and valid measures of health-related QOL in patients with cancer and takes about 15 minutes to administer. 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 study drug is administered.

Upon implementation of Amendment 8, quality of life data will no longer be collected.

7.4.13 Pain Assessment

Pain assessments will be performed at study visits as described in the Schedules of Events in Section 15.12 and Section 15.13 to collect the pain severity, location, and interference information with a 24-hour recall period. This must be completed prior to other assessments or study drug being administered.

Patients who experience new or worsening pain between scheduled visits should be seen at an unscheduled visit, if necessary, or when the next scheduled visit is more than 4 weeks in the future. At the unscheduled visits, pain assessments should be completed and appropriate management instituted. In addition, patients who report new or worsening pain at either a regularly scheduled visit or are seen for pain at an unscheduled visit should have a follow-up visit 3 to 5 weeks later for confirmation of the pain progression and for appropriate pain management.

The Brief Pain Inventory-Short Form (BPI-SF) will be the principal pain assessment tool for this study. The BPI-SF contains 15 items designed to capture the pain severity ("worst," "least," "average," and "now" [current pain]), pain location, medication to relieve the pain, and the interference of pain with various daily activities including general activity, mood, walking activity, normal work, relations with other people, sleep, and enjoyment of life.

The questionnaire employs a 24-hour recall period. The pain severity items are rated on a 0 to 10 scale, with 0 = no pain and 10 = pain as bad as you can imagine. The PRO secondary endpoint will be "pain response rate" as measured by the worst pain item (Item 3) in the BPI-SF or analgesic use. The use of the single item, worst pain, is supported by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for assessing pain in clinical trials and by the European Medicines Agency 2003 Guidance on Clinical Investigation of Medicinal Products for Nociceptive Pain issued by the Committee for Proprietary Medicinal Products. In addition, the newly released FDA Guidance uses the following example while discussing conceptual frameworks: "The conceptual framework of a PRO instrument may be straightforward if a single item is a reliable and valid measure of the concept of interest (eg, pain intensity)."

At the time of each pain assessment including unscheduled visits, the patient will be queried regarding concomitant use of analgesics, if any, as specified in the Schedule of Events. The

patient-recalled amount of analgesic use during the 24 hours prior to pain assessment will be recorded on both the 24 hour analgesic form and concomitant medication eCRFs.

Upon implementation of Amendment 8, pain assessments will no longer be collected.

7.4.14 Utility Measurement

Because oncology therapies may positively or negatively affect a subject's QOL, a common methodologic approach is used to quantify this effect by "quality-adjusting" survival in comparative treatment groups. The result, quality-adjusted life years (QALYs), is a measure of both the length and quality of life and is used as a measure of benefit in cost–utility analysis. General PRO instruments such as the EORTC QLQ-C30 are not specifically designed to measure subject preferences (or utilities) in a way that is suitable for calculating QALYs. Therefore, a separate validated instrument, in this case the EuroQoL EQ-5D, will be used to quantify utilities to calculate QALYs for a cost–utility analysis

The EQ-5D consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). The EQ VAS records the respondent's self-rated health on a 20-cm vertical, visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D will be administered as specified in the Schedules of Events in Section 15.12 and Section 15.13.

Upon implementation of Amendment 8, EQ-5D data will no longer be collected.

7.4.15 Skeletal Survey

A complete skeletal survey, using roentgenography, will be performed at screening (within 8 weeks of the first dose of study drug) and annually in all patients, as specified in the Schedule of Events in Section 15.12. If at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions, a repeat of the skeletal survey should be performed. For imaging of symptomatic sites, plain films may be obtained for additional clarity.

At the discretion of the investigator and where regionally permitted, CT scan, a positron emission tomography-computed tomography (PET-CT) scan, or 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.

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

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, skeletal survey will no longer be done for protocol purposes for patients on study therapy.

7.4.16 Skeletal-Related Events

Selected skeletal-related events (SREs), defined as new fractures (excluding vertebral compression or rib fractures), irradiation of or surgery on bone, or spinal cord compression, will be captured from the start of the study treatment through death at the time points listed in the Schedules of Events in Section 15.12 and Section 15.13.

Upon implementation of Amendment 8, skeletal-related events data will no longer be collected.

7.4.17 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 (within 8 weeks of randomization) and at the time points specified in the Schedule of Events in Section 15.12, 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.

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, radiographic disease assessments will no longer be done for protocol purposes for patients on study therapy.

7.4.18 β2-Microglobulin

A blood sample will be collected at screening for serum β2-microglobulin testing. A sample for both central and local laboratory evaluation is required. Stratification by ISS stage 1 or 2

vs 3 will be conducted using local results and will be confirmed by the central laboratory. Local and central results will be utilized for analysis.

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, β2-microglobulin testing will no longer be done for protocol purposes for patients on study therapy.

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.

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, M-protein quantification will no longer be done for protocol purposes for patients on study therapy.

7.4.20 Quantification of Immunoglobulin (Ig)

Blood samples for quantification of immunoglobulins will be obtained as specified in the Schedule of Events.

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, Ig quantification will no longer be done for protocol purposes for patients on study therapy.

7.4.21 Serum Free Light Chain Assay

A blood sample for serum free light chain assay will be obtained at the time points specified in the Schedule of Events.

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, the serum free light chain assay will no longer be done for protocol purposes for patients on study therapy.

7.4.22 Immunofixation of Serum and Urine

Serum and urine samples for the analysis of immunofixation of immunoglobulins will be obtained at the time points specified in the Schedule of Events (refer to Section 15.2).

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, immunofixation will no longer be done for protocol purposes for patients on study therapy.

7.4.23 Bone Marrow Evaluation

As of Amendment 6, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, central and local laboratory evaluations will no longer be done for protocol purposes for patients on study therapy, with the exception of the optional aspirate for molecular analysis that may be collected at the time of disease relapse only if the patient had previously responded to study drug and consents to this procedure.

Central Lab Evaluation

Molecular Analyses and Cytogenetics

The sample of the bone marrow aspirate obtained at screening will be used for molecular analyses and for evaluation of cytogenetics that will cover a panel of high-risk abnormalities including the following: del(13), +1q21, t(4;14), t(4;16), and del(17). This aspirate sample will also be used to assess mutation status of key genes of the RAS/RAF pathway and expression levels of key genes involved in MM. This sample will be submitted to a central laboratory (See Study Laboratory Manual for sample handling and shipping instructions). The first or second pull of the bone marrow aspirate is the preferred specimen to be sent to the central lab for this analysis. An optional aspirate for molecular analysis will also be collected at the time of disease relapse only if the patient had previously responded to study drug and consents to this procedure. This sample may be collected at the time of PD confirmation, at the End of Study visit, or prior to starting a new therapy and will be sent to the central laboratory for analysis.

Upon implementation of Amendment 8, bone marrow aspirate for molecular analysis will no longer be performed.

Local Lab Evaluations

Disease Assessment

A bone marrow aspirate will be obtained at screening for disease assessment and at any time bone marrow aspirate sample is obtained to assess CR or to investigate suspected PD. This evaluation will be performed locally. Determination of the kappa/lambda ratio by

immunohistochemistry or immunofluorescence should be performed to assess for stringent CR (sCR) when a CR has been documented. A bone marrow biopsy can additionally be performed per local standards for disease assessments.

Upon implementation of Amendment 8, bone marrow aspirate is not needed for assessment of CR or PD for protocol purposes. Investigators may continue to take bone marrow aspirate per standard of care for response assessment.

Cytogenetics

An additional bone marrow aspirate or bone marrow sample may also be submitted for cytogenetics to be analyzed locally, according to local standards, if the site has capability to perform analysis and there is sufficient sample available. The central laboratory cytogenetic results will be utilized for study analysis, whereas local laboratory cytogenetic results (where available) will only be utilized in instances when central laboratory results are not available.

Upon implementation of Amendment 8, a bone marrow sample for evaluation of cytogenetics is no longer needed. Investigators should follow local standard of care for bone marrow aspirate samples.

7.4.24 Response Assessment

Patients will be assessed for disease response according to the IMWG criteria, versions 2006 and 2011 (see Section 15.11).[49,50]

Response assessments should occur every cycle until progression. The MPI/designee clinician will confirm the investigator assessment of PD prior to the investigator taking the patient off treatment.

Response and relapse 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 must be confirmed with follow-up assessments of SPEP, UPEP, immunofixation of blood and urine, and serum free light chains as outlined in Section 15.11. One bone marrow assessment has to occur to document CR; no second bone marrow confirmation is needed.

Please note that in order to determine a response of sCR, bone marrow, immunohistochemistry, or immunofluorescence for kappa/lambda ratio, as well as serum free light chain assay, should be performed for all patients suspected to be in CR to meet this response category's requirements.

Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these 2 tests and not by the free light chain assay. Free light chain response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of stringent CR.

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued. Therefore, response assessment will no longer be done for protocol purposes for patients on study therapy.

7.4.25 Pharmacokinetic Measurements

Plasma concentrations of the complete hydrolysis product of MLN9708 (MLN2238) will be measured using a validated LC/MS/MS assay.

Details regarding the preparation, handling, and shipping of the pharmacokinetic samples are provided in the Study Manual. Blood samples for the determination of plasma concentrations of MLN2238 (the complete hydrolysis product of MLN9708) will be collected during Cycles 1 through 10. Samples are to be collected at the time points specified in the MLN9708 Pharmacokinetic Sampling Schedule immediately following the Schedule of Events.

As of Amendment 6, PK sample collection has been completed for all patients. The PK sampling schedule has been moved to Section 15.12.

7.4.26 Blood Sample for Biomarker Analysis

Two blood samples will be collected at screening for testing candidate biomarker relationship to response or resistance to MLN9708 therapy. Polymorphisms in mechanism and pathway-related genes including proteasome subunits, such as PSMB1, and NFKB regulators, such as NFKB1, TRAF3, and IKB, will be assessed. Polymorphisms of NFKB family genes are associated with development of multiple myeloma and treatment outcome in patients receiving bortezomib-based regimens and may be relevant for the efficacy of proteasome inhibitors generally. Relationship between response to MLN9708 and proteasome levels in plasma will also be analyzed. These have been linked to the efficacy of bortezomib. Polymorphisms of NFKB family genes are associated with development of MM and treatment outcome in patients undergoing bortezomib-based regimens.

As of Amendment 6, however, the primary endpoint of PFS has been met; as such, all assessments of response for protocol purposes are now discontinued.

7.4.27 Concomitant Medications and Procedures

Concomitant medications and therapy will be recorded from the first dose of study drug through 30 days after last dose of study drug, with the exception of narcotics and other analgesics, which will be recorded from first dose of study drug until PD (see the Schedule of Events). See Section 6.6 for a list of prohibited concomitant medications and therapies and Section 6.7 for a list of allowed concomitant medications and therapies.

7.4.28 Adverse Events

Monitoring of AEs, both nonserious and serious, will be conducted throughout the study as specified in the Schedule of Events. See Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.29 Follow-up Assessments (PFS and OS)

Prior to implementation of Amendment 6, patients who stopped treatment for any reason had PFS follow-up visits. See the Schedule of Events in Section 15.12 for the appropriate assessments. All subsequent antineoplastic therapies were to be recorded, regardless if they were initiated before or after PD. Patients who started an alternative antineoplastic therapy prior to disease progression continued to be followed for progression. As of Amendment 6,

however, the primary endpoint has been met. As such, the PFS follow-up phase was discontinued for all patients receiving study therapy and for any patients who discontinued treatment for other reasons, including patients who started an alternative therapy before PD.

Prior to implementation of Amendment 8, patients who stopped treatment due to PD continued to have overall survival visits/assessments. During the OS follow-up, assessments could be made over the phone and did not require a clinic visit. Data may have been collected by methods that included but were not limited to telephone, e-mail, mail, and social security indexes. The OS follow-up was conducted every 12 weeks after documented PD until death or termination of the study by the sponsor. All subsequent antineoplastic therapies were to be recorded during the OS follow-up period.

Upon implementation of Amendment 8, patients will no longer be followed during any of the follow-up periods. NOTE: Prior to implementation of Amendment 8, related SAEs must have been reported to the Millennium Department of Pharmacovigilance or designee. This included deaths that the investigator considered related to study drug that occurred during the posttreatment follow-up. In addition, new primary malignancies that occurred during the follow-up periods, irrespective of causality to study regimen, must have been reported to the Millennium Department of Pharmacovigilance or designee.

Refer to Section 10 for details regarding definitions, documentation, and reporting of SAEs.

7.5 Unscheduled Visits

Unscheduled visits may occur between treatment cycles as required. At unscheduled visits prior to implementation of Amendment 8, the BPI-SF and HU data should be captured. Upon implementation of Amendment 8, pain assessments and HU data will no longer be collected. Other assessments may be performed as clinically indicated at the discretion of the investigator.

7.6 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.

7.7 Completion of Treatment

Prior to implementation of Amendment 8, patients were considered to have completed study treatment if they received study drug until disease progression or until discontinuation for

unacceptable toxicity, withdrawal of consent, or death. An MPI/designee clinician reviewed the source data documenting disease progression prior to the investigator taking the patient off treatment or stopping disease assessments for PD. As of Amendment 6, however, the primary endpoint has been met; as such, the PFS follow-up phase has been discontinued for patients currently receiving study therapy. All central and investigator assessments of response and progression for protocol purposes will be discontinued, such that there will no longer be an MPI/designee clinician review of the source data documenting disease progression.

Upon implementation of Amendment 8, only patients who are demonstrating clinical benefit and are unable to access a commercial supply of ixazomib and/or lenalidomide and dexamethasone will remain in the study, until such time as other means of accessing the study drugs are arranged. Completion of study treatment will occur when patients discontinue study drugs provided by the sponsor in this clinical trial setting, or when the patient experiences disease progression, unacceptable toxicity, withdrawal of consent, or death. The reason for treatment discontinuation must be recorded in the eCRF but no approval is required.

Patients will attend an EOT visit 30 days (+1 week) after receiving their last dose of the study drug regimen unless next-line therapy is started before 30 days after the last dose of study drug, in which case the EOT visit should occur before the start of the next-line therapy.-Refer to the Schedule of Events-for End of Treatment visit assessments.

7.8 Completion of Study

Prior to implementation of Amendment 8, patients were considered to have completed the study if they were followed until death or until the sponsor terminated the study. Upon implementation of Amendment 8, patients will no longer be followed during any of the follow-up periods, as PFS and OS data are not being collected. Patients will be considered to have completed the study if they completed study treatment (see Section 7.7).

7.9 Discontinuation of Treatment With Study Drug

Treatment with study drug may be discontinued for any of the following reasons:

- AE
- Protocol violation

- Study terminated by sponsor
- Withdrawal by patient
- Lost to follow-up
- PD
- Other

Prior to the investigator taking the patient off treatment, the investigator is required to submit the rationale to the MPI/designee clinician for review. Note that this is no longer required as of Amendment 6.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

7.10 Withdrawal of Patients From Study

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

- Study terminated by sponsor
- Withdrawal by patient
- Lost to follow-up
- Death
- Other

Upon implementation of Amendment 8, PFS and OS follow-up will no longer be performed. Patients will now complete the study immediately following the end of treatment visit. 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.

8. STATISTICAL AND QUANTITATIVE ANALYSES

The final analysis data cutoff has been conducted and as such, the study is considered complete for statistical analysis purposes. The final analysis occurred in the fourth quarter of

2020. Upon implementation of Amendment 8, the investigator will unblind all patients remaining on study treatment and will follow the new Schedule of Events presented in this amendment. No subsequent formal inferential statistical analyses will be conducted; minimal descriptive analyses of safety will be performed on patient data collected after the final analysis. The description of the statistical methods presented below reflects the full design for the study for reference.

8.1 Statistical Methods

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

Details for the final analysis will be provided in the statistical analysis plan (SAP). The SAP will be written by Millennium and will be finalized prior to the first planned IA.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

8.1.1 Determination of Sample Size

The primary objective of this study is to determine if MLN9708 plus lenalidomide and dexamethasone improves PFS compared with placebo when added to lenalidomide and dexamethasone in patients with relapsed and/or refractory MM. The study will not be stopped after the PFS analysis, however, even if a significant PFS is observed, in order to obtain an adequate event rate and statistical power for OS analysis. To maintain the overall strong control of Type I error rate at a 2-sided alpha level of 0.05, the closed sequential testing procedure will be used to test PFS and OS sequentially both at a 2-sided alpha level of 0.05. That is, only if PFS is significant based on the O'Brien-Fleming alpha spending function (the Lan-DeMets method) at the first IA and the second IA, the test of OS will be conducted on its own alpha spending functions.

The total sample size was calculated based on maintaining 80% power to test the OS. The study is also adequately powered to test PFS. Assuming a hazard ratio of 0.77 (median survival of 30 months in control arm versus 39 months in treatment arm), the number of death events needed is 486 (80% power and 2-sided alpha of 0.05). A total of approximately

703 patients will need to be randomized in a 1:1 ratio into those 2 arms, assuming an average enrollment rate of approximately 13 patients/month for the first 6 months, approximately 45 patients/month thereafter, and approximately 10% dropout rate at month 35. The final analysis of OS is estimated to occur approximately 80 months from the enrollment of first patient, including a 20-month randomization period and an additional 60-month follow up from the last patient enrolled. With an observed hazard ratio of 0.833 (eg, median OS of 30 months for control versus 36 months for treatment, 20% improvement), statistical significance can be claimed at the final analysis with 486 death events.

Assuming a hazard ratio of 0.728 (median PFS of 15 months in control arm versus 20.6 months in treatment arm), 365 PFS events will be needed (85% power and 2-sided alpha of 0.05) with 2 planned IAs and the second IA as the final PFS analysis. The first IA will be performed when approximately 262 PFS events have occurred. This will be the first analysis for PFS for statistical testing purpose. Based on the O'Brien-Fleming stopping boundary, the alpha level at the first IA and second IA on PFS would be 0.0163 and 0.0337, respectively, if the number of PFS events at the first IA is exactly 262.[41] Correspondingly, if the observed p value is less than 0.0163 and 0.0451 at the first IA and the second IA, respectively, the test for PFS will be claimed to be statistically significant. With an assumption of approximately 13 patients/month for the first 6 months, 45 patients/month thereafter, and approximately 10% dropout rate over 30-month follow-up period, 262 PFS events is expected to occur at approximately 24.5 months after the first patient is enrolled and approximately 703 patients have been enrolled. This is the first IA of the study with the opportunity to claim PFS benefit. With an observed hazard ratio of 0.743 (eg, median PFS of 15 months in control arm versus 20.2 months in treatment arm), statistical significance can be claimed at the analysis for PFS with 262 progression/death events. If the test for PFS is statistically significant at the first IA, a non-inferential analysis of PFS will be performed at the second IA where the PFS data is considered mature.

If the test for PFS is not statistically significant at the first IA, the study will continue and PFS testing will be conducted at the second IA when approximately 365 PFS events have occurred, which will also be the final analysis of PFS for statistical testing purpose. An observed hazard ratio 0.810 (median PFS of 15 months in control arm versus 18.5 months in treatment arm) or better will lead to statistical significance for the PFS endpoint. If the test for PFS is not statistically significant at second IA, the study will be claimed as unsuccessful and no further testing will be conducted. If the test for PFS is significant at an IA, the OS will be tested; however, the trial will not be stopped for overwhelming evidence of efficacy

or futility at the first IA. The third IA will be for OS and will be performed when approximately 322 deaths (two-thirds of the total expected deaths) have occurred, with the opportunity to stop the study for overwhelming evidence of efficacy or futility. This IA is expected to occur approximately 44 months after the first patient is enrolled.

Based on the O'Brien-Fleming stopping boundary, the alpha levels at the 3 planned OS IAs and final analysis would be 0.00014, 0.0017, 0.0100, and 0.0382, respectively if the numbers of events at these analysis time points are exactly 154, 222, 322, and 486.[41] Correspondingly, if the nominal p value is less than 0.0001, 0.0018, 0.0112, and 0.0462, respectively, at the first, second, and third IAs, and the final analysis, the test for OS will be claimed to be statistically significant. However, the study will not be stopped after the first IA based on the test for OS. However, the actual boundary could be adjusted if the actual number of events does not correspond to the projected number of events in the IAs or in the FA.

8.1.2 Randomization and Stratification

Randomization scheme will be generated by an independent statistician at Millennium who is not on the study team. Prior to dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an IVRS.

Eligible patients will be randomized in a 1:1 ratio into those 2 treatment arms, stratified by: 1) 1 versus 2 or 3 prior therapies, 2) proteasome inhibitor exposed versus proteasome inhibitor naïve, and 3) ISS stage at screening of 1 or 2 versus stage 3.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

Safety population: The safety population is defined as all patients who receive at least 1 dose of any study drug. Patients will be analyzed according to the treatment actually received. That is, those patients who are randomized to the active arm but received the regimen in the control arm will be included in the control arm; those patients who are randomized to the control arm but received the regimen in the active arm will be included in the active arm for safety analyses.

Intent-to-Treat (ITT) population: The ITT population is defined as all patients who are randomized. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

Per-Protocol (PP) population: The PP population is a subset of the ITT population. The PP population consists of all patients who do not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the study clinician, who is blinded to study drug assignment. All decisions to exclude patients from the PP population will be made before the unblinding of the study.

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. No imputation of values for missing data will be performed, unless specified otherwise. The relevance of missing sample data will be assessed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized in a descriptive fashion. Data to be evaluated will include age, gender, race, weight, baseline disease characteristics, and other parameters, as appropriate.

8.1.6 Efficacy Analysis

8.1.6.1 Analyses for Primary Efficacy Endpoints

Note that, as of Amendment 6, the primary endpoint of PFS has been met, and analyses for the PFS have been completed.

The analysis of primary endpoint, PFS, will be based on the ITT population using IRC-assessed progression data. PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first. Patients without documentation of PD will be censored at the date of last response assessment that is stable disease (SD) or better.

PFS will be analyzed when approximately 262 and 365 PFS events have occurred for the first IA and for the second IA, respectively. A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.0163 and 0.0337, which corresponds to a nominal p value of 0.0451 based on O'Brien-Fleming stopping boundary (the Lan-DeMets method). In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The Kaplan Meier (K-M) survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Sensitivity analyses for PFS include:

1. PFS assessed by investigator will be analyzed in the ITT population.

2. PFS assessed by IRC will be analyzed in the per protocol population.

PFS assessed by IRC using different censoring mechanisms will be analyzed in the ITT population, for example, not censoring for patients who discontinue treatment and go on transplant or alternative neoplastic therapy. Details of different censoring approaches will be included in the SAP.

Subgroup analyses will be performed for PFS relative to baseline stratification factors, demographic data such as sex, race and age, and disease characteristics such as type of prior regimen.

If it is determined that the study will continue after PFS is significant at a 2-sided alpha level of 0.0163 at the first IA, a non-inferential analysis of PFS will be performed at the second IA. The PFS data will be considered as matured at the second IA.

8.1.6.2 Analyses of Key Secondary Efficacy

In addition to the primary comparison of PFS and the first key secondary endpoint OS, there is 1 additional key secondary endpoint: OS in high-risk patients carrying del(17). This key secondary endpoint will be tested only if the test of OS is statistically significant at the IAs or final analysis at the same significance level as OS to ensure strong type I error control for both key secondary endpoints.

Overall Survival

OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed based on the ITT population.

A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to OS. The test significance level at the IAs and final analysis is decided by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Subgroup analyses will be performed for OS relative to baseline stratification factors, demographic data such as sex, race, age, and disease characteristics such as type of prior regimen.

Overall Survival in High-Risk Patients With del(17)

OS within the high-risk subgroup will be analyzed using the similar method as OS in the overall population.

8.1.6.3 Analyses of Other Secondary Efficacy Endpoints

Other secondary efficacy parameters include overall response rate (ORR), the combined CR + VGPR rate, time to progression, duration of response, time to subsequent antineoplastic therapy, OS and PFS in high-risk population carrying del(13), del(17), +1q21, translocation t(4;14) or t(14;16), and pain response rate.

Disease response-related endpoints will be analyzed using IRC-assessed response rate.

ORR

ORR is defined as the proportion of patients who achieved PR or better relative to the ITT population. Stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare ORR between the 2 treatment arms. A logistic regression model will be used to estimate the treatment effect in terms of odds ratio. The odds ratio and its associated 95% CIs will be presented.

The IRC-assessed response data will be used for the analysis. Investigator-assessed response data will be used as sensitivity analysis.

Combined CR + VGPR rate

The combined CR + VGPR rate will be analyzed using the same similar method as ORR.

Time to Progression

TTP is defined as the time from the date of randomization to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of last response assessment that is SD or better. TTP will be analyzed based on the ITT population using the similar method as PFS.

Duration of Response

DOR is defined as the time from the date of first documentation of a PR or better to the date of first documentation of PD for responders. Responders without documentation of PD will be censored at the date of last response assessment that is SD or better. DOR will be summarized descriptively using the Kaplan-Meier method.

OS and PFS in High-Risk Population

OS and PFS in a high-risk population, defined as patients carrying del(13), del(17), +1q21, translocation t(4;14), or t(14;16) will be analyzed using the similar method as PFS and OS in ITT population.

8.1.7 Analyses of Patient-Reported Outcomes and Health Economics

8.1.7.1 Quality of Life Analysis

Patient-reported outcome (PRO) assessments using the EORTC QLQ-C30 and the MY-20 will be analyzed using the ITT population. The analysis will be performed on summary scores as well as on subscales and individual symptoms.

Differences between treatment groups in the EORTC QLQ-C30 and MY-20 scores will be evaluated using published minimally important difference (MID) values. Specific interest centers on physical functioning, global quality of life summary scores, and individual item scores for fatigue, nausea/vomiting, pain, dyspnea, appetite loss, and constipation/diarrhea.

The main endpoint for the PRO analysis will be the global health status/quality of life subscale of the EORTC QLQ-C30 and MY-20. The change in PRO scores between baseline and each postbaseline assessment will be described overall and according to the response to treatment. The other PRO endpoints include the remaining EORTC QLQ-C30 and MY-20 subscale and individual item scores. The change in scores will be presented using cumulative frequency distribution figures.

The analysis of PRO scores will be performed as a repeated-measures analysis using all available time points. The analysis will use mixed model analysis of variance.

8.1.7.2 Health Economics Analysis

EQ-5D scores will be summarized in descriptive statistics for treatment arms.

Health Utilization data will be summarized 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 care-giver for treatment arms.

8.1.7.3 Pain

Pain response rate will be analyzed in patients with baseline pain score ≥ 4 in the ITT population. Pain Response Rate is the proportion of patients who have a pain response and will be summarized by treatment groups. The CMH test will be used to compare the 2 treatment groups by stratification factors. In addition, the absolute treatment difference in pain response rate will be provided, along with 95% CI.

Pain response is defined as the occurrence of a ≥ 30% reduction from baseline in BPI-SF worst pain score over the last 24 hours without an increase in analgesic use at 2 consecutive evaluations.

Additional analyses on pain include:

- Time to pain response/progression, as assessed by the time from randomization to initial response/progression classification
- Duration of pain response, measured as the time from the first documented pain response to the first documented pain progression classification

Time to pain progression and duration of pain response will be compared using the stratified log-rank test between the 2 treatment groups. An unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The K-M survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment arm. Time to pain response will be summarized descriptively among patients with pain response.

Pain progression is defined as the occurrence of 1 of the following and confirmed by 2 consecutive evaluations. To qualify as progression, the patient must have a BPI-SF worst pain score ≥ 4 during progression.

- A ≥ 2 point and 30% increase from baseline in BPI-SF worst pain score without an increase in analgesic use, or

- A 25% or more increase in analgesic use from baseline without a decrease in BPI-SF worst pain score from baseline

Analgesic use can be stable or increased according to the following definitions:

- Stable analgesic use is defined as less than a 25% change of the oral morphine equivalent (OME) dose from baseline
- Increased analgesic use is defined as an increase of 25% or more in OME from baseline

Confirmation is not required if surgical treatment for pain, palliative radiation for pain, or subsequent antineoplastic therapy has been received prior to a confirmatory assessment (refer to Section 15.2 for a list of Step II and III analgesics).

In addition to the primary analysis for pain response rate, the change in BPI-SF worst pain scores between baseline and each postbaseline assessment will be described overall and according to the response to treatment.

8.1.8 Pharmacokinetics and Biomarkers

Pharmacokinetic Analysis

PK data collected in this study will contribute to population PK analyses.

As of Amendment 6, PK sample collection has been completed for all patients. The PK sampling schedule has been moved to Section 15.12.

CCI

CCI

[redacted]

8.1.9 Safety Analysis

Summary tabulations will be presented that will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data.

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.

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

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

Development of new or worsening of existing selected 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 changes from baseline of vital signs and weight will be tabulated by scheduled time point. ECOG performance scores will be summarized using a shift table.

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

All concomitant medications collected from the first dose of study drug 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 Interim Analyses

There are 3 planned IAs. The first IA will be performed when approximately 262 of the disease progression/death events have occurred. This IA is expected to occur approximately 24.5 months after the first patient is enrolled. This is the first analysis for PFS for statistical testing purpose and first IA for OS. During this IA, enrollment to the study will continue. If the test for PFS is not statistically significant at 2 sided alpha level of 0.0163, the study will continue and PFS testing will be conducted again at the second IA when approximately 365 PFS events have occurred, which will also be the final analysis of PFS for statistical testing purpose. Based on the projected number of PFS events, the statistical significance of PFS could be claimed if the observed p value is less than 0.0451 (corresponding to nominal alpha of 0.0337). The trial will not be stopped due to the test for OS at the first IA. The third

IA will be performed when approximately 322 deaths (two-thirds of the total expected deaths) have been observed. The third IA is expected to occur approximately 44 months after the first patient is enrolled. At that time, all patients have been enrolled.

The test significance for the interim and final analyses of OS will be determined using O'Brien-Fleming boundaries (the Lan-DeMets method). Based on the projected number of death events, the trial will be stopped for overwhelming efficacy if the observed p value is less than 0.0018 and 0.0112 at the second and third IA, respectively. The final analysis will be tested at 2-sided alpha level of 0.0462 (corresponding to nominal alpha of 0.0382).

9. STUDY COMMITTEES

9.1 Steering Committee

A steering committee that includes a subset of investigators in this study and representatives from Millennium will be formed to provide advice on the conduct of the study and publications (see also Section 12).

9.2 Independent Review Committee

An independent review committee (IRC) has completed review of all disease evaluation data from the study and determined disease status (response and progression). Data from the IRC will not be provided back to the investigator during the conduct of the study. As of Amendment 6, however, because PFS follow-up is now completed for this study, for all patients still receiving study therapy, no further IRC reviews of disease response will take place.

9.3 Independent Data Monitoring Committee

An IDMC supported by an independent statistician will review safety and efficacy data at 3 planned IAs. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on the IDMC recommendation, Millennium will notify the appropriate regulatory authorities. In addition, the IDMC will periodically review safety data at regularly scheduled meetings prespecified in the IDMC charter. As part of the IDMC safety monitoring, this committee will receive reports of all cases of new primary malignancies occurring during the trial.

The first formal safety review will occur after approximately 60 subjects (30 in each arm) have been randomized and received at least 1 cycle of study treatment. Subsequently, periodic safety reviews will also occur as prespecified in the IDMC charter.

Study accrual will not be interrupted due to the scheduled safety reviews. The IDMC or MLN9708 study team may request an ad hoc meeting for any reason, including a significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, subject incidence rates of AEs (including all serious, treatment-related, and serious treatment-related events, and events requiring the discontinuation of study drug) will be tabulated by System Organ Class, preferred term, and severity grade. Listings and/or narratives of "on-study" deaths and other serious and significant AEs, including any early withdrawals due to AEs, will be provided. Records of all meetings will be archived. The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Millennium. Further details will be provided in the IDMC charter.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 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.

10.1.2 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.

10.1.3 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 lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[51] 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 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

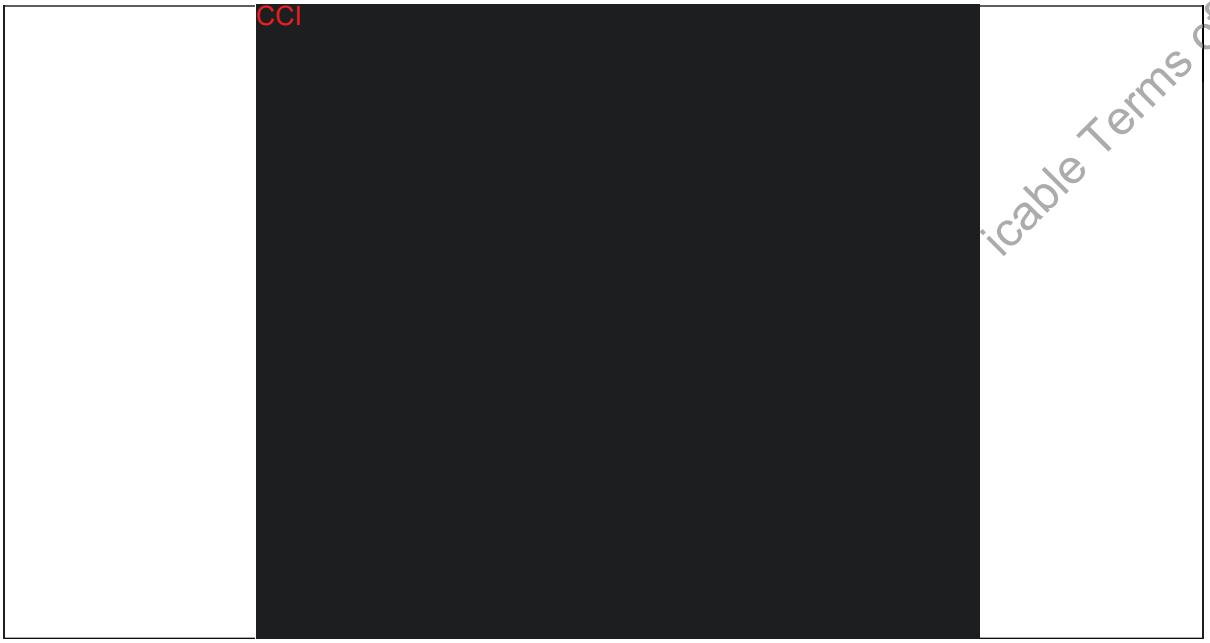
10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

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 10.3 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 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below) 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. SAE report information must be consistent with the data provided on the eCRF.

The paper SAE forms must be submitted via fax (see fax numbers below) within 24 hours of awareness. In case of fax, site personnel must confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. E-mail submission of paper SAE forms with a PDF attachment should only be used in the case where fax is not possible within 24 hours of receiving the event. In case of e-mail, site personnel must confirm successful transmission by awaiting an acknowledgment of the receipt via e-mail within 1 business day. If SAEs are reported via fax or by e-mail, the EDC application must be updated as soon

as possible with the appropriate information.



Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (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 lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010.[51] 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?

10.3 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. In addition, skeletal-related events that occur during the follow-up periods must be reported from the first dose of study drug through death or termination of the study by the sponsor. AEs 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).

- Serious pretreatment events will be reported to Millennium Pharmacovigilance 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 Millennium Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever comes first, and recorded in the eCRF. After this period only related SAEs must be reported to the Millennium Department of Pharmacovigilance 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 study regimen, to the Millennium Department of Pharmacovigilance for a minimum of 3 years after last dose of the investigational product, from the first dose of study drug through death or termination of the study by the sponsor.

10.4 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 subject occurring while the subject is on study drug, or within 90 days of the subject'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 or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to CCI [redacted] Drug Safety

immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify CCI Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to CCI Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to CCI Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study drug must notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 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.

11.2 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.

11.3 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.

eCRFs 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.

11.4 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.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the IRB/IEC.

11.5 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.

11.6 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.

Upon implementation of Amendment 8, patients on study treatment must be reconsented before dosing on Day 1 of the next full treatment cycle. Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations.

11.7 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.

11.8 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.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium/designee 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.

11.10 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. Refer to the Pharmacy Manual for additional details.

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

11.11 Product Complaints and Medication Errors (Including Overdose)

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 Dohmen Life Sciences (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.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately report this via the phone number or e-mail address provided below.

For Product Complaints or Medication Errors (Including

CCI [redacted]

Product complaints or medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, an SAE form should be completed and sent to CCI [redacted] (refer to Section 10.2).

11.12 Closure of the Study

The study will be considered complete after the third interim analysis (if OS endpoints are met) or after the final analysis for OS has been completed or the study has been terminated by the sponsor. Patients remaining on study after the final analysis will be assessed for either

access to commercial drug supply (if available and reimbursable in their region) or continued treatment in another extension or rollover study, if and when such a study is made available.

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 study 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 analyses
- 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.

11.13 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.

12. USE OF INFORMATION

All information regarding MLN9708 supplied by Millennium to the investigator is privileged and confidential 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.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical study results pursuant to the terms contained in the applicable Clinical Trial Agreement.

A Steering Committee that includes a subset of investigators in this study and representatives from Millennium will be formed to advise on the conduct of the study and development of publications and presentations. This policy may be changed with the agreement of both the investigators and Millennium.

13. INVESTIGATOR AGREEMENT

I have read Protocol C16010 Amendment 8: A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma.

I agree to conduct the study as detailed herein and in compliance with 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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15. APPENDICES

15.1 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.[52]

15.2 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] [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.

15.3 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:

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[53]

15.4 ISS Staging Criteria and Durie-Salmon Criteria

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: 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.[54]

Abbreviations: ISS = International Staging System.

a There are two categories for stage II: serum ß$_2$-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 of 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

Durie-Salmon sub classifications (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)

15.5 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.[55]

15.6 World Health Organization Steps of Analgesics and OME Conversions

15.6.1 Steps of Analgesics

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

WHO Step I
ACETAMINOPHEN & ASPIRIN
ACETAMINOPHEN & ASPIRIN & CAFFEINE
ACETAMINOPHEN & BUTALBITAL
ACETAMINOPHEN & BUTALBITAL & CAFFEINE
ACETAMINOPHEN & CAFFEINE
ACETAMINOPHEN CAP 500 MG
ACETAMINOPHEN CHEW TAB 80, 160 MG
ACETAMINOPHEN ELIXIR 80, 120 or 160 MG/5ML
ACETAMINOPHEN SOLN 100 MG/ML, 120 MG/2.5ML, 130 MG/5 ML, 160 MG/5ML
ACETAMINOPHEN SUPPOS 120 MG, 325 MG, 650 MG
ACETAMINOPHEN SUSP 80, 160 MG/5ML
ACETAMINOPHEN TAB 160, 325, 500, 650 MG
ACETAMINOPHEN TAB CR 650 MG
ACETAMINOPHEN W/ CALCIUM CARBONATE TAB 500-250 MG
ACETAMINOPHEN-BUTALBITAL CAP 650-50 MG
ACETAMINOPHEN-BUTALBITAL TAB 325-50 MG
ACETAMINOPHEN-BUTALBITAL TAB 650-50 MG
ACETAMINOPHEN-CAFFEINE-BUTALBITAL CAP 325-40-50 MG; 325-40-50 MG; 500-4-50 MG
ALUMINUM GLYCOLATE & ASPIRIN & MAGNESIUM CARBONATE
ALUMINUM HYDROXIDE & ASPIRIN & MAGNESIUM HYDROXIDE
ASPIRIN & BUTALBITAL & CAFFEINE
ASPIRIN & BUTALBITAL & CAFFEINE & PHENACETIN
ASPIRIN & CAFFEINE
ASPIRIN & CAFFEINE & PHENACETIN
ASPIRIN & PHENOBARBITAL
ASPIRIN BUFFERED (MG CARBONATE-AL GLYCINATE) TAB 325 MG
ASPIRIN BUFFERED (MG CARBONATE-AL GLYCINATE) TAB 500 MG
ASPIRIN BUFFERED TAB 325 MG; 500 MG
ASPIRIN CHEW TAB 75 MG
ASPIRIN EC TAB 81; 165; 325; 500;650;975 MG
ASPIRIN TAB 325; 500; 650 MG
ASPIRIN TAB CR 800 MG
ASPIRIN-ACETAMINOPHEN TAB 325-325 MG
ASPIRIN-ACETAMINOPHEN-CAFFEINE POWDER 260-130-16 MG

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

ASPIRIN-ACETAMINOPHEN-CAFFEINE TAB 230-125-30 MG;240-125-32 MG

ASPIRIN-ACETAMINOPHEN-CAFFEINE TAB 250-250-65 MG

ASPIRIN-AL HYDRO-MG HYDRO-CA CARB TAB 325-50-50-87 MG; 325-75-75-71 MG; 500-80-80-71 MG

ASPIRIN-AL HYDROXIDE-MG HYDROXIDE TAB 325-150-150 MG

ASPIRIN-AL HYDROXIDE-MG HYDROXIDE TAB 325-75-75 MG

ASPIRIN-APAP-CAFFEINE-CALCIUM GLUCONATE TAB 230-160-33-60 MG

ASPIRIN-BUTALBITAL TAB 650-50 MG

ASPIRIN-CAFFEINE TAB 400-30 MG; 500-30 MG

ASPIRIN-CAFFEINE-BUTALBITAL CAP 200-40-50 MG; 325-40-50 MG; 200-4-50 MG; 325-40-50 MG

ASPIRIN-CAL CARB-MAG CARB-MAG OXIDE TAB 325-158-34-63 MG

ASPIRIN & PHENYLTOLOXAMINE CITRATE & SALSALATE

ASPIRIN EFFER TAB 325, 500 MG

ASPIRIN GUM 210 MG

ASPIRIN SUPPOS 125; 325; 650 MG

APC TAB 260-130-15 MG

BENOXAPROFEN

CHOLINE & MAGNESIUM SALICYLATES LIQ 500 MG/5ML

CHOLINE & MAGNESIUM SALICYLATES TAB 500, 750, 1000 MG

CHOLINE MAGNESIUM TRISALICYLATE

CHOLINE SALICYLATE

CINNAMEDRINE

DICLOFENAC POTASSIUM TAB 50 MG

DICLOFENAC SODIUM EC TAB 25, 50, 75 MG

DIFLUNISAL TAB 250, 500 MG

DIHYDROXYALUMINUM AMINOACETATE

ETHOHEPTAZINE CITRATE

ETODOLAC CAP 200, 300, 400 MG

FENOPROFEN CALCIUM CAP 200, 300, 600 MG

FLURBIPROFEN TAB 50, 100 MG

IBUPROFEN CHEW TAB 100 MG

IBUPROFEN POWDER

IBUPROFEN SUSP 100 MG/5ML

IBUPROFEN SUSP 40 MG/ML

IBUPROFEN TAB 100,200,300,400,600,800 MG

INDOMETHACIN CAP 25,50, 75 MG

INDOMETHACIN SODIUM IV FOR SOLN 1 MG

INDOMETHACIN SUPPOS 50 MG

INDOMETHACIN SUSP 25 MG/5ML

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

KETOPROFEN CAP 12.5, 25, 50, 75 MG
KETOPROFEN CAP CR 100, 150,200 MG
KETOROLAC TROMETHAMINE IM INJ 15, 30 MG/ML
KETOROLAC TROMETHAMINE TAB 10 MG
MAGNESIUM SALICYLATE TAB 500, 545, 600 MG
MAGNESIUM TRISILICATE
MECLOFENAMATE SODIUM CAP 50, 100 MG
MEFENAMIC ACID CAP 250 MG
MEPROBAMATE
METHOTRIMEPRAZINE HYDROCHLORIDE
NABUMETONE TAB 500, 750 MG
NAPROXEN SODIUM TAB 220, 275,550 MG
NAPROXEN SUSP 125 MG/5ML
NAPROXEN TAB 250, 375,500 MG
OXYPHENBUTAZONE
OXAPROZIN TAB 600 MG
PAMABROM
PHENYLBUTAZONE
PHENYLTOLOXAMINE
PHENYLTOLOXAMINE CITRATE
PIROXICAM CAP 10, 20 MG
PYRILAMINE
PYRILAMINE MALEATE
SALICYLAMIDE
SALSALATE TAB 500, 750 MG
SODIUM SALICYLATE TAB 325, 650 MG
SODIUM THIOSALICYLATE
SODIUM THIOSALICYLATE INJ 50 MG/ML
SULINDAC TAB 150, 200 MG
SUPROFEN
TOLMETIN SODIUM TAB 200, 400, 600 MG
ZOMEPIRAC SODIUM
WHO Step II
ACETAMINOPHEN & BUTALBITAL & CAFFEINE & CODEINE PHOSPHATE
ACETAMINOPHEN & HYDROCODONE BITARTRATE
ACETAMINOPHEN & OXYCODONE HYDROCHLORIDE
ACETAMINOPHEN & PROPOXYPHENE HYDROCHLORIDE
ACETAMINOPHEN & PROPOXYPHENE NAPSYLATE

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

ACETAMINOPHEN W/ CODEINE CAP 300-30 MG
ACETAMINOPHEN W/ CODEINE ELIXIR 120-12 MG/5ML
ACETAMINOPHEN W/ CODEINE TAB 300-15 MG; 300-30 MG; 300-60 MG; 300-7.5 MG; 650-30 MG
ACETAMINOPHEN W/ HYDROCODONE CAP 500-5 MG
ACETAMINOPHEN W/ HYDROCODONE ELIXIR 167-2.5 MG/5ML; 120-2.5 MG/5ML
ACETAMINOPHEN W/ HYDROCODONE TAB 500-2.5 MG;500-5 MG; 500-7.5 MG; 650-10 MG; 650-7.5 MG; 750-7.5 MG
ACETAMINOPHEN-CAFF-BUTALBITAL W/ COD CAP 325-40-50-30 MG
ACETAMINOPHEN-CAFFEINE-DIHYDROCODEINE CAP 356.4-30-16 MG
AL. HYDROXIDE & ASPIRIN & CODEINE PHOSPHATE & MG. HYDROXIDE
ASPIRIN & BUTALBITAL & CAFFEINE & CODEINE
ASPIRIN & BUTA & CAFF & CODEINE PHOSPHATE & PHENACETIN
ASPIRIN & CAFFEINE & CODEINE PHOSPHATE & PHENACETIN
ASPIRIN & CAFFEINE & HYDROCODONE BITARTRATE
ASPIRIN & CAFFEINE & PHENACETIN & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & CAFFEINE & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & CODEINE PHOSPHATE
ASPIRIN & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & PROPOXYPHENE NAPSYLATE
ASPIRIN W/ CODEINE TAB 325-15 MG; 325-30 MG; 325-60 MG
ASPIRIN W/ HYDROCODONE TAB 500-5 MG
ASPIRIN-CAFF-BUTALBITAL W/ CODEINE CAP 325-40-50-30 MG
ATROPINE SULFATE & MEPERIDINE HYDROCHLORIDE
ATROPINE SULFATE & MORPHINE SULFATE
BUPRENORPHINE HCL INJ 0.324 MG/ML
BUPRENORPHINE HYDROCHLORIDE
BUTORPHANOL TARTRATE INJ 1 MG/ML; 2 MG/ML
BUTORPHANOL TARTRATE NASAL SOLN 10 MG/ML
DEZOCINE INJ 10, 15 MG/ML
DIHYDROCODEINE COMPOUND CAP
MEPERIDINE W/ APAP TAB 50-300 MG
MEPERIDINE W/ ATROPINE INJ 50-0.4 MG/ML; 75-0.4 MG/ML
NALBUPHINE HCL INJ 10, 20 MG/ML
NALOXONE
NALTREXONE HCL TAB 50 MG
OXYCODONE W/ ACETAMINOPHEN SOLN 5-500 MG/5ML
OXYCODONE W/ ACETAMINOPHEN 5-325; 5-500 MG
OXYCODONE W/ ASPIRIN TAB FULL/half STRENGTH
OXYCODONE TEREPHTHALATE

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

PENTAZOCINE LACTATE INJ 30 MG/ML
PENTAZOCINE W/ APAP TAB 25-650 MG;12.5-325 MG
PROMAZINE HCL
PROMETHAZINE HCL (CAP & INJ)
PROPOXYPHENE COMPOUND CAP 65 MG
PROPOXYPHENE HCL W/ APAP TAB 65-650 MG;100-650 MG; 50-325 MG
WHO Step III
ALFENTANIL INJ 500 MCG/ML
CODEINE PHOSPHATE INJ 30, 60 MG/ML
CODEINE PHOSPHATE SOLN 15 MG/5ML
CODEINE PHOSPHATE SOLUBLE TAB 30, 60 MG
CODEINE SULFATE
CODEINE SULFATE TAB 30, 60 MG
FENTANYL CITRATE INJ 0.05 MG/ML
FENTANYL CITRATE POWDER
FENTANYL TD SYS 25, 50, 75, 100 MCG/HR
HYDROCODONE BITARTRATE
HYDROMORPHONE HCL INJ 1,2,3,4, 10 MG/ML
HYDROMORPHONE HCL LIQD 1 MG/ML
HYDROMORPHONE HCL POWDER
HYDROMORPHONE HCL SUPPOS 3 MG
HYDROMORPHONE HCL TAB 2,3,4,8 MG
LEVOMETHADYL ACETATE HCL SOLN 10 MG/ML
LEVORPHANOL TARTRATE INJ 2 MG/ML
LEVORPHANOL TARTRATE TAB 2 MG
MEPERIDINE HCL INJ 25, 50, 75, 100 MG/ML
MEPERIDINE HCL SYRUP 50 MG/5ML
MEPERIDINE HCL TAB 50, 100 MG
METHADONE HCL CONC 10 MG/ML
METHADONE HCL SOLN 5, 10 MG/5ML
METHADONE HCL TAB 5, 10, 40 MG
METHADONE HYDROCHLORIDE
MORPHINE SULFATE CAP 15, 30 MG
MORPHINE SULFATE IN DEXTROSE INJ 0.2 MG/ML
MORPHINE SULFATE IN DEXTROSE INJ 1 MG/ML
MORPHINE SULFATE INJ 1,2,3,4,5,8, 10,15,25,50 MG/ML
MORPHINE SULFATE INJ PF 0.5, 1 MG/ML
MORPHINE SULFATE ORAL SOLN 10, 20 MG/5ML; 20 MG/ML

Table 15-1 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

MORPHINE SULFATE SUPPOS 5, 10, 20, 30 MG
MORPHINE SULFATE TAB 10, 15, 30 MG
MORPHINE SULFATE TAB CR 15, 20,60,100,200 MG
OXYCODONE HCL CONC 20 MG/ML
OXYCODONE HCL SOLN 5 MG/5ML
OXYCODONE HCL TAB 5 MG
OXYCODONE HYDROCHLORIDE
OXYMORPHONE HCL INJ 1 MG/ML
OXYMORPHONE HCL SUPPOS 5 MG
OXYMORPHONE HYDROCHLORIDE
PROPOXYPHENE HCL CAP 65 MG
PROPOXYPHENE NAPSYLATE SUSP 50 MG/5ML
PROPOXYPHENE NAPSYLATE TAB 100 MG
SUFENTANIL CITRATE INJ 50 MCG/ML
TRAMADOL HCL TAB 50 MG

Source: World Health Organization. Cancer Pain Relief. Geneva: World Health Organization, 1986.[56]

15.6.2 Oral Morphine Equivalent (OME) Conversions

Table 15-2 Oral and Parenteral Opioid Equivalences and Relative Potency of Drugs as Compared with Morphine

Opioid Agonists[a]	Oral Dose (mg)	Parenteral Dose (mg)	Factor (IV to PO)
Morphine[b]	***30***[b]	10	3
Codeine	200	130	1.5
Fentanyl[c]		0.1 (100 μg)	
Hydrocodone	30 to 200		
Hydromorphone	7.5	1.5	5
Levorphanol	4	2	2
Oxycodone	15 to 20		
Oxymorphone	10	1	10
Tramadol[d]	50 to 100		

Source: Adapted from the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, Adult Cancer Pain, V.1.2010.[7]

a Opioid drugs NOT recommended include meperidine, methadone, propoxyphene, partial agonists (buprenorphine), and mixed agonist-antagonists (pentazocine, nalbuphine, butorphanol, dezocine).

b Oral morphine equivalent (OME) score is based on an oral morphine dose of 30 mg; the conversion factor listed is for chronic dosing. Avoid using morphine in renal failure.

c Available in transdermal system for extended dosing. See the calculation below for dose conversion from other opioids to transdermal fentanyl.

d Weak opioid receptor agonist with some antidepressant activity; for mild to moderate pain. Recommended dose of 100 mg 4 times daily (maximum daily dose of 400 mg) to avoid central nervous system toxicity. At maximum dose, tramadol is less potent than other opioid analgesics.

Oral Morphine Equivalence Conversion Calculation

To calculate the oral morphine equivalent (OME) score of an opioid in Table 15-2:

X = dose of an opioid equivalent to an oral morphine dose of 30 mg

Y = dose of that opioid consumed by the patient in the last 24 hours

OME of that opioid consumed in the last 24 hours = Y / X × 30

Example: A patient consumed 100 mg of oral codeine in the last 24 hours. The OME calculation is:

X = 200 mg

Y = 100 mg

OME of oral codeine = 100 / 200 × 30 = 15 mg

Table 15-3 Recommended Dose Conversion From Other Opioids to Transdermal Fentanyl

Transdermal Fentanyl (µg/d)	*Morphine*		Oxycodone		Hydromorphone		Codeine	
	Oral[a] (mg/d)	IV/SubQ[b] (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)
25	***60***	20	30	15	7.5	1.5	200	130
50	120	40	60	30	15	3.0	400	260
75	180	60	90	45	22.5	4.5	600	390
100	240	80	120	60	30.0	6.0	800	520

Source: Adapted from the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, Adult Cancer Pain, V.1.2010.[7]

Due to patient variability the recommended doses are estimates; clinical judgment should be used to titrate to the desired response.

a Oral morphine equivalent (OME) score is based on an oral morphine dose of 60 mg (as adapted from Foley KM. The treatment of cancer pain. NEJM 1985; 313:84-95 [57]).

b Parenteral dosing such as intravenous or subcutaneous.

15.7 EQ-5D

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

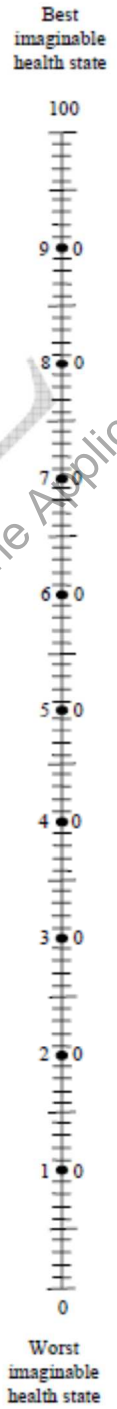
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

15.8 Brief Pain Inventory-Short Form (BPI-SF)

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

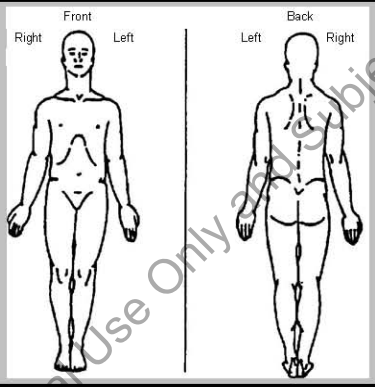
Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

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STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:____/____/____ Time:_____

Name:_____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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15.9 QLQ-MY20

EORTC Multiple Myeloma Module (QLQ-MY20)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

15.10 European Organization for Research and Treatment of Cancer (EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): |_|_|_|_|_|_|_|_|

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

15.11 Response Criteria

Patients will be assessed for disease response according to the IMWG criteria below, versions 2006 and 2011.

Table 1. IMWG uniform response criteria by response subcategory for multiple myeloma[7]

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 or 2- to 4-color flow cytometry		If serum and urine M-protein are not 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%		Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or*
			In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required		Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
					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[19] 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.

International Myeloma Working Group Uniform Response Criteria: Disease Progression and Relapse [58]

Relapse Subcategory	Relapse Criteria
Progressive disease (PD)[a] To be used for calculation of time to progression and PFS endpoints for all subjects, including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any 1 or more of the following: Increase of ≥25% from nadir in Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[b] Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Bone marrow plasma cell percentage: the absolute % 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[c] Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.85 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Abbreviations: CR = complete response; PFS= progression-free survival.

a All relapse categories require 2 consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.

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

c A definite increase of plasmacytoma is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion.

15.12 Full Schedule of Events (as of Amendment 3)

This full Schedule of Events is no longer in effect, as of Amendment 8.

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond			
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1		Every 4 weeks	Every 12 weeks
Window		± 2 days[b]												± 1 wk	± 1 wk	± 1 wk
Informed Consent	X															
Inclusion/Exclusion Criteria[c]	X															
Demographics	X															
Complete Medical History	X															
Complete Physical Exam	X													X		
Symptom-Directed Physical Exam	X					X				X		X	X		X	
ECOG Performance Status	X					X				X		X	X	X	X	
Vital Signs	X	X				X				X		X	X	X	X	
Height (cm) & Weight (kg)	X[d]													X[d]		
Pregnancy Test[e]	X	X	X	X	X	X				X		X	X	X		
12-lead ECG	X					X								X		
Hematology Laboratory[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry Laboratory[f]	X	X				X				X		X	X	X		
Thyroid testing	X											X[g]	X[g]	X		
Urinalysis	X													X		

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond			
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1		Every 4 weeks	Every 12 weeks
Window		± 2 days[b]												± 1 wk	± 1 wk	± 1 wk
EORTC-QLQ-C30 and MY-20[h]	X	X				X						X[i]	X[i]	X	X	
EQ-5D[h]	X	X				X				X		X	X	X	X	X
BPI-SF & 24 hour analgesic form (also for unscheduled visit)[h]	X	X				X				X		X	X	X	X	
HU Asssessment[h]		X				X				X		X	X	X	X	X
Skeletal Survey[j]	X											X	X		X	
Radiographic Disease Assessment[k]	X					X						X	X	X	X	
β2-microglobulin	X															
M-protein Measurements (SPEP)	X	X[l]				X				X		X	X	X	X	
M-protein Measurements (UPEP [24hr Urine collection])	X	X[l]				X				X		X	X	X	X	
Serum Free Light Chain Assay	X	X[l]				X				X		X	X	X	X	
Immunofixation - serum and urine	X	X[l]				X				X		X	X	X	X	
Quantification of Ig	X	X[l]				X				X		X	X	X	X	
Bone Marrow Aspiration																
Disease Assessment	X[m]					X[m]				X[m]		X[m]	X[m]	X[m]	X[m]	

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		**C1**	**C1**	**C1**	**C1**	**C2**	**C2**	**C2**	**C2**	**C3**	**C3**	**C4 Through 12**	**C13 and Beyond**			
Days	**-28 to -1**	**1**	**7**	**14**	**21**	**1**	**7**	**14**	**21**	**1**	**14**	**1**	**1**		**Every 4 weeks**	**Every 12 weeks**
Window		**± 2 days[b]**												**± 1 wk**	**± 1 wk**	**± 1 wk**
Molecular analysis and high-risk cytogenetic assessment	X[n]													X[n]		
Cytogenetics	X[o]															
Blood samples for biomarker analysis																
Plasma biomarker (proteasome level)	X															
Blood samples for germline DNA	X															
Adverse Event Reporting	Recorded from the first dose of study drug through 30 days after last dose of study drug															
	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 any study drug															
Concomitant Medications/Procedures	Recorded from the first dose of study drug through 30 days after last dose of study drug															
Skeletal-related Events	Continuous from the start of study drug administration until death or termination of the study by the sponsor															
New Primary Malignancy Assessment	Continuous from the start of study drug administration until death or termination of the study by the sponsor															
Survival																X
Study Drug Administration																
MLN9708/Placebo		Days 1, 8, and 15 of each cycle														
Lenalidomide		Continuous D1-21 of each cycle														

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond			
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1		Every 4 weeks	Every 12 weeks
Window		± 2 days[b]												± 1 wk	± 1 wk	± 1 wk
Dexamethasone		Days 1, 8, 15 and 22 of each cycle														

Abbreviations: D = study day; del = deletion; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; SPEP = serum protein electrophoresis; t = translocation; UPEP = urine protein electrophoresis; wk = week.

a Review by MPI/designee clinician required prior to discontinuing patient from treatment.

b Tests and procedures should be performed on schedule, but occasional changes may be allowed (± 2 days) for holidays, vacations, and other administrative reasons. If the study schedule is shifted, assessments must be shifted to ensure that 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 MPI/designee clinician.

c Confirmation of patient eligibility by MPI/designee clinician required prior to randomization.

d Height assessed at screening only.

e Pregnancy tests (Refer to Section 7.4.7):

- Screening: Females of childbearing potential (FCBP) must have 2 negative pregnancy tests prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug.
- On-Treatment: Pregnancy tests for FCBP to be collected weekly during Cycle 1 and then within 24 hours before the first dose of each subsequent cycle. Lenalidomide package insert must be followed while patients remain on therapy. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on therapy.
- End of Treatment: Pregnancy tests for FCBP to be collected at treatment discontinuation and at Day 28 following therapy. If menstrual cycles are irregular, the pregnancy testing must occur at drug discontinuation and at Days 14 and 28 following drug discontinuation.

f 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 central labs as well. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing and 24 hours before Days 8, 15 and 22 dosing, where required. Local laboratory evaluations may be done more frequently at the investigators discretion, ie, for acute management of TEAEs (refer to Section 7.4.9).

g Thyroid testing required every 4 cycles on treatment.

h Patient-reported outcomes and HU assessment should be completed before any other study procedures are performed or study drug is administered. During the OS follow-up, assessments can be made over the phone and do not require a clinic visit. (Refer to Sections 7.4.11 to 7.4.14.)

Study Procedures	Screening	Treatment Period												End of Treatment[a]	Follow-up	
		28-Day Cycles													PFS	OS
Cycle		C1	C1	C1	C1	C2	C2	C2	C2	C3	C3	C4 Through 12	C13 and Beyond			
Days	-28 to -1	1	7	14	21	1	7	14	21	1	14	1	1		Every 4 weeks	Every 12 weeks
Window		± 2 days[b]												± 1 wk	± 1 wk	± 1 wk

i Required every other cycle, after Cycle 2 (ie, Cycles 1, 2, 4, 6, etc.) during the treatment period.

j Skeletal survey will be performed at screening (within 8 weeks prior to the first dose of study drug) and, at a minimum, annually for all patients. More frequent assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions).

k Patients with documented extramedullary disease must have radiographic disease assessments (CT/PET-CT/MRI) performed at screening, every other cycle during treatment, and every 8 weeks during the PFS follow-up period, until disease progression.

l If the screening test was performed more than 14 days prior to the first dose, the test will be repeated at baseline.

m To be performed at local lab to assess disease status at baseline. Only to be repeated if patient is considered to possibly have resolution of serum and urine M-protein consistent with CR or to investigate suspected PD if applicable.

n Bone marrow aspirate (first or second pull preferred) for molecular analysis and cytogenetics are required to be sent to the central lab at baseline. For patients who had responded to therapy and subsequently relapsed, a bone marrow aspirate sample is requested at end of study treatment. This sample is not mandatory but highly recommended.

o Cytogenetics may also be done locally if the site has the capability to perform analysis and sufficient specimen available. Assessment of the following: +1q21, translocations t(4;14) and t(14;16), del(17), del(13).

MLN9708 Pharmacokinetic Sampling Schedule

Cycle 1			Cycle 2		Cycles 3-10
Day 1		Day 14	Day 1	Day 14	Day 1
1 hour postdose[a] (± 15 minutes)	4 hour postdose[a] (± 45 minutes)		Predose[c]		Predose[c]
X	X	X[b]	X	X[b]	X

a Sample to be obtained after MLN9708 and can be obtained either before or after lenalidomide and dexamethasone dose.

b If PK sample is taken on a dosing day (due to allowable ± 2-day window of visits), PK sample must be taken within 4 hours prior to dose of any study drug. If PK sample is taken on non-dosing day, ie sample on Day 14 and dose on Day 15, PK sample can be taken at any time during the visit.

c Day 1 predose PK assessments should occur within 4 hours of dosing. Note: If a pre-dose sample is drawn from a patient and the patient does not receive a dose on that protocol visit day, a second pre-dose sample does not need to be drawn on the subsequent visit where the dose is administered. All future visits should be done per the protocol.

15.13 Schedule of Events (as of Amendment 6)

This full Schedule of Events is no longer in effect, as of Amendment 8.

Study Procedures	**Treatment Period**	**End of Treatment**	**OS Follow-up**
	28-Day Cycles		
Cycle	**Cycle 13 and Beyond**		
Days	**1**		**Every 12 weeks**
Window	**± 2 days**[a]	**± 1 wk**	**± 1 wk**
Complete Physical Exam		X	
Symptom-Directed Physical Exam	X		
ECOG Performance Status	X	X	
Vital Signs	X	X	
Weight (kg)		X	
Pregnancy Test[b]	X	X	
12-lead ECG		X	
Hematology Laboratory[c]	X	X	
Chemistry Laboratory[c]	X	X	
EORTC-QLQ-C30 and MY-20[d]	X[e]	X	
EQ-5D[d]	X	X	X
HU Asssessment[d]	X	X	
BPI-SF & 24 hour analgesic form (also for unscheduled visit)[d]	X	X	

Study Procedures	**Treatment Period**	**End of Treatment**	**OS Follow-up**
	28-Day Cycles		
Cycle	**Cycle 13 and Beyond**		
Days	**1**		**Every 12 weeks**
Window	**± 2 days**[a]	**± 1 wk**	**± 1 wk**
Bone Marrow Aspiration for molecular analysis and high-risk cytogenetic assessment		X[f]	
Adverse Event Reporting	Recorded from the first dose of study drug through 30 days after last dose of study drug		
	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 any study drug		
Concomitant Medications/Procedures	Recorded from the first dose of study drug through 30 days after last dose of study drug		
Skeletal-related Events	Continuous from the start of study drug administration until death or termination of the study by the sponsor		
New Primary Malignancy Assessment	Continuous from the start of study drug administration until death or termination of the study by the sponsor		
Survival			X
Study Drug Administration			
MLN9708/Placebo	Days 1, 8, and 15 of each cycle		
Lenalidomide	Continuous Days 1-21 of each cycle		
Dexamethasone	Days 1, 8, 15 and 22 of each cycle		

Abbreviations: D = study day; del = deletion; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PET-CT = positron emission tomography-computed tomography; PFS = progression-free survival; SPEP = serum protein electrophoresis; t = translocation; UPEP = urine protein electrophoresis; wk = week.

a Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons or a longer window after discussion with the Millennium Pharmaceuticals Inc. (Millennium) project clinician or designee. If the study schedule is shifted, assessments must be shifted to ensure that collection of assessments is completed before dosing. .

b Pregnancy tests (Refer to Section 7.4.7):

	Treatment Period	End of Treatment	OS Follow-up
Study Procedures	**28-Day Cycles**		
Cycle	**Cycle 13 and Beyond**		
Days	**1**		**Every 12 weeks**
Window	**± 2 days[a]**	**± 1 wk**	**± 1 wk**

- On-Treatment: Pregnancy tests for FCBP to be collected weekly during Cycle 1 and then within 24 hours before the first dose of each subsequent cycle. Lenalidomide package insert must be followed while patients remain on therapy. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on therapy.
- End of Treatment: Pregnancy tests for FCBP to be collected at treatment discontinuation and at Day 28 following therapy. If menstrual cycles are irregular, the pregnancy testing must occur at drug discontinuation and at Days 14 and 28 following drug discontinuation.

c Centralized clinical laboratory evaluations of safety will be performed by a central laboratory on Day 1 of every cycle. For dosing decisions and for all other safety assessments for the patient, local hematology and chemistry laboratory results may be used; however, samples must still be sent to central labs as well. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing. Local laboratory evaluations may be done more frequently at the investigators discretion, ie, for acute management of TEAEs (refer to Section 7.4.9).

d Patient-reported outcomes and HU assessment should be completed before any other study procedures are performed or study drug is administered. During the OS follow-up, EQ-5D assessments can be made over the phone and do not require a clinic visit. (Refer to Section 7.4.14.)

e Required every other cycle, after Cycle 2 (ie, Cycles 1, 2, 4, 6, etc.) during the treatment period.

f For patients who had responded to therapy and subsequently relapsed, a bone marrow aspirate sample is requested at end of study treatment. This sample is not mandatory but highly recommended.

15.14 Amendment 1 Rationale and Purposes

Rationale for Amendment 1

This protocol amendment addresses regulatory feedback received from several competent authorities and clarifies inconsistencies identified in the original protocol.

Purposes for Amendment 1

The purposes of this amendment are to:

- Clarify the time of collection for EORTC-QLQ-C30, EQ-5D, and MY-20 outcome measures
- Change the term from 'progressive disease confirmation' to 'progressive disease review'
- Clarify the pharmacokinetics schedule with regard to study dosing and requirements for fasting
- Clarify the duration of collection and evaluation of new or worsening of existing selected skeletal events from baseline through the last survival assessment to be in line with the Schedule of Events
- Clarify the reference to baseline creatinine clearance values and permitted re-escalation of lenalidomide
- Clarify that urine pregnancy tests are acceptable if they meet minimum sensitivity levels
- Clarify the definition of abstinence to be in line with the preferred and usual lifestyle of the patient
- Clarify the use of aspirin for prophylactic anticoagulation in the inclusion criteria
- Clarify that subjects with deep vein thrombosis can take low molecular weight heparin in the inclusion criteria
- Clarify the acceptable grade for recovery from effects of prior chemotherapy in the exclusion criteria
- Clarify reference to hepatitis B and C virus infections in the exclusion criteria
- Clarify comorbid systemic illness or other severe concurrent disease in the exclusion criteria
- Change the volume of water that should be taken with the study drug from 150 mL to 240 mL
- Clarify dose modification procedures
- Clarify the toxicity recovery before beginning the next cycle of treatment
- Clarify the procedures for dose modifications due to nonhematologic toxicity judged to be related to study drug
- Clarify the reference to St. John's wort and Ginkgo biloba as medicinal products
- Clarify that palliative radiotherapy for pain control in a preexisting lesion may be considered

- Clarify the timing for collection of concomitant medications
- Clarify the contraception requirements, pregnancy prevention plans, and reference the Study Manual (in place of Sections 15.11 through 15.14)
- Update the clinical management of erythematous rash with or without pruritus to include Stevens-Johnson Syndrome
- Update the clinical management of thrombocytopenia to include thrombotic thrombocytopenic purpura (TTP)
- Clarify the clinical management of fluid deficit
- Add the clinical management of hypotension
- Add the clinical management of Posterior Reversible Encephalopathy Syndrome
- Remove the typographical error that refers to the 5.5-mg dose of MLN9708 capsules, as this is not a dose used in this study
- Clarify how lenalidomide will be supplied worldwide
- Clarify the reference to contact information for study personnel in the Study Manual
- Clarify that treatment groups will be assigned using interactive voice response system
- Add thyroid testing and additional hematology testing to align with the lenalidomide SmPC
- Clarify the collection of pain assessments on the BPI-SF and 24-hour analgesic forms
- Change the frequency of the skeletal survey and clarify acceptable alternatives to skeletal surveys
- Clarify the radiographic disease assessments that are needed for patients with extramedullary disease
- Remove cost assessment section
- Clarify that bone marrow aspirate is used to confirm complete response and/or progressive disease
- Clarify that local labs may be used for dosing decisions, management of treatment-emergent adverse events, and collection and analyses of cytogenetics samples
- Remove the requirement for a bone marrow biopsy in the study procedures
- Clarify the biomarker analyses that are to be performed at local versus central laboratories
- Clarify that the plasma concentrations will be measured using a validated LC/MS/MS assay and remove the optional PK collection at the time of SAEs
- Clarify that radiographic disease assessments are to be performed every 8 weeks during the progression-free survival (PFS) follow-up period
- Clarify collection and reporting requirements for SAEs related to study drug during posttreatment follow-up
- Clarify that assessments to be performed for the End of Treatment visit are listed in the Schedule of Events
- Add an analysis for pain response

- Update the definition of pain progression
- Clarify that Eastern Cooperative Oncology Group (ECOG) performance scores will be summarized using a shift table
- Correct the role of the independent data monitoring committee
- Indicate that serious adverse events will be reported within 24 hours rather than 1 business day
- Update language to current company standards and remove text regarding the start of antineoplastic or anticancer therapy as it relates to follow-up AEs
- Update the version of the International Myeloma Working Group (IMWG) uniform response criteria in Section 15.11 from the 2006 version to the 2011 version
- Correct typographical errors, punctuation, grammar, and formatting

15.15 Amendment 2 Rationale and Purposes

Rationale for Amendment 2

The primary rationale for this amendment is to establish a China continuation of Study C16010. This amendment describes modifications to the global study procedures specifically for patients who enroll in the China continuation. Patients from China who enroll in the global study will not be affected. Following completion of enrollment in the global study (703 patients), up to approximately 120 additional patients from China will be enrolled in the China continuation.

The China continuation is an extension of the global study that will continue to assess the primary objective of progression-free survival (PFS) in patients from China. Select other secondary objectives that directly relate to disease response assessment and safety will also be evaluated to thoroughly characterize the efficacy and safety signals of MLN9708 in this population. These objectives are overall survival (OS), overall response rate (ORR), complete response + very good partial response rate (CR + VGPR), duration of response (DOR), time to progression (TTP), and safety. Additional secondary and exploratory objectives will be explored in the global study but are not included in the China continuation because they are signal-seeking in nature. Objectives that are subsequently determined to be of clinical relevance may be evaluated in future clinical studies.

The primary objective of PFS will be assessed when 50% of PFS events have occurred or a minimum of 18 months after the first patient is enrolled in the China continuation, whichever occurs first. OS will be assessed when 50% of events have occurred or a minimum of 2 years after the last patient is enrolled in the China continuation, whichever occurs first. These assessment times will allow detection of any trends in the data and demonstrate consistency with the global dataset.

This amendment will allow for in-depth characterization of the pharmacokinetic (PK) properties of MLN9708 for patients in China. While the global study implements sparse PK sampling, the China continuation includes extensive PK sampling on up to 30 patients to obtain data on approximately 12 PK-evaluable patients in the MLN9708 plus lenalidomide and dexamethasone (LenDex) arm.

Purposes for Amendment 2

The purposes of this amendment are to:

- Add background epidemiology information on multiple myeloma in the Chinese population
- Clarify that the primary objective will be assessed in patients from China
- Update the number of patients from 703 to 120 to reflect the approximate number of patients from China that will be enrolled in the China continuation
- Modify the PK objective and corresponding endpoint to remove sparse PK sampling and add full characterization of PK in up to 30 patients
- Remove secondary objectives (and corresponding endpoints and study procedures) that do not directly contribute to the characterization of the efficacy or safety of MLN9708

- Remove exploratory objectives (and corresponding endpoints and study procedures) that do not directly contribute to the characterization of the efficacy or safety of MLN9708
- Modify the duration of study for patients in the China continuation
- Modify the time and number of events required for the primary analysis of PFS
- Modify the time and number of events required for the secondary analysis of OS
- Remove the 2 interim analyses
- Modify the inclusion criteria to specify patients from China
- Modify the populations for analysis to be specific for the China continuation
- Clarify independent data monitoring committee (IDMC) procedures as they specifically relate to the China continuation

15.16 Amendment 3 Rationale and Purposes

Rationale for Amendment 3

The primary reason for this amendment is to add an additional progression-free survival (PFS) analysis, which will be considered the final PFS analysis. The second PFS analysis will allow more PFS data at a later date in addition to the first PFS analysis in the current protocol, and update the assumption on median PFS for both arms for sample size calculation based on the reported delayed events in 2 ongoing phase 3 studies (also being conducted in the same disease setting with the same primary endpoint). The original planned first interim analysis (IA [which was the final analysis (FA) for PFS]) will be conducted at a later date when approximately 262 PFS events have occurred. The added PFS analysis (the new FA) is to be conducted when approximately 365 PFS events have occurred. The alpha allocation for PFS will be based on the O'Brien-Fleming alpha spending function (the Lan-DeMets method). If the PFS IA is statistically significant, the PFS FA will be a non-inferential test only. Those 2 PFS analyses also serve as the first IA and second IA for overall survival (OS).

Purposes for Amendment 3

The purposes of this amendment are to:

- Update the statistical and quantitative analyses sections to include the assumptions on PFS for sample size calculation and additional IA
- Remove the non-inferential test on PFS at the original planned second IA
- Reclassify of the secondary biomarker objectives to exploratory objectives
- Update the cover page with current signatories
- Update the study overview diagram to remove subsequent anti-neoplastic therapy as a grounds for treatment discontinuation
- Clarify the timing of the EuroQol 5-Dimensional Health Questionnaire (EQ-5D) and skeletal survey
- Clarify the pharmacokinetic sampling schedule
- Remove assessments of specific gene mutations of the P13K pathway and indicate that similar analyses will be done in tumor samples from patients who initially responded to therapy and subsequently relapsed
- Indicate that circulating proteasome levels will be assessed
- Clarify the PFS and OS assessment intervals in the Overview of the Study Design section to be consistent with the Schedule of Events
- Update the inclusion criteria to align with current standard informed consent form (ICF) contraception durations
- Clarify lenalidomide administration guidelines
- Clarify that use of alternative dose modifications must be approved by sponsor/designee clinician
- Clarify lenalidomide treatment modification guidelines

- Clarify the gastrointestinal and metabolic adverse event severities for dexamethasone-related treatment modification guidelines
- Clarify dexamethasone dose modification guidelines
- Update language describing the management of clinical events
- Indicate that protocol changes will be communicated to the investigative sites at the time the study is unblinded
- Update the description of the investigational agents
- Clarify the description of the preparation, reconstitution, and dispensation of MLN9708 to be consistent across studies
- Clarify the description of the storage and handling of MLN9708 to be consistent across studies
- Clarify wording about permitted changes to the timing of tests and procedures
- Clarify the roles of the central and local laboratories for eligibility and progressive disease assessment
- Clarify the M-protein and free light chain to be followed for response assessment according to IMWG criteria
- Clarify the proteasome subunits that will be assessed
- Update the criteria for completion of treatment
- Indicate that the investigator is required to submit the rationale for discontinuing a patient from study treatment
- Clarify that the intent-to-treat (ITT) population is used for patient-reported outcome assessments
- Replace "time to pain response" with "duration of pain response" and indicate how data for this response will be summarized
- Add that the independent data monitoring committee (IDMC) will receive reports of all cases of new primary malignancies during the study
- Indicate proper reporting of cases of overdose
- Update the serious adverse event (SAE) reporting contact information
- Update the SAE reporting information
- Update the procedures for reporting drug exposure during pregnancy to be consistent throughout the protocol
- Correct the bracket placement in the Cockcroft–Gault equations
- Clarify the International Myeloma Working Group (IMWG) response criteria version used for the study and clarify very good partial response (VGPR) in terms of plasmacytoma
- Correct typographical errors, punctuation, grammar, and formatting

15.17 Amendment 4 Rationale and Purposes

Rationale for Amendment 4

This amendment describes modifications that were made to the global study procedures (Global Amendment 3) that apply to the China-specific protocol continuation.

Purposes for Amendment 4

The purposes of this amendment are to:

- Update the cover page with current signatories
- Update the study overview diagram to remove subsequent antineoplastic therapy as a grounds for treatment discontinuation
- Clarify the timing of the skeletal survey
- Clarify the pharmacokinetic sampling schedule
- Update terms in the List of Abbreviations
- Remove assessments of specific gene mutations of the P13K pathway and indicate that similar analyses will be done in tumor samples from patients who initially responded to therapy and subsequently relapsed
- Clarify the progression-free survival and overall survival assessment intervals in the Overview of the Study Design section to be consistent with the Schedule of Events
- Clarify the timing of the End of Treatment visit
- Update the inclusion criteria to align with current standard informed consent form (ICF) contraception durations
- Remove references to country-specific pregnancy risk guidelines other than for China
- Clarify lenalidomide administration guidelines
- Clarify dexamethasone administration guidelines
- Clarify lenalidomide treatment modification guidelines
- Clarify the gastrointestinal and metabolic adverse event severities for dexamethasone-related treatment modification guidelines
- Clarify that use of alternative dose modifications must be approved by sponsor/designee clinician
- Update language describing the management of clinical events
- Indicate that protocol changes will be communicated to the investigative sites at the time the study is unblinded
- Update the description of the investigational agents
- Clarify the description of the preparation, reconstitution, and dispensation of MLN9708 to be consistent across studies
- Clarify the description of the storage and handling of MLN9708 to be consistent across studies
- Remove references to country-specific suppliers of lenalidomide other than for China

- Remove references to country-specific suppliers of dexamethasone other than for China
- Clarify wording about permitted changes to the timing of tests and procedures
- Clarify the roles of the central and local laboratories for eligibility and progressive disease assessment
- Clarify the M-protein and free light chain to be followed for response assessment according to IMWG criteria
- Update the criteria for completion of treatment
- Indicate that the investigator is required to submit the rationale for discontinuing a patient from study treatment
- Add that the independent data monitoring committee (IDMC) will receive reports of all cases of new primary malignancies during the study
- Indicate proper reporting of cases of overdose
- Update the serious adverse event (SAE) reporting contact information
- Update the SAE reporting information
- Update the procedures for reporting drug exposure during pregnancy to be consistent throughout the protocol
- Update the product complaint reporting contact information
- Correct the bracket placement in the Cockcroft–Gault equations
- Clarify the International Myeloma Working Group (IMWG) response criteria version used for the study and clarify very good partial response (VGPR) in terms of plasmacytoma
- Define "definite increase of plasmacytoma" in the Response Criteria appendix
- Correct typographical errors, punctuation, grammar, and formatting

15.18 Amendment 5 Rationale and Purposes

Rationale for Amendment 5
The rationale for this amendment is to require prophylactic antiviral therapy for every patient receiving study treatment (unless there is a clinical contraindication) to prevent herpes zoster reactivation. This amendment is in response to the Independent Data Monitoring Committee (IDMC), which has recommended this modification to the study.

Purposes for Amendment 5

- Update the cover page with current signatories.
- Require prophylactic antiviral therapy for all patients receiving study treatment.
- Correct typographical errors, punctuation, grammar, and formatting.

15.19 Amendment 6 Rationale and Purposes

Rationale for Amendment 6

The primary reason for this amendment is to discontinue study assessments and the PFS follow-up period for patients still receiving study therapy, now that the primary endpoint of progression-free survival (PFS) is complete. Endpoints relating to disease response (ie, PFS, response rate, time to progression) will not be assessed for protocol purposes after the primary endpoint is met; as such, all efficacy response data (ie, blood, serum, and urine samples for assessment of response) will stop being collected/sent to the central laboratory to minimize the burden on study patients and avoid unnecessary procedures. The other main reason for this amendment is to remove the futility boundary for overall survival (OS) at the third interim analysis to ensure the collection of sufficient long-term safety data and avert potential premature termination of OS evaluation, a key secondary endpoint.

Other changes clarify study procedures, as noted in the following list.

Purposes for Amendment 6

The purposes of this amendment are to:

- Remove mention of the Safety Management Attachment, which no longer exists
- Discontinue the PFS follow-up period and all efficacy response assessments, including laboratory assessments, for protocol purposes because PFS significance has been met in the study
- Remove the futility boundary for OS at the third interim analysis and note that the actual efficacy boundaries may be adjusted if the actual number of events does not correspond to the projected number of events in the remaining analyses
- Update the excluded concomitant medication information to reflect recent population pharmacokinetics (PK) analyses and drug-drug interaction study results from Study C16009 demonstrating that cytochrome P450 inhibitors do not affect MLN9708 PK
- Clarify the management of rash, including adding a table of steroid equivalent doses
- Clarify the management of overdose
- Clarify the instructions for study drug dispensing
- Clarify the procedure for performing the physical examination
- Clarify when central laboratory results must be reviewed before initiating the next treatment cycle
- Note that PK sample collection for the study has now been completed for all patients
- Add an email address for reporting adverse events (AEs) and serious AEs in Japan
- Clarify the monitoring of AEs and period of observation
- Update the procedures for product complaints to include instructions for reporting medication errors and overdose
- Clarify the definition of closure of the study
- Correct typographical errors, punctuation, grammar, and formatting

15.20 Amendment 7 Rationale and Purposes

Rationale for Amendment 7

This document describes the changes in reference to the protocol incorporating Amendment No. 7. This amendment describes modifications to the study procedures specifically for patients who are enrolled in the China-specific protocol continuation of Study C16010. Patients from China who are enrolled in the global C16010 study will not be affected by this amendment.

As of Amendment 7, analysis of the primary endpoint of progression-free survival (PFS) (at the primary analysis) and of the secondary endpoint of overall survival (OS) (at the final analysis) have been completed. The rationale for this amendment is to discontinue disease response assessments (ie, PFS, response rate, time to progression), discontinue efficacy response assessments (ie, blood, serum, and urine samples), discontinue PFS and OS follow-up assessments for all patients, and discontinue all follow-up of patients who have completed study treatment. In addition, the objective of this amendment is to provide patients who are still on study treatment with continued access to study drugs and to continue to collect relevant safety information. Also, after unblinding of patients after the positive final survival analysis, this amendment will allow patients who are currently receiving placebo in combination with lenalidomide and dexamethasone the option to continue receiving lenalidomide and dexamethasone alone or, based on the investigator's opinion, MLN9708 in combination with lenalidomide and dexamethasone.

Other changes clarify study procedures as noted in the following list.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Section 15.15.

Changes in Amendment 7

1. Discontinue all disease and efficacy response assessments, including laboratory assessments, for protocol purposes because PFS and OS analyses have been completed in the study.
2. Include final C16010 China Continuation study results.
3. Discontinue the PFS and OS follow-up periods.
4. Include the option for patients, based on the investigator's opinion, currently receiving placebo in combination with lenalidomide and dexamethasone to continue with lenalidomide and dexamethasone alone, or cross over to receive MLN9708 in combination with lenalidomide and dexamethasone.
5. Revise the definition of the duration of study treatment.
6. Define the long-term safety assessments as of Amendment 7.

7. Update the excluded concomitant medication information.
8. Clarify the management of rash, including adding a reference table of steroid equivalent doses.
9. Clarify the management of overdose.
10. Clarify study unblinding.
11. Clarify the storage conditions for MLN9708.
12. Clarify withdrawal of patients from study.
13. Clarify details regarding review and entry of laboratory results.
14. Clarify the population for analysis of safety as of Amendment 7.
15. Remove the efficacy analysis.
16. Revise the safety analysis.
17. Specify that no further independent review committee reviews are needed as of Amendment 7.
18. Specify that no further independent data monitoring committee reviews of safety and efficacy are needed as of Amendment 7.
19. Clarify the monitoring of adverse events.
20. Update the procedures for product complaints to include instructions for medication errors and overdose.

15.21 Amendment 8 Detailed Summary of Changes

THE PRIMARY SECTIONS OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 8 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Change 1: Clarify the study objectives as of Amendment 8.

The primary change occurs in Section 2 STUDY OBJECTIVES:

Added text: **Note that the primary objective and corresponding endpoint have been met. Upon implementation of Amendment 8, the objective is to continue to collect long-term safety data from patients who are continuing on ixazomib (MLN9708) and LenDex or LenDex (note the placebo capsule will be discontinued) because of continuing clinical benefit. Data collection for all other study objectives and endpoints will be complete at the time of the final analysis and no further formal analyses will be conducted. The original lists of objectives are retained below for reference only.**

Rationale for Change:

To clarify the study objective at this point in the study.

The Protocol Summary also contains this change.

Change 2: Clarify the study endpoints as of Amendment 8.

The primary change occurs in Section 3 STUDY ENDPOINTS:

Added text: **Note that the primary endpoint has been met. Upon implementation of Amendment 8, evaluation of the safety profile of MLN9708 and/or LenDex is the only endpoint being assessed. Analysis of all other study endpoints will be complete at the final analysis and no further formal statistical analyses will be performed. However, the complete list of endpoints is retained below for reference.**

Rationale for Change:

To clarify the study endpoint at this point in the study.

Change 3: Clarify that the final analysis data cutoff has been conducted and the study is considered complete for statistical analysis purposes.

The primary change occurs in Section 8 STATISTICAL AND QUANTITATIVE ANALYSES:

Added text:	**The final analysis data cutoff has been conducted and as such, the study is considered complete for statistical analysis purposes. The final analysis is expected to occur in the fourth quarter of 2020. Upon implementation of Amendment 8, the investigator will unblind all patients remaining on study treatment and will follow the new Schedule of Events presented in this amendment. No subsequent formal inferential statistical analyses will be conducted; minimal descriptive analyses of safety will be performed on patient data collected after the final analysis. The description of the statistical methods presented below reflects the full design for the study for reference.**

Rationale for Change:

To note that the data cutoff date for the final analysis has now occurred; no subsequent formal inferential statistical analyses will be conducted after the final analysis.

Change 4: Add language to clarify ongoing treatment of patients—patients still receiving study treatment will stay on their assigned study regimen. Patients should be moved off study and onto an alternative supply of (eg, commercially available) ixazomib and/or LenDex, or onto another standard of care treatment.

The primary change occurs in the Schedule of Events:

Initial wording:	As of Amendment 6, the primary endpoint of PFS has been met, and as such, the PFS follow-up period is now completed and for all patients still receiving study therapy, all central and investigator assessments of response and progression for protocol purposes will be discontinued. Thus, for ease of study conduct, the Schedule of Events now presented has been simplified to apply to the remainder of the study. The full Schedule of Events as of Amendment 3 has been moved to Section 15.12. The PK sampling schedule has also been moved to Section 15.12, as it was applicable through Cycle 10, which has been completed for all patients.
Amended or new wording:	**The final analysis data cutoff has been conducted and as such, the study is considered complete for statistical analysis purposes. Upon implementation of Amendment 8, the investigator will unblind all patients remaining on study treatment and will follow the new Schedule of Events.** **Only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Because no further formal statistical analyses will be performed, only assessments contributing to long-term safety monitoring are required. Most study assessments besides safety are discontinued to ease the burden of protocol-mandated assessments on patients. Patients continuing their**

current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib (MLN9708) and/or LenDex, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care.

Patients who are receiving ixazomib plus LenDex will continue to receive ixazomib plus LenDex. Patients who are receiving placebo plus LenDex will receive LenDex only; the placebo capsule will no longer be administered and patients receiving placebo will not be crossed over to ixazomib in this study. Upon implementation of Amendment 8, data collection requirements will be limited to collection of AEs, SAEs, and concomitant medications. Quality of life, health care utilization, EQ-5D, and pain assessments are discontinued. Survival data will no longer be collected because the analysis of OS will be complete at the time of the final analysis. Other study assessments are no longer required, as noted in the new Schedule of Events. Patients will not be followed for the OS follow-up period because OS data are no longer being collected.

~~As of Amendment 6, the primary endpoint of PFS has been met, and as such, the PFS follow-up period is now completed and for all patients still receiving study therapy, all central and investigator assessments of response and progression for protocol purposes will be discontinued. Thus, for ease of study conduct, the Schedule of Events now presented has been simplified to apply to the remainder of the study. The full Schedule of Events as of Amendment 3 has been moved to Section 15.12. The PK sampling schedule has also been moved to Section 15.12, as it was applicable through Cycle 10, which has been completed for all patients.~~

Rationale for Change:

To clarify which patients may remain on study at this point and what treatment they will receive.

The following sections also contain this change:

- Protocol Summary.
- Study Overview Diagram.
- Section 4.1 Overview of Study Design.
- Section 4.3 Duration of Study.
- Section 6.1 Test Article (MLN9708) and Matched Placebo.
- Section 6.11 Blinding and Unblinding.

Change 5: Discontinue all remaining efficacy assessments (eg, OS, Quality of Life) and clarify ongoing safety laboratory evaluations.

The primary change occurs in the Schedule of Events:

Description of Change:	Added a new Schedule of Events table that details assessments that will be conducted upon implementation of Amendment 8. The only assessments that will continue to be collected are: • Informed Consent (reconsent) • Complete Physical Examination • Symptom-Directed Physical Exam • Pregnancy Test • Hematology • Clinical Chemistry • Adverse Event/Serious Adverse Event Reporting • New Primary Malignancy Assessment • Concomitant Medications/Procedures The previous Schedule of Events table was moved to Section 15.13 Schedule of Events (as of Amendment 6).

Rationale for Change:

To clarify what procedures patients on study will follow.

The following sections also contain this change:

- Section 7.4 Study Procedures.
- Section 7.4.5 Eastern Cooperative Oncology Group Performance Status.
- Section 7.4.8 Electrocardiogram.
- Section 7.4.9 Clinical Laboratory Evaluations.
- Section 7.4.10 Clinical Chemistry, Hematology, and Urinalysis.
- Section 7.4.11 Health Utilization Data Collection.
- Section 7.4.12 Quality of Life Assessment (European Organization for Research and Treatment of Cancer).
- Section 7.4.13 Pain Assessment.
- Section 7.4.14 Utility Measurement.
- Section 7.4.15 Skeletal Survey.
- Section 7.4.16 Skeletal-Related Events.
- Section 7.4.17 Radiographic Disease Assessments.
- Section 7.4.23 Bone Marrow Evaluation.
- Section 7.5 Unscheduled Visits.

Change 6: Discontinue the OS follow-up period.

The primary change occurs in Section 7.4.29 Follow-up Assessments (PFS and OS):

Initial wording:	Patients who stop treatment for any reason will continue to have OS follow-up visits. See the Schedule of Events for appropriate assessments. All subsequent antineoplastic therapies will be recorded, regardless if they are initiated before or after PD. Patients who start an alternative antineoplastic therapy prior to disease progression will continue to be followed for progression. As of Amendment 6, however, the primary endpoint has been met. As such, the PFS follow-up phase has been discontinued for all patients currently receiving study therapy and for any patients who discontinued treatment for other reasons, including patients who start an alternative therapy before PD. All patients discontinuing study treatment will be assessed for OS but no longer for PFS. Patients who stop treatment due to PD will continue to have overall survival visits/assessments. During the OS follow-up, assessments can be made over the phone and do not require a clinic visit. Data may be collected by methods that include but are not limited to telephone, e-mail, mail, and social security indexes. The OS follow-up should be conducted every 12 weeks after documented PD until death or termination of the study by the sponsor. All subsequent antineoplastic therapies will be recorded during the OS follow up period. Information for new primary malignancy should be collected during the study, including the PFS and OS follow-up periods. As of Amendment 6, however, the primary endpoint has been met; as such, the PFS follow-up phase has been discontinued for patients currently receiving study therapy. All patients discontinuing study treatment will be assessed for OS but no longer for PFS. NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance 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 or designee.
Amended or new wording:	**Prior to implementation of Amendment 6,** ~~P~~**p**atients who ~~stop~~**stopped** treatment for any reason ~~will continue to have~~**had** ~~O~~**OPF**S follow-up visits. See the ~~Schedule of Events for~~**Schedule of Events in Section 15.12 for the** appropriate assessments. All subsequent antineoplastic therapies ~~will~~**were to** be recorded, regardless if they ~~are~~**were** initiated before or after PD. Patients who start**ed** an alternative antineoplastic therapy prior to disease progression ~~will~~ continue**d** to be followed for progression. As of Amendment 6, however, the primary endpoint has been met. As such, the PFS follow-up phase ~~has been~~**was** discontinued for all patients ~~currently~~ receiving study therapy and for any patients who discontinued treatment for other reasons, including patients who start**ed** an alternative therapy before PD. ~~All patients discontinuing study treatment will be assessed for OS but no longer for PFS.~~ **Prior to implementation of Amendment 8,** ~~P~~**p**atients who ~~stop~~**stopped** treatment due to PD ~~will~~ continue**d** to have overall survival visits/assessments. During the OS follow-up, assessments ~~can~~**could** be made over the phone and ~~do~~**did** not require a clinic visit. Data may ~~be~~**have been** collected by methods that include**d** but ~~are~~**were** not limited to telephone, e-mail, mail, and social security

indexes. The OS follow-up ~~should be~~**was** conducted every 12 weeks after documented PD until death or termination of the study by the sponsor. All subsequent antineoplastic therapies ~~will~~**were to** be recorded during the OS follow-up period.

~~Information for new primary malignancy should be collected during the study, including the PFS and OS follow-up periods. As of Amendment 6, however, the primary endpoint has been met; as such, the PFS follow-up phase has been discontinued for patients currently receiving study therapy. All patients discontinuing study treatment will be assessed for OS but no longer for PFS.~~

~~NOTE:~~**Upon implementation of Amendment 8, patients will no longer be followed during any of the follow-up periods. NOTE: Prior to implementation of Amendment 8,** ~~R~~**r**elated SAEs must ~~be~~**have been** reported to the Millennium Department of Pharmacovigilance or designee. This includes~~d~~ deaths that the investigator considers~~ed~~ related to study drug that occur**red** during the posttreatment follow-up. In addition, new primary malignancies that occur**red** during the follow-up periods, irrespective of causality to study regimen, must ~~be~~**have been** reported to the Millennium Department of Pharmacovigilance or designee.

Rationale for Change:

To explain that patients will not be followed for the PFS or OS follow-up periods upon implementation of Amendment 8.

The following sections also contain this change:

- Study Overview Diagram.
- Section 7.4 Study Procedures.
- Section 7.10 Withdrawal of Patients From Study.

Change 7: Revise information regarding the interim analyses.

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

Initial wording:	As of Amendment 6, the first 2 IAs have been performed. The primary analysis (data cutoff date, 30 October 2014) occurred when 286 patients had experienced disease progression or death; at this analysis, the primary endpoint of PFS was met. The next analysis (data cutoff date, 12 July 2015) occurred when 372 patients had experienced disease progression or death. This was the first analysis for OS. It was found that OS data were not yet mature and the study was to continue, following the patients for survival. The third IA for OS will occur when approximately 322 deaths have been reported. The trial will be stopped for overwhelming efficacy if the O'Brien-Fleming efficacy boundary is crossed at the third IA.[41] However, the actual boundary could be adjusted if the actual number of events does not correspond to the projected number of events in the remaining IA or in the final analysis (FA). An independent data monitoring committee (IDMC) will review safety and efficacy data at the IAs. See Section 9.3 for more information.
Amended or new wording:	As of Amendment ~~6~~**8**, the ~~first 2~~**3** IAs have been performed. The primary analysis (data cutoff date, 30 October 2014) occurred when 286 patients had experienced disease progression or death; at this analysis, the primary endpoint of PFS was met. The next analysis (data cutoff date, 12 July 2015) occurred when 372 patients had experienced disease progression or death. This was the first analysis for OS. ~~It was found that OS data were not yet mature and~~**A total of 171 deaths had been reported and the threshold for OS statistical significance was not met. Per the study design and statistical analysis plan,** the study was to continue, following ~~the~~ patients for survival. **The third IA (data cutoff date, 25 October 2017) occurred when 333 deaths had been reported. The threshold for statistical significance was not met and the study was to continue to the final analysis. The final analysis occurred in the fourth quarter of 2020.** ~~The third IA for OS will occur when approximately 322 deaths have been reported. The trial will be stopped for overwhelming efficacy if the O'Brien-Fleming efficacy boundary is crossed at the third IA.[41] However, the actual boundary could be adjusted if the actual number of events does not correspond to the projected number of events in the remaining IA or in the final analysis (FA).~~

Rationale for Change:

To update the results from the 3 interim analyses.

Change 8: Update language about the management of clinical events in patients receiving ixazomib.

The primary change occurs in Section 6.10 Management of Clinical Events:

Initial wording:

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 or valacyclovir may be initiated as clinically indicated.

…

Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor (5-HT3) 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.

Erythematous Rash With or Without Pruritus

…

Rash may range from some 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 and self-limiting and is typically Grade 1 to 2 in severity. As in many other oncology trials, rash may occur in patients receiving placebo and in patients receiving MLN9708. If rash occurs, consideration should be given to alternate causes of the rash such as concomitant medications, infections, etc.

…

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when MLN9708 (or placebo) was given with concomitant medications that are known to cause rash

(eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding TEAEs. These severe, potentially life-threatening or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. Additional information regarding these reactions can be found in the IB.

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. Lenalidomide or study drug administration should be modified as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-1). 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.

Fluid Deficit

Dehydration should be avoided since lenalidomide is substantially excreted by kidney, and 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 gastrointestinal toxicities and dehydration. Fluid deficit should be corrected before initiation of study drug as needed during treatment to avoid dehydration (see Section 6.8).

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope 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 decreased appetite. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- 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.

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, as well as abrupt increase in

blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). 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

One case of transverse myelitis has been reported with MLN9708. It is not known whether MLN9708 causes transverse myelitis; however, because it happened to a patient 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.

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. If overdose occurs, consider close observation including hospitalization for hemodynamic support. Gastric lavage may be considered if instituted within 1 hour of ingestion of MLN9708 overdose.

Amended or new wording:

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. **Unless there is a clinical contraindication, prophylactic** ~~A~~antiviral therapy ~~such as acyclovir or valacyclovir may be initiated as clinically indicated.~~ **is required for all patients while receiving study treatment. Examples of acceptable antiviral therapy include acyclovir (eg, 400 mg given orally, 3 times a day), famciclovir (eg, 125 mg given orally, twice a day), or valacyclovir (eg, 500 mg given orally, twice a day) or standard of care/local practice.**

…

Nausea and/or Vomiting

~~Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor (5-HT3) 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.~~

Prophylaxis with standard antiemetics, including serotonin 5-hydroxytryptamine 3 receptor antagonists, is recommended for emesis. Any fluid deficit occurring during treatment should be promptly corrected.

Diarrhea

~~Prophylactic antidiarrheals will not be used in this protocol. However, d~~**D**iarrhea 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. **Any** ~~F~~**f**luid deficit ~~should be corrected before initiation of treatment and~~**occurring** during treatment **should be promptly corrected**.

Erythematous Rash With or Without Pruritus

…

Rash may range from ~~some~~**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 and self-limiting and is typically Grade 1 ~~to~~**or** 2 in severity. As in many other oncology trials, rash may occur in patients receiving placebo and in patients receiving MLN9708. If rash occurs, consideration should be given to alternate causes of the rash such as concomitant medications, infections, etc**; these other causative agents should be discontinued and alterative agents considered if medically necessary**.

…

The rare risks of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when MLN9708 (or placebo) was given with concomitant medications that are known to cause rash (eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding TEAEs. These severe, potentially life-threatening or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. **Study medications should be discontinued in the event of severe, potentially life-threatening rash.** Additional information regarding these reactions can be found in the IB.

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. Lenalidomide or study drug administration should be modified as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-1). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. ~~A rare risk is~~**Thrombotic microangiopathy (TMA), including** thrombotic

thrombocytopeni~~c~~a purpura~~, a~~ **and hemolytic uremic syndrome, are** rare**, serious** blood disorder**s** ~~where~~**that cause low levels of platelets and red blood cells and result in** 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~~**. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders, including fatal cases, have been reported in patients receiving MLN9708. If TMA is suspected, consider withdrawal of the suspected causative agent and manage** according to standard medical practice.

Fluid Deficit

Dehydration should be avoided since lenalidomide is substantially excreted by kidney, and 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 gastrointestinal toxicities and dehydration. Fluid deficit should be **promptly** corrected before initiation of study drug **and** as needed during treatment to avoid dehydration (see Section 6.8).

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with MLN9708. Blood pressure should be closely monitored **as per standard of care** 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 decreased appetite. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- 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.

Posterior Reversible Encephalopathy Syndrome

~~One case of p~~**P**osterior reversible encephalopathy syndrome (PRES)~~, which ultimately resolved,~~ has been reported with MLN9708. This condition is **usually transient and reversible. It is** characterized by headache, seizures, and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI) **or computed tomography (CT)**. 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

~~One case of t~~**T**ransverse myelitis has been reported with MLN9708. It is not known whether MLN9708 causes transverse myelitis; however, because it happened to a patient 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.

Rationale for Change:

To add information currently available around clinical events.

Change 9: Clarify the procedures for storage, handling, and accountability.

The primary change occurs in Section 6.15 Storage, Handling, and Accountability:

Added text:

On receipt at the investigative site, study drug should remain in the blister **pack** and carton provided until use or dispensation. All excursions that occur at the site storage or during transportation from depot to the site should **immediately** 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.

Study drug dispensed to the patient should remain in the blister packaging and carton until the point of use. Refer to the Pharmacy Manual or equivalent storage guidelines. **In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), sites may use alternative strategies to deliver study drug to patients (eg, via courier or site staff), per local standard practice and regulations and with prior approval from the investigator and the sponsor's project clinician/designee.** Comprehensive instructions should be provided to the patient in order to ensure compliance with**, and understanding of,** dosing procedures. Patients who are receiving take-home medication **ordinarily** should be given only 1 cycle of study drug at a time; more than 1 cycle of medication may be dispensed on a case-by-case basis for holidays, travel, or other circumstances upon discussion with the investigator and sponsor project clinician/designee. **(Note: patients in France are only permitted to receive 1 cycle of medication at a time).** Should more than 1 cycle of medication be dispensed, the investigator and/or health care provider must review the proper dosing instructions with the patient to avoid the potential for incorrect self-administration or overdose of medication.

Patients should be instructed to store the medication according to the storage conditions that are outlined in the Pharmacy Manual or equivalent storage guidelines. 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 study drug. **In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), drug packs and dosing diaries should be returned at the next available on-site clinic visit.** Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Rationale for Change:

To add clarification to this protocol.

Change 10: Add flexibility in study conduct in unavoidable circumstances (eg, the COVID-19 pandemic).

The primary change occurs in Section 7.4 Study Procedures:

Initial wording:	Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, End of Treatment (EOT), and Follow-Up (PFS and OS). As of Amendment 6, however, the primary endpoint has been met; as such, the PFS follow-up phase has been discontinued for patients currently receiving study therapy and for patients who discontinued therapy for reasons other than PD. As of Amendment 6, the follow-up period will solely be for OS follow-up.
Amended or new wording:	~~Patients will be evaluated at scheduled visits over 4 study periods: Screening, Treatment, End of Treatment (EOT), and Follow-Up (PFS and OS). As of Amendment 6, however, the primary endpoint has been met; as such, the PFS follow-up phase has been discontinued for patients currently receiving study therapy and for patients who discontinued therapy for reasons other than PD. As of Amendment 6, the follow-up period will solely be for OS follow-up.~~ **In acknowledgement of hospital, local, state or national government restrictions, or other site-related factors caused by unavoidable circumstances (eg, the COVID-19 pandemic) that may prevent investigators from conducting the study according to the Schedule of Events at the clinical study site, investigators may continue patients in the study despite departure from the Schedule of Events. Investigators are expected to evaluate the impact to the safety of the study participants and site personnel for patients to continue. In evaluating such requests, the investigator/study site staff will give the highest priority to the safety and welfare of the patients. Patients must be willing and able to continue taking study medication and remain compliant with the protocol. For patients that are impacted by these unavoidable circumstances, any procedures not conducted per the study protocol will be documented in the eCRF.** **Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having lab assessment performed at a facility closer to the patient's home, etc.) If a patient misses an in-person study visit, the investigator/study team staff will speak directly with the patient by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact with the patient, the study site physician or other qualified site staff should at minimum conduct AE collection and an assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Assessments/procedures that cannot be completed during the protocol-specified window because a site visit is done remotely (eg, complete physical**

	examination, symptom-directed physical examination, hematology, clinical chemistry, concomitant medications/procedures) are waived.

Rationale for Change:

To account for unavoidable circumstances affecting study conduct.

The following sections also contain this change:

- Schedule of Events, window for Study Procedures.
- Schedule of Events, footnote "e".

Change 11: Add language requiring all patients to reconsent.

The primary change occurs in Section 7.4.1 Informed Consent:

Added text:	**Patients remaining on study treatment will need to be reconsented. Reconsenting should be done in person. Remote reconsenting is permitted as long as the process adheres to site, IRB/IEC, and GCP standards and local regulations.**

Rationale for Change:

To clarify the need for reconsenting.

The following sections also contain this change:

- Schedule of Events, footnote "c".
- Section 11.6 Patient Information and Informed Consent.

Change 12: Clarify the definition of Completion of Treatment.

The primary change occurs in Section 7.7 Completion of Treatment:

Initial wording:	Patients will be considered to have completed study treatment if they receive study drug until disease progression or until discontinuation for unacceptable toxicity, withdrawal of consent, or death. An MPI/designee clinician will review the source data documenting disease progression prior to the investigator taking the patient off treatment or stopping disease assessments for PD. Refer to the Schedule of Events for End of Treatment visit assessments. As of Amendment 6, however, the primary endpoint has been met; as such, the PFS follow-up phase has been discontinued for patients currently receiving study therapy. All central and investigator assessments of response and progression for protocol purposes will be discontinued, such that there will no longer be an MPI/designee clinician review of the source data documenting disease progression.

Amended or new wording:	**Prior to implementation of Amendment 8, P**patients ~~will be~~**were** considered to have completed study treatment if they receive**d** study drug until disease progression or until discontinuation for unacceptable toxicity, withdrawal of consent, or death. An MPI/designee clinician ~~will~~ review**ed** the source data documenting disease progression prior to the investigator taking the patient off treatment or stopping disease assessments for PD~~. Refer to the Schedule of Events for End of Treatment visit assessments~~. As of Amendment 6, however, the primary endpoint has been met; as such, the PFS follow-up phase has been discontinued for patients currently receiving study therapy. All central and investigator assessments of response and progression for protocol purposes will be discontinued, such that there will no longer be an MPI/designee clinician review of the source data documenting disease progression. **Upon implementation of Amendment 8, only patients who are demonstrating clinical benefit and are unable to access a commercial supply of ixazomib and/or lenalidomide and dexamethasone will remain in the study, until such time as other means of accessing the study drugs are arranged. Completion of study treatment will occur when patients discontinue study drugs provided by the sponsor in this clinical trial setting, or when the patient experiences disease progression, unacceptable toxicity, withdrawal of consent, or death. The reason for treatment discontinuation must be recorded in the eCRF but no approval is required.** **Patients will attend an EOT visit 30 days (+1 week) after receiving their last dose of the study drug regimen unless next-line therapy is started before 30 days after the last dose of study drug, in which case the EOT visit should occur before the start of the next-line therapy. Refer to the Schedule of Events for End of Treatment visit assessments.**

Rationale for Change:

To clarify the definition of completion of treatment upon implementation of Amendment 8.

Change 13: Clarify the definition of Completion of Study.

The primary change occurs in Section 7.8 Completion of Study:

Initial wording:	Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study.
Amended or new wording:	~~Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study.~~ **Prior to implementation of Amendment 8, patients were considered to have completed the study if they were followed until death or until the sponsor terminated the study. Upon implementation of Amendment 8, patients will no longer be followed during any of the follow-up periods, as PFS and OS data are not being collected. Patients will be considered to have completed the study if they completed study treatment (see Section 7.7).**

Rationale for Change:

To clarify the definition of completion of study upon implementation of Amendment 8.

Change 14: Update the procedures for SAE reporting.

The primary change occurs in Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Added text:

The paper SAE forms must be submitted via fax (see fax numbers below) within 24 hours of awareness. In case of fax, site personnel must confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. E-mail submission of paper SAE forms with a PDF attachment should only be used in the case where fax is not possible within 24 hours of receiving the event. In case of e-mail, site personnel must confirm successful transmission by awaiting an acknowledgment of the receipt via e-mail within 1 business day. If SAEs are reported via fax or by e-mail, the EDC application must be updated as soon as possible with the appropriate information.

Rationale for Change:

To assist in timely submission of SAE reports.

Change 15: Add information about alternative monitoring approaches, such as remote source data verification, in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.

The primary change occurs in Section 11.4 Study Monitoring:

Added text:

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the IRB/IEC.

Rationale for Change:

To clarify remote source data verification procedures to account for unavoidable circumstances due to the COVID-19 pandemic.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	12-Jan-2021 16:07 UTC
	Clinical Science Approval	12-Jan-2021 16:24 UTC
	Medical Monitor Approval	12-Jan-2021 22:54 UTC