CLINICAL STUDY PROTOCOL

NCT Number: NCT01659658

Study Title: A Phase 3, Randomized, Controlled, Open-label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physician's Choice of Treatment Administered to Patients With Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

Study Number: C16011

Protocol Version and Date:

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CLINICAL STUDY PROTOCOL C16011 AMENDMENT 6

MLN9708

A Phase 3, Randomized, Controlled, Open-label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physician's Choice of Treatment Administered to Patients With Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

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Protocol Number:	C16011
Indication:	Amyloidosis
Phase:	3
Sponsor:	Millennium Pharmaceuticals, Inc
EudraCT Number:	2011-005468-10
Therapeutic Area:	Oncology

Protocol History	**Region**	**Date**
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Amendment 5	For use in France only	09 July 2015
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[redacted], PhD [redacted], Statistical and Quantitative Sciences (or designee)	Signature	*Date DD Month YYYY*

Confidentiality Statement

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Rationale for Amendment 6

This document describes the changes to the protocol incorporating Amendment 6. The primary rationale for this amendment is to modify the study assessments. The first interim analysis (IA) was conducted (data cut-off date 20 February 2019) and the primary endpoint of overall hematologic response rate (complete response [CR] + very good partial response [VGPR] + partial response [PR]) did not reach statistical significance. However, patients in both treatment arms appeared to receive benefit. In light of the primary endpoint not being met, the sponsor has decided to remove the planned second IA and final analysis (FA) and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients. Ixazomib (MLN9708) and control drugs (if Takeda has been supplying them) will continue to be provided for patients who continue to derive benefit.

Upon implementation of this amendment, data collection requirements will be limited to the following safety assessments: all serious adverse events (SAEs) (regardless of causality, including all deaths), any adverse event (AE) resulting in dose modification or discontinuation of any study drug, Grade ≥3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no longer required. All central laboratory and investigator assessments of response and progression for protocol purposes are discontinued—Adjudication Committee (AC) review of response data will no longer be performed. Patients will not be followed for the progression-free survival (PFS) or overall survival (OS) follow-up periods, as PFS and OS are no longer being collected. Quality of Life (QOL) and pharmacokinetic (PK) assessments will no longer be performed or recorded. Patients should otherwise be treated by the investigator according to standard of care. See the updated Schedule of Events—Amendment 6 and beyond for more detailed information.

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 15.18.

Purposes for Amendment 6

The purposes of this amendment are to:

1. Add primary study results from the first interim analysis (IA) and clarify details about subsequent analyses.
2. Clarify the study objectives as of Amendment 6.
3. Clarify the study endpoints as of Amendment 6.
4. Define the ongoing safety assessments as of Amendment 6.

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5. Discontinue all disease and efficacy response assessments, including central laboratory assessments of efficacy and safety, for protocol purposes because no further analyses will be performed.
6. Discontinue pharmacokinetic (PK) sampling for ongoing patients.
7. Discontinue Quality of Life (QOL) and Health Utilization assessments for ongoing patients.
8. Discontinue collection of concomitant medications and procedures.
9. Specify that no further Adjudication Committee (AC) reviews are needed as of Amendment 6.
10. Update the number of patients in the study.
11. Update the estimated study duration.
12. Discontinue the PFS and OS follow-up periods.
13. Clarify the exclusion criterion for patients diagnosed with or treated for another malignancy.
14. Define overdose.
15. Clarify the procedures for management of medication errors, including overdose.
16. Remove mention of the Safety Management Attachment (SMA).
17. Update the procedures for SAE reporting.
18. Specify that no further independent data monitoring committee reviews of safety and efficacy are needed as of Amendment 6.

For specific examples of changes in text and where the changes are located, see Section 15.18.

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PROTOCOL SUMMARY

Study Title: A Phase 3, Randomized, Controlled, Open-Label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physician's Choice of Treatment Administered to Patients With Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

Study Phase: 3

Number of Patients: Approximately 176 patients

Study Objectives

As of this amendment, the objectives are to provide continued access of MLN9708 and/or other study medications and to continue collecting relevant safety data to monitor patient safety. All other study objectives will no longer be assessed. However, the complete list of objectives is retained below for reference.

Primary Objectives

- To determine whether dexamethasone plus MLN9708 improves hematologic response (PR + VGPR + CR) versus a physician's choice of a chemotherapy regimen as selected from the list of offered treatment options in patients diagnosed with relapsed or refractory AL amyloidosis.
- To determine whether dexamethasone plus MLN9708 improves 2-year vital organ (that is, heart or kidney) deterioration and mortality rate versus a physician's choice of a chemotherapy regimen as selected from the list of offered treatment options in patients diagnosed with relapsed or refractory AL amyloidosis. Cardiac deterioration is defined as the need for hospitalization for heart failure. Kidney deterioration is defined as progression to end-stage renal disease (ESRD) with the need for maintenance dialysis or renal transplantation.

Key secondary objectives are:

- To determine overall survival (OS).
- To determine the complete hematologic response rate (CR).

Other secondary objectives are:

- To determine progression-free survival (PFS).
- To measure hematologic disease PFS.
- To determine best response in the vital organs allowed at study entry (heart and kidney).
- To determine time to vital organ deterioration or death.
- To measure vital organ PFS.
- To measure the duration of hematologic response (DOR).
- To evaluate safety.
- To measure time to treatment failure (TTF).
- To measure time to subsequent anticancer therapy.
- To describe the impact of treatment on quality of life (QOL) using the Medical Outcomes

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Study 36- item Short Form General Health Survey (SF-36 v2) (Section 15.3), FACT-neurotoxicity subscale (FACT/GOG-Ntx) (Section 15.4) and a symptom scale questionnaire (Section 15.5).

- To evaluate Health Utilization (HU) and to collect EuroQol 5-Dimensional (EQ-5D) (Section 15.9) data.
- To collect PK data to contribute to population PK analyses.

Overview of Study Design:

This is a phase 3, randomized, controlled, open-label, multicenter study of the oral formulation of dexamethasone plus MLN9708 compared with treatment chosen by the investigator from a prespecified list of regimens available in clinical practice. Treatment options will include: dexamethasone alone, dexamethasone plus an alkylating agent (melphalan or cyclophosphamide), or dexamethasone plus an immunomodulatory drug (IMiD, thalidomide or lenalidomide) in patients with relapsed or refractory AL amyloidosis. Crossover to the investigational treatment arm is not permitted during participation in this study.

Eligible patients must have: 1) biopsy-proven AL amyloidosis with relapsed or refractory disease despite 1 or 2 prior therapies; 2) disease requiring further treatment; 3) measureable disease as defined by serum differential free light chain concentration (dFLC); and 4) objective and measurable major organ involvement (ie, cardiac or renal) as defined by the standard International Society of Amyloidosis (ISA) criteria. Patients must not have been previously treated with proteasome inhibitors. (The sponsor reserves the right to open the trial to proteasome inhibitor-exposed patients in the future, at some time point after the first interim analysis [IA].)

Physicians will choose a treatment regimen from a list of options provided by the sponsor. Before randomization, physicians will declare which treatment regimen they plan to select for each screened patient; the selection will be recorded in the database. To maintain a balanced representation of the disease characteristics, patients enrolled in this study will be stratified by: 1) Cardiac Risk Stage: 1 versus 2 versus subgroup Cardiac Risk Stage 3 (ie, both NT-proBNP and troponin T over threshold [but NT-proBNP < 8000 pg/mL]); 2) relapsed versus refractory (relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy); and 3) proteasome inhibitor naïve versus exposed.

Eligible patients will be randomized in a 1:1 ratio into 1 of the 2 study arms:

Arm A: dexamethasone plus MLN9708

Arm B: physician's choice

In both treatment arms, each patient will continue to receive sequential cycles of therapy until disease progression, unacceptable toxicity, or until the study is terminated, whichever occurs first. Patients in Arm B receiving melphalan and dexamethasone will be treated to best response plus 2 additional cycles (see Section 6.4.2).

Response to therapy will be evaluated by an AC which will include the assessment of hematologic response and organ response according to the criteria outlined in the Revised Consensus Response Criteria of the ISA. The AC will also review specific data elements and corresponding data documentation to support criteria of vital organ (that is heart or kidney) deterioration. An independent data monitoring committee (IDMC) will review safety and efficacy data at the IAs.

Safety will be assessed through adverse events (AEs), clinical laboratory tests, and vital sign measurements. In addition, QOL and HU will be assessed using questionnaires.

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After disease progression, patients will be followed for survival, vital organ deterioration, and subsequent therapy at least every 12 weeks.

As of Amendment 6, however, the first IA has been conducted and the primary endpoint of overall hematologic response rate (CR + VGPR + PR) did not reach statistical significance. As such, the sponsor has decided to remove the planned second IA and final analysis and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients. Ixazomib (MLN9708) and control drugs (if Takeda has been supplying them) will continue to be provided for patients who continue to derive benefit.

Upon implementation of this amendment, data collection requirements will be limited to the following safety assessments: all SAEs (regardless of causality, including all deaths), any AE resulting in dose modification or discontinuation of any study drug, Grade ≥3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no longer required. Central laboratory and investigator assessments of response and progression for protocol purposes are discontinued—AC review of response data and IDMC review of efficacy and safety data will no longer be performed. Patients will not be followed for the PFS or OS follow-up periods, as PFS and OS are no longer being collected. Patients should otherwise be treated by the investigator according to standard of care.

Study Population:

Adult patients with biopsy-proven systemic AL amyloidosis with relapsed or refractory disease.

Duration of Study:

The duration of the study will be approximately 120 months (ie, 10 years), including 84 months of enrollment and 36 months of follow-up after the last patient is enrolled.

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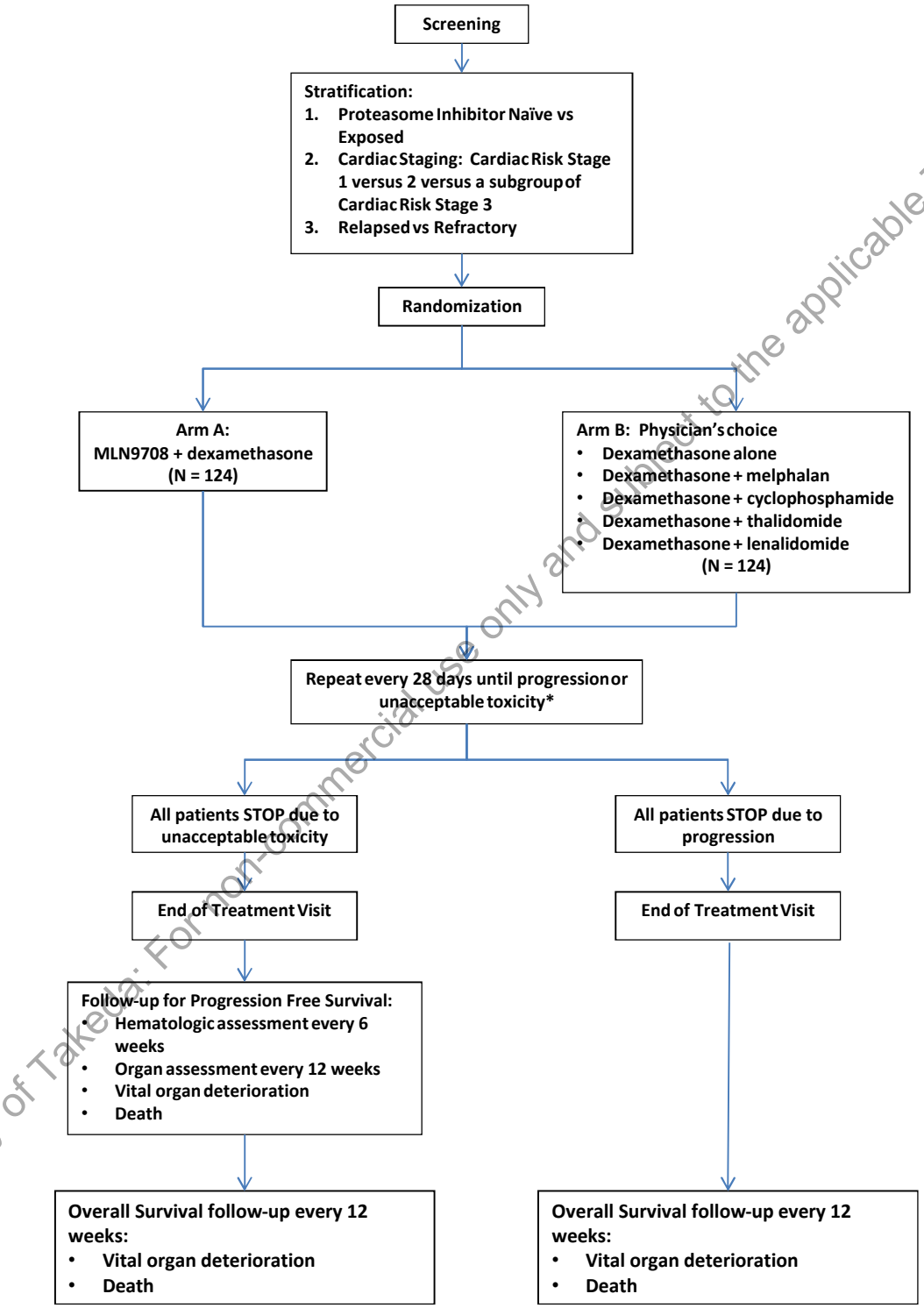
STUDY OVERVIEW DIAGRAM



* Refer to Section 6.4.2 for treatment duration guidelines for patients in the melphalan + dexamethasone group

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SCHEDULE OF EVENTS—AMENDMENT 6 AND BEYOND

As of Amendment 6, the first IA has been conducted and the primary endpoint of overall hematologic response rate (CR + VGPR + PR) did not reach statistical significance. As such, the sponsor has decided to remove the planned second IA and final analysis (FA) and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients. Ixazomib (MLN9708) and control drugs (if Takeda has been supplying them) will continue to be provided for patients who continue to derive benefit.

For ease of study conduct, the Schedule of Events now presented has been simplified to apply to the remainder of the study. Beyond the assessments noted here, patients should be treated by the investigator according to standard of care.

The full Schedule of Events prior to Amendment 6 has been moved to Section 15.11. The PK sampling schedule has been moved to Section 15.12, as PK sample collection is no longer applicable for ongoing patients.

Study Procedures	**Treatment Period 28-Day Cycles**	**End of Treatment[b]**
Cycle	**Cycle X[a] and Beyond**	
Day	**1**	
Window	**± 3 days**	**+ 10 days**
Complete Physical Examination		X[c]
Symptom-Directed Physical Exam	X[c]	
Pregnancy Test[d]	X	X
Hematology	X[e]	X[e]
Clinical Chemistry	X[e]	X[e]

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Study Procedures	**Treatment Period 28-Day Cycles**	**End of Treatment[b]**
Cycle	**Cycle X[a] and Beyond**	
Day	**1**	
Window	**± 3 days**	**+ 10 days**
Adverse Event Reporting	Recorded from the first dose of study drug through 30 days after last dose of study drug. Only AEs leading to dose modification or discontinuation, Grade ≥3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors are to be reported upon implementation of Amendment 6 through 30 days after the last dose of study drug.	
Serious Adverse Event Reporting	Serious AEs will be reported from signing of the informed consent form through 30 days after the last dose of study drug.	
Study Drug Administration		
MLN9708	MLN9708 on Days 1, 8, and 15	
Dexamethasone	Dexamethasone on Days 1, 8, 15, and 22	
Dexamethasone and Melphalan	Days 1-4	
Dexamethasone and Cyclophosphamide	Cyclophosphamide Days 1, 8, and 15 and dexamethasone Days 1, 8, 15, and 22	
Dexamethasone and Thalidomide	Thalidomide daily and dexamethasone Days 1, 8, 15, and 22	
Dexamethasone and Lenalidomide	Lenalidomide Days 1-21 and dexamethasone Days 1, 8, 15, and 22	

AE=adverse event; eCRF=electronic case report form; IMiDs=immunomodulatory drugs.

a Follow this Schedule of Events at the start of the next full treatment cycle upon implementation of Amendment 6.

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 Collect and record in the electronic case report form (eCRF) only in the event that they are needed to evaluate an AE. Otherwise, patients should be treated according to standard of care.

d Treatment with immunomodulatory drugs (IMiDs) requires pregnancy testing in female patients of child-bearing age prior to each cycle. A serum pregnancy test will be performed for all women of childbearing potential.

e All central laboratory assessments are discontinued. Local hematology and chemistry panels to be collected and recorded in the eCRF only in the event that they are needed to evaluate an AE. Otherwise, patients should be treated according to standard of care and laboratory assessments to inform dosing decisions do not need to be recorded in the eCRF.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AC	Adjudication Committee
AE	adverse event
ACE	Angiotensin converting enzyme (ACE)
AL amyloidosis	primary systemic light chain amyloidosis
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}24hr}$	area under the plasma concentration versus time curve zero to 24 hours
$AUC_{0\text{-}tau}$	area under the plasma concentration versus time curve zero to next dose
AV	atrioventricular
BIW	biweekly (ie, twice weekly)
BP	bodily pain
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CDF	cumulative distribution function
CHF	congestive heart failure
CI	confidence interval
CL	clearance, IV dosing
CL_b	blood clearance
CL_P	plasma clearance
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CYP	cytochrome P_{450}
DDI	drug-drug interaction
dFLC	serum differential free light chain concentration; difference between amyloid forming and non amyloid forming FLC
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
eGFR	estimated glomerular filtration rate; eGFR according to the recently recommended CKD-EPI equation
E_{max}	maximum effect
EMG	electromyography
EDC	electronic data capture

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Abbreviation	Term
eGRF	estimated glomerular filtration rate
EOT	End of Treatment (visit)
ESRD	end-stage renal disease
EQ-5D	EuroQol 5-Dimensional (questionnaire)
F	bioavailability
FA	final analysis
FISH	fluorescent in situ hybridization
FLC	free light chain
GADD34	Growth Arrest DNA Damage 34
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GH	general health
GI	gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
hERG	human ether-à-go-go related gene
HDT-SCT	high-dose therapy- stem cell transplantation
HIV	human immunodeficiency virus
HU	Health Utilization
MLN9708 IB	Investigator's Brochure
IA	interim analysis
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IEM	immunogold electron microscopy
IHC	immunohistochemistry
IMiDs	immunomodulatory drugs
IRB	institutional review board
ISA	International Society of Amyloidosis
ITT	intent-to-treat (population)
IV	intravenous; intravenously
K_i	inhibition constant
K-M	Kaplan-Meier
LVEF	left ventricular ejection fraction
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MPD	maximum planned dose
MR	minimal response

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Abbreviation	Term
MRI	magnetic resonance imaging
msec	millisecond
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
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal proBNP
NYHA	New York Heart Association
OS	overall survival
PCS	physical component summary
PD	progressive disease (disease progression)
PF	physical function
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PN	peripheral neuropathy
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
RRMM	relapsed and refractory multiple myeloma
QALYs	quality adjusted life years
QD	*quaque die*; each day; once daily
QLQ	Quality of Life Questionnaire
QLQ-C30	EORTC Core Quality of Life Questionnaire
QOL	quality of life
QTc	rate-corrected QT interval (millisecond) of electrocardiograph
Q3C	every 3 cycles
RBC	red blood cell
RE	role emotional
RP	role physical
RP2D	recommended phase 2 dose
RRAL	relapsed or refractory AL amyloidosis
SAE	serious adverse event
SCT	stem cell transplant
SF	social function
SMA	Safety Management Attachment
SPEP	serum protein electrophoresis
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event ; may or may not be treatment related
TE_{max}	time of occurrence of E_{max}

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Abbreviation	Term
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
TTF	time to treatment failure
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis
US	United States
VT	vitality
VGPR	very good partial response
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization

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1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Primary systemic light chain (AL) amyloidosis is a rare, progressive, lethal disease caused by proteotoxic light chain proteins produced by a small clonal plasma cell.[1, 2, 3] This plasma cell dyscrasia is characterized by monoclonal plasma cells in the bone marrow and their production of excess errant monoclonal immunoglobulin light-chains that tend to misfold, form aggregates, and deposit as amyloid fibrils in visceral organs. Tissue damage is caused when these toxic amyloid light chains interact with cells and when they accumulate in organs causing end-organ dysfunction.[4] Murray, et al demonstrated that the monoclonal protein secreted by these neoplastic plasma cells is the pathogenetic protein causing the amyloid deposits.[5] While the disease is a clonal plasma cell disease similar to multiple myeloma (MM), the clonal plasma cells are present at a low percentage in the bone marrow, the paraprotein is often not an intact immunoglobulin, but rather a free light chain, or fragment thereof, which is predominantly of the λ isotype rather than the κ (κ-to-λ ratio is 1:4).[1, 6, 7] Further, unlike multiple myeloma, the clinical picture and prognosis for patients with AL amyloidosis is determined by the organ dysfunction caused by the toxic amyloidogenic light chains. Hence, hematologic response is fundamentally linked to organ response and survival, unlike multiple myeloma.[8] Thus, if the plasma cell clone is not first substantially suppressed thereby abolishing the production of circulating amyloidogenic free light chains (FLC), important clinical outcomes such as improved organ function and survival are not possible.[9]

Early diagnosis and treatment of AL amyloidosis are key to patient outcomes. Unfortunately, late diagnosis remains a major problem. Accumulation of extracellular amyloid fibril deposits disrupts normal tissue structure and function notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues.[1] This progressive accumulation leads to organ dysfunction, organ failure, and ultimately death, often due to cardiac causes. The disease carries a grim prognosis which is predominantly influenced by the patient's performance status and extent of organ involvement, particularly cardiac involvement, at diagnosis. One-fourth of patients present with clinical involvement of 1 organ; however, the majority present with clinical involvement of more than 1 organ.[1, 10] Renal dysfunction is the most common clinical manifestation, while liver involvement is reported but is less common. The severity of the cardiac involvement dictates the prognosis.

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Notably, the majority of patients with AL amyloidosis die from cardiac complications, which is often sudden death.[11]

The incidence of systemic AL amyloidosis has been estimated globally at 8.9 to 10 patients per million per year an incidence similar to Hodgkin lymphoma or chronic myelogenous leukemia).[2, 12] It is about one-fifth as common as multiple myeloma; however, median survival time is shorter (47 months for multiple myeloma, but ranging from 4.6 months-36.8 months depending on cardiac involvement).[13, 14, 15] Further, patients with hematologic refractory disease have a poor survival, approximately 14 months, while those that have relapsed after previous hematologic response have an overall survival of approximately 32 months (personal communication, Prof. [redacted] and Dr. [redacted], July 7, 2011). Overall, the natural history of AL amyloidosis includes progression to death within 2 years from diagnosis in about 80% of patients.[10]

The diagnosis of a systemic, as opposed to localized, amyloidosis relies on the identification of amyloid deposits in tissues, eg, abdominal adipose aspiration, salivary glands, and organ biopsy.[16] Current practice involves Congo red staining of these tissues where a characteristic apple-green birefringence of the amyloid fibrils is seen under polarized light. Once amyloidosis has been confirmed, amyloid typing is necessary to distinguish clinically between different types of amyloidosis for prognosis, clinical management, and necessitates adequate techniques. Combination methods such as Congo red staining plus immunoelectron microscopy, immunofluorescence, immunoperoxidase, immunohistochemistry, proteomic mass spectrometry-based methods, and genetic testing play a major role in tissue typing.[17] The importance of these techniques is to enable differentiation of the various types of systemic amyloidosis, to identify specific mutation associated with hereditary forms,[16] and to confirm the diagnosis of AL amyloidosis in certain instances (Section 15.1) The correct identification of the underlying amyloid precursor protein is critical as different therapies exist for different types of amyloid. Amyloidosis of the light chain derivation is the only type that is responsive to cytotoxic chemotherapy.[18, 19, 20, 21] Given the rarity of systemic AL amyloidosis, diagnostic tests and response criteria have historically been based on multiple myeloma. However, recent technical advances have now enabled the establishment of diagnostic and response criteria specifically relevant to AL amyloidosis. The characterization of amyloidosis as light chain type requires the demonstration of the underlying plasma cell clone which produces the amyloidogenic immunoglobulin light chain. Serum free light chain (FLC) assay in combination with serum and urine protein electrophoresis, immunofixation,

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immunoglobulin quantification, and bone marrow examination are required tests.[20] Once the diagnosis of AL amyloidosis has been established, prompt initiation of treatment is required to eliminate the malignant clone and to reduce the supply of the amyloidogenic free light chains.

The assessment of disease and response to therapy in AL amyloidosis is more complex than in multiple myeloma. In AL amyloidosis, the disease involves both the persistence of the clonal plasma cell and its production of the amyloid-forming FLC that directly causes fibrillar aggregation, toxic damage, and organ failure. Hence, hematologic response is fundamentally linked to organ response and survival unlike multiple myeloma. However historically, hematologic response was defined using the same tests and criteria for reduction of bone marrow plasma cells and monoclonal proteins developed for multiple myeloma. Assessments of response to therapy in AL amyloidosis must reliably determine objective changes in the clonal hematologic disorder and in organ disease while acknowledging that organ responses can lag up to 12 months behind hematologic response.[8] The serum FLC assay, a test that can quantify serum amyloidogenic FLC, is a recent advance that has significantly changed how patients with AL amyloidosis are diagnosed and monitored during therapy given its documented sensitivity and prognostic utility.[22, 23, 24, 25, 26, 27, 28] This assay is critical in this disease because, different than MM, patients with AL amyloidosis typically have modest plasma cell infiltrates in the bone marrow and small or no circulating intact immunoglobulin thus making accurate quantification of monoclonal protein with the typical assays from serum, urine, and bone marrow difficult and not useful for response evaluations.[9] Since 2003, a growing number of clinical trials have reported that reducing the concentration of serum amyloidogenic FLC results in prolonged survival, thereby increasing the importance of the FLC evaluations.[26, 29, 30, 31, 32, 33]

In 2010, the International Society of Amyloidosis (ISA) Panel, noting recent technical advances and the clinical observations that FLC responses correlated with survival better than traditional monoclonal protein responses, convened to develop better response criteria for the management of this complex disease.[34] The panel aimed to identify criteria of hematologic response that would make a distinction in survival outcomes. The absolute concentration of FLC, the difference between involved (that is, clonal amyloidogenic) and uninvolved FLC, and the currently used monoclonal protein response criteria established by the 2005 ISA Consensus were evaluated. The Consensus Panel demonstrated that hematologic response criteria based on FLC correlated better with survival than did the monoclonal protein criteria of the 2005 Consensus Panel, underscoring the importance of

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measuring the amyloidogenic precursor protein which is responsible for organ damage.[34] The panel also showed that in AL amyloidosis, the preferred method of quantifying changes in amyloidogenic FLC concentrations is to estimate the difference between involved and uninvolved immunologlobulin light chains. This is accomplished by subtracting the uninvolved light chain from that of the involved light chain to obtain the FLC difference, known as dFLC. The dFLC is preferred over absolute FLC concentration or even involved FLC (iFLC) concentration because dFLC compensates for altered FLC metabolism in patients with renal failure.[34, 35] The value of the FLC component estimated as the dFLC has now been established and validated.[32, 36]

According to the ISA 2010 criteria, a 50% decrease in dFLC is considered a partial response (PR), a reduction in the absolute dFLC to less than 40 mg/L is a very good partial response (VGPR), and normal FLC levels with a normal kappa/lambda ratio and negative serum and urine immunofixation for the clonal FLC is an amyloid complete response [aCR].[19, 34] Data now also supports that achievement of at least a 50% reduction in the serum amyloidogenic free light chain is often sufficient to lead to stabilization or regression of amyloid deposits in the organs with potential for improved organ function, improvements in performance status, the ability to carry out activities of daily living, the ability to return to work, improved QOL, and survival.[29, 37]

The 2010 ISA Consensus Panel also gave consideration to, validated, and updated definitions for organ involvement as well as response based upon recent technologic advances since the establishment of the first criteria in 2005.[20, 38] Cardiac response was updated to include NT-proBNP and cardiac troponins, which are validated, accessible and reproducible cardiac biomarkers, diagnostic tools of cardiac failure, and prognostic factors in congestive heart failure (CHF), which are predictors of survival in AL amyloidosis.[34, 39, 40, 41] Additionally, an adequate decrease (defined as > 50%) in serum FLC can translate into a parallel decrease in the cardiac biomarker, NT-proBNP, and cardiac function and symptoms of heart failure can improve despite the amount of cardiac amyloid deposits remaining relatively unaltered by other measures such as echocardiograms.[26, 41] Hence, ventricular wall thickness and left ventricular ejection fraction measured by echocardiogram as in the 2005 Consensus Opinion response criteria are not useful for response assessments.[39] The Consensus Panel therefore determined that validated cardiac biomarker measurements are important in the overall monitoring of patients receiving treatment for AL amyloidosis and added them into the response criteria. Renal response continued to focus on urinary protein excretion with consideration given to the patient's estimated glomerular

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filtration rate (eGFR) (Section 15.2). Criteria for hepatic disease were not changed. The Consensus Panel did not change criteria for peripheral and autonomic nervous system involvement given the lack of reliable, widely available methodologies.[38]

1.1.2 Treatment Approaches

The goal of chemotherapy in AL amyloidosis is the prompt elimination of the plasma cells that produce the toxic light chain proteins that have an affinity for visceral organs, extension of survival, minimization of treatment toxicity, and support of end organ function.[19, 22, 34, 39, 42, 43] Treatment choices in AL amyloidosis have utilized advances made in the chemotherapy of MM and thus involve intensive regimens such stem cell transplant and various nonintensive chemotherapy regimens, including corticosteroids, alkylating agents, immunomodulatory drugs (IMiDs), and proteasome inhibitors. However, unlike MM in which survival is determined by the plasma cell tumor mass, in AL amyloidosis, hematologic response based on FLC is of key importance with concomitant achievement of organ improvement, which lags significantly behind hematologic response, so unfortunately some patients may not survive long enough to enjoy this clinical benefit.[2, 44] Moreover, there is a desperate need for alternative treatments for the significant proportion of patients not eligible for dose-intensive therapy, for those who decline dose-intensive therapy given its morbidity, or for those who have progressive disease (PD) despite such therapy. Furthermore, disease can recur or progress even after a response has been achieved, thereby necessitating subsequent effective therapies. When the patient's disease relapses or does not respond to therapy, there is no standard therapy, and data are limited even for those agents used in this setting. Given the rarity of AL amyloidosis, there have not been any randomized controlled trials in the relapsed disease setting, but rather there have been anecdotal case reports, retrospective series, and small, single-institution trials utilizing various single-agent or combination therapy regimens shown active in MM. The National Comprehensive Cancer Network (NCCN) therefore recommends treatment in a clinical trial because data are insufficient to identify an optimal treatment.[4] Treatment choices are thus based on the patient's age, organ dysfunction, pace of disease, and regimen toxicities.[19]

Nonintensive Therapies

Intensive therapy such as high-dose therapy- stem cell transplantation (HDT-SCT) may be a preferable treatment option; however, only a quarter of newly diagnosed patients are eligible for this therapeutic option.[39, 45]

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Melphalan- dexamethasone was compared to HDT-SCT in a randomized trial of 100 patients. After a median follow up of 3 years, there was no significant difference in response rates and the median overall survival was better for patients treated with melphalan-dexamethasone than with HDT-SCT (56.9 months versus 22.2 months respectively).[46] The response rate and its durability were similar in this study to others reported in the literature; [47] however, these authors reported that the HDT-SCT group had a lower than expected outcome because of a high mortality rate and possible differences in patient selection compared with other trials. Lastly they hypothesized that a trial of these 2 treatments in a tertiary referral center where the treatment-related mortality rate would likely be lower, might have a different outcome.[46] Even so, the use of melphalan and dexamethasone appears at least comparable to HDT-SCT and is considered a standard frontline treatment option.[46]

There is no consensus on the optimal regimen for patients whose disease has relapsed or did not respond to therapy. The choice of treatment depends on a balance between the perceived efficacy of the chosen regimen and the individual patient's expected ability to tolerate the treatment's toxicity considering their age, organ dysfunction, and pace of disease. Given the limited treatment options, the treatment chosen may mean exposure to an agent from the same drug class or the use of an agent used previously. As noted, clinical trial data are limited in patients previously treated and even the available data are from trials that include both previously untreated and treated patients.

Conventional Agents: Alkylating Agents and Corticosteroids

Corticosteroids

Dexamethasone is a versatile agent in the treatment of plasma cell dyscrasias. Experience in MM using dexamethasone (dex) to reduce the plasma cell tumor burden led to the use of this drug, both as a single agent and in combination with melphalan, in the treatment of AL amyloidosis. A Southwest Oncology Group (SWOG) phase 2 trial reported hematologic response rates of 53%, an organ response rate of 45%, and median survival of 31 months with single-agent pulse high-dose dexamethasone (40 mg/day on Days 1-4, 9-12, and 17-20 every 35 days for 3 cycles) followed by dexamethasone plus alpha interferon maintenance.[48] Though tolerated well in MM and despite the reported AL amyloidosis disease benefit, a 7% treatment-related mortality and Grade 3 or greater toxicities, including cardiovascular/fluid overload, hematologic, gastrointestinal, renal and infection AEs, necessitate dose reductions during the initiation of therapy. Consequently, Palladini and

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colleagues investigated a modified high-dose dexamethasone regimen (40 mg/day on Days 1-4 every 21 days) in patients both treatment naïve and previously treated. This regimen was active with a 35% hematologic response rate, a median survival of 20.6 months, and no significant toxicity.[49] The authors concluded this modified regimen was an important treatment option as it could serve as a bridge for patients who do not tolerate intensive dexamethasone regimens or those who might benefit from combination therapy. Recently, based on the results of low-dose dexamethasone (40 mg weekly on Days 1, 8, and 15 every 28 days) in MM, this dose and schedule is being incorporated into AL amyloidosis treatment combinations.[50]

Corticosteroids Plus Alkylating Agents

Subsequent phase 2 data have confirmed the activity of dexamethasone and melphalan, which is considered standard therapy for patients who have not undergone HDT-SCT. In 46 patients with newly diagnosed AL amyloidosis, the combination (dexamethasone 40 mg/day plus melphalan 0.22 mg/kg each on Days 1-4 every 28 days) demonstrated a 67% hematologic response rate, 33% complete responses, a 48% organ response rate, and an actuarial survival at 6 years of approximately 50%. Severe adverse events consisting of respiratory infections, reversible cytopenia, and 1 case of myelodysplastic syndrome were reported in 11% of patients.[47, 51] Additionally, this trial demonstrated that in relapsing patients, the amyloid clone remains sensitive to the combination of melphalan and dexamethasone and hematologic response can still be achieved by repeating treatment. Thus, this combination represents an important option in the treatment of patients with AL amyloidosis.[51] The melphalan-dexamethasone combination was also reported based on a retrospective review of 70 patients not eligible for HDT-SCT where the hematologic response rate was 38%, complete response was 13%, and the median overall survival had not been reached. Though 2 different dexamethasone schedules (4-day pulse[49] and low-dose weekly[50]) were used in the treatment of these patients, no difference in hematologic response was observed. The authors noted that the difference in CR rate in this trial compared to others in the literature may be related to a difference in CR criteria, selection bias, referral bias, or other differences between the patients treated.[52] Further, the authors acknowledged that 27% of patients who did not achieve a partial response or less received additional therapy, including HDT-SCT in 3 patients, which led to an improvement in survival.[52] A retrospective review of 428 patients with AL amyloidosis treated in 3 major European centers reported outcomes including 204 patients treated with melphalan and dexamethasone.[51] The overall hematologic response rate was 44% with 26% and 23%

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achieving complete responses and organ response, respectively, again demonstrating the benefit of this combination.[51] Dexamethasone has also been combined with cyclophosphamide in the treatment of AL amyloidosis. Investigators from the United Kingdom (UK) report 2 series looking at cyclophosphamide in combination with dexamethasone and thalidomide. The hematologic response rate ranged from 63% to 74%, the complete response rate was approximately 22%, and the organ response rate ranged from 25% to 38%.[51, 53] One of the series reported a median overall survival of 41 months.[51] This combination appears to have similar efficacy, similar toxicity while being non-stem cell toxic, and without necessary dose adjustments in renal failure as compared with melphalan and dexamethasone. These data suggests that alkylating agents plus dexamethasone are active as upfront therapy and importantly in relapsing patients given that AL amyloidosis is an incurable disease.[51, 54]

Novel Agents: Immunomodulatory Agents and Proteasome Inhibitors

Immunomodulatory Agents (IMiD)

Though the exact mechanism of action remains unclear, the immunomodulatory agents thalidomide and lenalidomide were introduced into the therapeutic landscape in MM and as a result were incorporated into investigator-initiated clinical trials given the anticipated activity in patients with advanced AL amyloidosis. The first IMiD to be investigated in relapsed AL amyloidosis was thalidomide. The activity of thalidomide with or without dexamethasone has been reported by several investigators.[9, 53, 55, 56] In combination with dexamethasone, hematologic responses are reported in the range of 48% to 80% with approximately a 19% rate of organ response;[53, 57] however, toxicity at high doses is problematic with 50% of patients experiencing Grade 3 to 4 toxicity, specifically fatigue, sedation, fluid retention, constipation, orthostasis, peripheral neuropathy (PN), and worsening renal function.[9, 19, 53] In these trials, the median maximum tolerated dose of thalidomide was 300 mg/day. A risk-adapted dosing approach (thalidomide 100 mg/day increased to 200 mg/day after 4 weeks if tolerated or an even lower starting dose [50 mg/day] and slower escalation [50 mg/day every 4 weeks to a total dose of 200 mg/day] in elderly patients) plus dexamethasone and cyclophosphamide has been reported as active and well tolerated.[58] Hematologic responses were seen in 74% of patients with a median survival of 41 months.[58] The activity of thalidomide and dexamethasone in patients refractory to frontline melphalan and dexamethasone was reported by Jaccard, et al.[57] In this small retrospective review, hematologic responses were obtained in 4/5 patients treated with thalidomide plus sequential dexamethasone.[57] Overall, the combination of

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thalidomide and dexamethasone is an active option for patients with relapsed or refractory AL amyloidosis; however, reduced doses and careful monitoring for toxicity are required.[22]

Like thalidomide, data with full-dose lenalidomide demonstrate significant toxicity, but it is better tolerated at a dose of 15 mg/day for 21 days in a 28-day cycle. Rash, fatigue, myelosuppression (neutropenia and thrombocytopenia), and, to a lesser extent, thromboembolic complications were mainly reported.[43, 59, 60] Hematologic response rates of 40% to 60% and a median survival ranging from 2 to 3 years have been achieved.[22, 38, 39, 43, 61, 62] Single-agent lenalidomide provides limited activity, but response is improved when given in combination with dexamethasone.[60] Sanchorawala and colleagues reported a 16% complete response rate of which 60% were durable for a median of 24 months in 69 patients (most were previously treated) who were treated with lenalidomide and dexamethasone.[63] The effectiveness of lenalidomide and dexamethasone in patients refractory to frontline melphalan and dexamethasone was reported by Jaccard and colleagues.[57] In this small retrospective review, hematologic responses were obtained in 2/7 patients treated with the combination of lenalidomide and dexamethasone.[57] Taken together, the data support the combination of lenalidomide and dexamethasone as a treatment option for patients with relapsed or refractory AL amyloidosis.

Proteasome Inhibitors

The proteasome inhibitor was validated as an oncology target following the clinical success of VELCADE® (bortezomib) for Injection, the first-in-class, boronic acid-based proteasome inhibitor that is approved in the United States (US) by the Food and Drug Administration (FDA) for the treatment of patients with MM and mantle cell lymphoma (MCL). Biological and clinical data suggest that proteasome inhibition is an attractive treatment approach for patients with AL amyloidosis.

The biological rationale for the use of proteasome inhibitors stems from the clonal plasma cell and their secretion of a toxic light chain protein characteristic of this disease. Normal plasma cells and MM cells have both been proposed to be especially sensitive to proteasome inhibition due to their extremely high proteasome workload of misfolded and newly synthesized light chain proteins.[64, 65, 66, 67, 68, 69, 70] Under conditions of proteasome inhibition, even higher levels of proteins accumulate in the cells, placing great stress on the endoplasmic reticulum (ER), resulting in a terminal unfolded protein response (UPR) and cell death.[66, 67, 71, 72, 73] The additional stress imposed on the ER system makes plasma cells hypersensitive to proteasome inhibition. This same mechanism of cell death is expected to

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apply to the errant plasma cells in AL amyloidosis. In addition, evidence suggest that extracellular oligomers of amyloidogenic light-chains could inhibit proteasome activity, sensitizing amyloidogenic plasma cells in a sort of autocrine-inhibitory loop, thus creating a particularly compelling biological rationale for the research and development of proteasome inhibitors in this disease.[64, 68]

Pengo, et al[69, 74] have reported that differentiating plasma cells suffer from proteotoxicity with decreased proteasome capacity even with increased protein synthesis. This imbalance of the ubiquitin proteasome system results in the accumulation of ubiquitin-conjugates and apoptotic sensitization to proteasome inhibitors.[69, 74] Amyloidosis is a protein misfolding disease and as such may be particularly sensitive to proteasome inhibition.

Clinical rationale is based on small case studies and prospective trials of VELCADE with or without dexamethasone in relapsed and/or refractory AL amyloidosis. Most of the patients enrolled in these studies had failed previous therapies or were ineligible for SCT. Treatment with VELCADE with or without dexamethasone was characterized by rapid response and high rates of hematologic and organ responses.[75, 76] Data across these small trials demonstrate hematologic response rates in the range of 60% to 90% with an organ response rate of approximately 25%.[75, 77, 78] Although treatment-related mortality was uncommon in these studies, discontinuation of VELCADE due to adverse events was common. Peripheral neurotoxicity, fatigue, nausea, vomiting, diarrhea, constipation, edema, and hypotension were reported and, at times, necessitated dose modification or discontinuation of therapy. The effectiveness of VELCADE and dexamethasone in patients who are refractory to frontline melphalan and dexamethasone was reported by Jaccard and colleagues.[57] In this small retrospective review, hematologic responses were obtained in 17/20 patients treated with bortezomib-dexamethasone.[57]

Reece and colleagues reported on the first prospective study of single-agent VELCADE in relapsed amyloidosis.[79, 80] The primary objective of this phase 1/2 study was to determine the maximum tolerated dose (MTD) and evaluate safety. The determination of the hematologic response rate and duration of response at the MTD was a secondary objective, while assessment of organ response and overall survival were exploratory objectives. In the phase 1 portion of the study, VELCADE was generally well tolerated at doses of up to 1.6 mg/m^2 on a weekly schedule and 1.3 mg/m^2 on a twice-weekly schedule. The MTD was not reached with either dosing schedule therefore the maximum planned dose (MPD) was evaluated in the phase 2 portion of the study. A total of 70 patients were enrolled in this study, 18 at 1.6 mg/m^2 weekly, 34 at 1.3 mg/m^2 twice weekly, and 18 at lower doses during

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dose-escalation. Best hematologic response (CR/PR) rates were 68.8% and 66.7%, respectively, for the weekly and twice-weekly dosing schedules with 78% overall of responders with a durable (> 1 year) response. Responses were more rapid with the twice-weekly dosing schedule, but toxicity appeared lower with the weekly schedule. The most common adverse events were fatigue, thrombocytopenia, vomiting, diarrhea, pneumonia, and syncope. Together the biologic and clinical data support the use of a proteasome inhibitor in the treatment of AL amyloidosis.

Currently, no satisfactory therapy exists for patients with AL amyloidosis that has progressed despite previous chemotherapy including stem cell transplant. Amyloidosis is a protein misfolding disease and therefore may be particularly sensitive to proteasome inhibition. The retrospective review from 3 European centers provides the largest comparative review of treatment regimens in the literature.[51, 81] Between 2003 and 2010, 428 patients with AL amyloidosis were treated with melphalan-dexamethasone, cyclophosphamide-thalidomide-dexamethasone, cyclophosphamide-lenalidomide-dexamethasone, bortezomib-dexamethasone with or without an alkylating agent, or HD-SCT. The outcome of patients was comparable supporting the rationale for phase 3 trials confirming the benefits of proteasome inhibition as compared to other regimens for the frontline treatment of patients with AL amyloidosis. Two such trials are being conducted investigating the combination of melphalan plus dexamethasone, with or without bortezomib; 1 each in Europe (EMN-03/ NCT01277016) and the US (ECOG E4A08/ NCT01078454). Therefore, the intention of this study in patients with hematologic relapsed or refractory disease is to compare a proteasome inhibitor (MLN9708) to other classes of agents that are currently used in clinical practice.

1.1.3 MLN9708, A Next-Generation Proteasome Inhibitor

Like VELCADE, MLN9708 is a modified peptide boronic acid analog. The drug substance MLN9708 refers to the citrate ester of MLN2238. MLN2238 refers to the biologically active, boronic acid form of the drug substance, MLN9708. In water or aqueous environments, the equilibrium shifts from MLN9708 to the biologically active boronic acid form, MLN2238. All doses and concentrations are expressed as the boronic acid, MLN2238. MLN9708 is the first oral proteasome inhibitor undergoing clinical investigation in humans with safety, tolerability, PK, pharmacodynamics, and disease response assessed in each study.

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As Millennium's next-generation proteasome inhibitor, MLN9708 was designed to build upon the attributes of VELCADE while also providing an option for oral administration and increased activity in tumor types where VELCADE has shown activity, and improving the safety profile (refer to the MLN9708 Investigator's Brochure). Given the similarities between these 2 proteasome inhibitors, it is anticipated that MLN9708, which is directed against the same components of the ubiquitin-proteasome pathway (UPP) as VELCADE, will also prove useful in the treatment of AL amyloidosis.

1.2 Nonclinical 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.

In summary, the single- and repeat- dose studies of up to 5 cycles in duration in rats and dogs, using both the oral (PO) and intravenous (IV) routes of administration have been completed. Compromise of the gastrointestinal (GI) systems led to dose-limiting toxicity in both rats and dogs. At tolerated doses, alterations in leukocyte and coagulation parameters consistent with an inflammatory response were seen in both rats and dogs.

The principal toxicologic effects of MLN2238 administration to rats in 2- and 5-cycle PO (each cycle consisted of twice-weekly dosing for 2 weeks; cycles were separated by a 10-day nondosing period) and 2-cycle IV toxicology studies (following the same cycle

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schedule) include inhibition of erythropoiesis, decreased thrombocyte counts, leukocyte and coagulation profile changes consistent with an inflammatory response, intestinal mucosal inflammation, as well as lymphoid depletion of lymph nodes and other lymphoid organs. Differences of note with IV administration included a trend toward decreased leukocyte counts with corresponding bone marrow hypocellularity.

The IV administration of MLN9708 to beagles for a total of 5 cycles (each cycle consisted of twice weekly dosing for 2 weeks separated by a 10-day nondosing observation period) resulted in hematology parameters; neuronal degeneration of the sympathetic, dorsal root, and end organ ganglia with secondary axonal/nerve fiber degeneration of the peripheral nerves and ascending tracts in the spinal cord and medulla oblongata. Similar neurodegenerative changes were also observed in oral studies in dogs of 2 or 5 cycle duration, and in the 2-cycle rat IV study. The neurologic lesions in these studies are similar to what has been described after treatment with bortezomib and are believed to be the cause of the PN observed in patients treated with bortezomib. All of the effects seen in PO toxicology studies in both rats and dogs at tolerated doses were shown to resolve or were trending toward resolution after a 14-day nondosing recovery period. Recovery was not assessed in the 5-cycle IV study in dogs. All findings are expected to be monitorable with routine clinical, clinical pathology, and/or neurologic assessments.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN9708 may be found in the MLN9708 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 phase 1 and phase 1/ 2 study. As of 30 April 2012, 382 patients have been treated with MLN9708 across 9 enrolling sponsor-led phase 1 or phase 1/2 studies with a twice-weekly and a weekly dosing schedule being evaluated. MLN9708 is available as an intravenous and oral formulation. 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. To date, the development of oral MLN9708 has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a different yet related plasma cell dyscrasia, systemic light chain (AL) amyloidosis. A clinical pharmacology study looking at drug-drug interactions, the effect of

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food, and bioavailability also uses the oral formulation. Details of these trials can be found in ClinicalTrials.gov and the MLN9708 Investigator's Brochure (IB).

Clinical Trial Experience Using the Oral Formulation of MLN9708

In the 7 studies actively enrolling patients to investigate oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-1.

Table 1-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 58	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 = 52	PO, weekly (W), single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea
C16005 NDMM N = 65	PO W, combination with LenDex 28 day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D*: 4.0 mg fixed [switched to fixed dosing in Ph2, relevant to 2.23mg/m^2]
C16006 NDMM N = 20	PO TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A*: 3mg -3.7 mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B*: 3 mg - 5.5 mg fixed dose, W DLT: Esophageal ulcer
C16007 RRAL N = 14	PO, W, single agent	4 mg-5.5 mg fixed dose* W MTD: 4 mg DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest
C16008 NDMM N = 11	PO, TW, combination with LenDex 21 day cycle	3.0-3.7 mg fixed dose* W MTD: 4 mg DLT:

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Table 1-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16009 Solid tumors, Lymphomas N = 22	PO, weekly, single agent	5.5 mg fixed dose* 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; RPh2D= recommended phase 2 dose.

* Approximate BSA and fixed 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

In addition to the trials noted above and this study, there are currently 4 planned trials; each of which will use the oral formulation of MLN9708; these studies are being reviewed by IRB/ethic committees, but are expected to begin enrollment of patients in 2012:

- Study C16010 is a phase 3 trial of lenalidomide and dexamethasone with MLN9708 or placebo given weekly in patients with relapsed or refractory MM.
- Study C16012 is an open-label, phase 2 (with dose-finding lead-in) study of the oral MLN9708 formulation in adult patients with nonhematologic malignancies expressing elevated cytoplasmic p65/NFkB.
- Study C16013 is a phase 1 pharmacokinetic study of oral MLN9708 plus lenalidomide and dexamethasone in adult Asian patients with relapsed and/or refractory multiple myeloma.
- Study TB-MC010034 is a phase 1 trial of MLN9708 in Japanese patients with relapsed and/or refractory multiple myeloma.

Overview of the Oral Formulation of MLN9708

The emerging safety profile indicates that oral MLN9708 is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations, and manageable by dose reductions, discontinuation, or standard supportive care. From experience from phase 1 through 2 studies the major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 24 months. As noted in Table 1-2, the MTD has been established in most of the phase 1 trials with dose-escalation

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continuing in 1 study (Study C16006, NDMM). The potential risks reported with MLN9708 use, pooled from the enrolling 7 phase 1 and phase 1/2 clinical studies (N=242) using the oral formulation are shown in Table 1-2. As of 30 April 2012, one patient treated with the oral formulation of MLN9708 has reported Grade 3 PN; while 13% (32 patients) have reported Grade 1 or 2 PN; 11 of these patients reporting baseline Grade 1 neuropathy at study entry.

Table 1-2 MLN9708 Potential Risks (Pooled PO Formulation), as of 30 April 2012

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 Dyspnea Chills Dizziness Peripheral neuropathy Arthralgia, back pain, abdominal pain Peripheral edema

The clinical experience with MLN9708 also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent MLN9708, when combined with established therapies, and across the malignancies studied (advanced solid tumors, non-Hodgkin's disease, Hodgkin's disease, relapsed and/or refractory multiple myeloma [RRMM], relapsed or refractory systemic light chain amyloidosis [RRAL], and newly diagnosed multiple myeloma [NDMM]) to date. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of MLN9708.

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agent MLN9708 is administered weekly in patients with RRMM or RRAL, respectively. See section on Pharmacokinetics and Drug Metabolism and Figure 1-1 regarding MLN9708 dosing switch from BSA-based to fixed dose.

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C16004: Relapsed and/ or Refractory Multiple Myeloma

Study C16004 is an open-label, dose-escalation, phase 1 study of MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. The dose-escalation phase of the trial has completed. In this study, 2 of 3 patients experienced protocol-defined DLTs (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.

Once the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled in order to further evaluate the safety, tolerability, efficacy, PK, and pharmacodynamics of oral MLN9708. The MTD expansion cohorts enrolling are:

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];
2. Carfilzomib expansion cohort
3. Proteasome Inhibitor-Naïve expansion cohort
4. VELCADE-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest MLN9708 has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated.[82, 83]

As of the 30 April 2012 data cut, these patients are considered heavily pretreated as evidenced by a median number of 4 (range 1–13) prior lines of therapy, with 66% refractory to the last line of therapy. Patients have received a median of 2 cycles of therapy (range, 1-11). Five patients have achieved objective response: 1 patient achieved a VGPR and 4 patients achieved a PR. Additionally, 15 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 15 patients remain on treatment; discontinuation of treatment was primarily due to progressive disease (69%).

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A summary of the safety profile of patients treated in Study C16004 is outlined in Table 1-3. Overall, 92% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/ 2 in 6 patients, with 3 patients reporting baseline Grade 1 PN at study entry.

Table 1-3 Study C16004: Oral MLN9708, Single Agent Given Weekly Most Common TEAEs as of 30 April 12 (N = 52)

Most Common (> 20%) Any Grade and Irrespective of Cause	Thrombocytopenia (54%) Fatigue (48%) Nausea (44%), diarrhea (44%), Vomiting (37%) Decreased appetite (33%) Rash* (31%) Anemia (25%) Neutropenia (23%)
Drug-Related Grade ≥ 3 in> 5% of patients	Thrombocytopenia 38%, diarrhea and neutropenia 17% (each), fatigue and lymphopenia 10% (each), nausea and decreased appetite 8% (each), and vomiting 6%

*Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic, pruritus, rash erythematous, exfoliative rash, and rash popular.

Dose reductions required were due to AEs that included rash, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, hypotension, increase in serum creatinine, abdominal pain, ileus, fatigue, and pneumonia. The AEs reported for the 5 patients who were required to discontinue treatment included Grade 2 MLN9708-related nausea/vomiting in 1 patient treated above the MTD, Grade 3 MLN9708-related diarrhea in a second patient, related Grade 3 thrombocytopenia, related Grade 2 dyspnea, and not-related Grade 4 elevation in creatinine(1 patient each). There were no on-study deaths.

C16007: Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

Study C16007 is evaluating single agent weekly, Day 1, 8, and 15 of a 28-day cycle, oral dosing in patients with RRAL after at least 1 prior therapy. The objectives of this study are to determine the safety, tolerability, and MTD, as well as to determine hematologic and organ response rates in this patient population. The starting dose level was selected from Study C16004 as previously described. In Study C16007 the dose was switched from the BSA-based dosing to the fixed dose, thereby the 4.0 mg fixed starting dose in Study C16007 corresponds to the 2.23 mg/m^2 dose (one dose level below MTD) from Study C16004. This study is currently enrolling patients in the dose-expansion portion of the trial.

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As of 30 April 2012, 14 patients have been treated in this study. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which met the definition of a DLT due to the delay in starting Cycle 2). As per protocol, the dose was escalated to 5.5 mg for the next cohort of patients where 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram on study entry, but did have substantial renal involvement. After the occurrence of this DLT, diagnoses included cardiac involvement and CHF. The MTD of weekly oral MLN9708 was determined to be 4.0 mg. Following the establishment of the MTD, patients are currently being enrolled in to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed.[84]

As of the 30 April 2012 data cut, the patients enrolled in the study are considered heavily pretreated, as evidenced by a median number of 3 prior lines of therapy (range 1–7), with 38% and 46% of patients having been previously treated with bortezomib and lenalidomide, respectively. To be eligible for the study, patients must have amyloid involvement of the heart, kidney, or both; at the data cut the organ involvement distribution was 6, 4, and 4 patients, respectively. Patients have received a median of 2.5 cycles of therapy (range, 1-12). Eight patients remain on treatment. Early signs of activity have been reported. There were 11 patients who have received at least 1 cycle of therapy with completed response assessments (9 in the 4.0 mg [MTD] cohort and 2 in the 5.5 mg cohort). The overall hematologic response rate at MTD is 56% (5 patients achieved a hematologic response [4 VGPR and 1 PR]; 3 patients showed no change, and 1 patient had an early progression.

A summary of the safety profile of patients treated in Study C16007 is outlined in Table 1-4. Overall, 86% of patients experienced a TEAE of any grade and of any cause.

Table 1-4 Study C16007: Oral MLN9708, Single Agent Given Weekly Most Common TEAE as of 30 April 12 (N = 14)

Most Common (> 20%) Any Grade and Irrespective of Cause	Nausea (50%) Fatigue (36%) Thrombocytopenia (29%) Diarrhea (29%) Decreased appetite (21%) Peripheral edema (21%) Dyspnea (21%) Abdominal pain (21%)
Drug-Related Grade ≥ 3 in ≥ 2 patients	Thrombocytopenia 5 patients, rash 3 patients, dehydration 2 patients, fatigue 2 patients

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One patient discontinued study drug administration due to a TEAE (patient with DLT of acute rise in serum creatinine, dyspnea, and cardiac arrest treated at 5.5 mg, as noted above). No death has been reported.

The potential risks reported with MLN9708 use, pooled from all studies using the oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the MLN9708 IB and ICF documents. Regardless of whether MLN9708 is administered on the once weekly or twice weekly dosing schedule, there is consistency among the type of TEAEs reported, despite 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 MLN9708 IB for further information.

Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to single-dose first time of occurrence of maximum (peak) concentration (T_{max}) of approximately 0.5 to 2.0 hours and terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days.[(85)] Results of a population PK analysis (N = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance, IV dosing (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[(86)] Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. Please refer to the MLN9708 IB for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, and urinary excretion of the parent drug is negligible (< 3% of dose). In vitro studies indicate that MLN9708 is metabolized by multiple cytochrome P_{450s} (CYPs) and non-CYP enzymes/proteins. These data indicate that at clinically relevant concentrations of ixazomib, no specific CYP isozyme predominantly contributes to ixazomib clearance. At concentrations exceeding those observed clinically (10 µM), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%),

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2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), CYP2C19 (4.8%) and 2C9 (<1%). These studies were conducted at supra-therapeutic concentrations (10 μM ixazomib) that are >90 fold higher than the geometric mean clinical C_{max} (0.11 μM) at the 4 mg oral once weekly dose. At 0.1 μM and 0.5 μM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. The rate of ixazomib disappearance and the rate of formation of measurable metabolites were similar in control incubations that contained no active CYP isozymes and ones that had active CYP isozymes present when the same protein amounts were used. These data indicate that at clinically relevant concentrations of ixazomib, non-CYP proteins contribute to the clearance of ixazomib and no specific CYP isozyme predominantly contributes to the clearance of ixazomib. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated drug-drug interactions (DDIs) with a selective CYP inhibitor would be expected. MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5.

The PK of ixazomib (C_{max} and $AUC_{0\text{-}last}$) was similar with and without coadministration of clarithromycin, a strong CYP3A inhibitor, and hence no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. These findings are explained by the in vitro metabolism data indicating the lack of a discernible contribution of CYP-mediated metabolism at clinically relevant ixazomib concentrations. As discussed earlier, no CYP isoforms have been identified to contribute meaningfully to ixazomib metabolism at clinically relevant concentrations and CYP3A contribution to total metabolism was highest across all CYP isoforms when characterized at a supra-therapeutic concentration of 10 μM. Therefore, based on the totality of information from the clinical clarithromycin DDI study and the in vitro CYP phenotyping data, it can be concluded that ixazomib PK is not likely to be altered upon co-administration of any CYP isoform-selective inhibitor, including strong CYP1A2 inhibitors. Consistently, in the population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. MLN2238 may be a weak affinity substrate of P glycoprotein (P-gp) but not of breast cancer resistance protein (BCRP) and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN2238 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

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1.4 Study Rationale

Primary light chain (AL) amyloidosis is a rare, lethal plasma cell dyscrasia in which fibril deposits containing toxic monoclonal immunoglobulin light chains infiltrate tissues causing their dysfunction and failure. Unlike patients with MM, patients with AL amyloidosis not only have a hematologic malignancy, but also direct progressive involvement of 1 or more visceral organs. Given the rarity of AL amyloidosis, there have not been any randomized controlled trials in the relapsed disease setting, but rather there have been anecdotal case reports, retrospective series, and small single institution trials utilizing differing single-agent or combination therapy regimens shown active in a similar yet different plasma cell dyscrasia multiple myeloma. The National Comprehensive Cancer Network (NCCN) therefore recommends treatment in a clinical trial because there are no regulatory approved treatments and data are insufficient to identify an optimal therapy.[4] The treatment of patients with relapsed and/or refractory systemic light-chain (AL) amyloidosis is an area of unmet need. The current therapeutic approach to systemic amyloidosis is based on the observation that amyloid deposits can be reabsorbed and organ function restored if the concentration of the amyloidogenic protein precursor (known as the involved free light chains [FLC]) is reduced. Therefore, the aim of therapy in AL amyloidosis is to rapidly decrease the supply of errant amyloid-forming FLC by suppressing the underlying clonal plasma cell while using supportive measures to sustain and possibly preserve organ functions. The clinical course of the disease is improved by arresting progressive organ damage and allowing functional improvement of affected organs, thereby providing clinical benefit.

While reduction in the amyloidogenic-involved free light chains can improve the clinical course of the disease, the therapies that achieve these results are not curative adding to the uniformly fatal prognosis for this disease with the currently available approaches. When the patient's disease relapses or does not respond to first-line therapy, there is no standard therapy, and data are limited even for those agents used in this setting.[4] Unfortunately, the current choice of treatment is primarily based on nonrandomized studies and investigator personal experience, which accounts for discrepancies in the treatment strategies proposed by different investigators. Because there is no consensus, the choice of treatment depends on a fine balance between the perceived efficacy of the chosen regimen and the individual patient's expected ability to tolerate the treatment's toxicity considering their age, organ dysfunction, and pace of disease, and given the limited treatment options, may mean exposure to an agent from the same drug class. Available treatment options in AL amyloidosis have used advances made in the chemotherapy of MM, including the use of

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corticosteroids, alkylating agents, proteasome inhibitors, and immunomodulatory agents (IMiDs), more frequently as combination regimens but also as single agents.

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, improving drug administration, while building on the efficacy seen with VELCADE. This study has been designed based on the results of VELCADE in previously treated AL amyloidosis,[80, 87] the emerging activity seen with MLN9708 in the treatment of previously treated and untreated MM and AL amyloidosis (see Section 1.3), and the urgent need for better treatment options for this rare disease, especially in the relapsed setting where no standard treatment exists.

Amyloidosis is a protein misfolding disease and may therefore be particularly sensitive to proteasome inhibition. The hypothesis of this study, therefore, is to compare a proteasome inhibitor, oral MLN9708, to oral agents of other drug classes that are currently used in clinical practice. Given that the AL amyloidosis population is predominantly a frail and elderly patient population, the convenience of an oral regimen is expected to increase compliance and possibly duration of treatment, which in turn should result in more durable hematologic responses. This study is designed to determine the safety and efficacy of oral MLN9708 with dexamethasone compared with treatment as chosen by the investigator from a selected list of oral regimens routinely available in clinical practice, dexamethasone alone or with an alkylating agent (melphalan or cyclophosphamide) or dexamethasone with an IMiD (thalidomide or lenalidomide) in patients with relapsed AL amyloidosis. Inclusion of patients with amyloid involvement of heart and kidney was selected because these organs represent the major organs most commonly involved in AL amyloidosis, but more importantly, the criteria for involvement, response, and progression are based on objective clinical laboratory and imaging tests which can be analyzed by central laboratories to reduce variability and bias. The primary objective of this study is to determine the overall hematologic response based on dFLC (difference between the involved and uninvolved FLC) assessment and to determine the rate of vital organ (that is heart and kidney) deterioration at 2 years. An improvement in hematologic response, as measured by reduction in FLC, and a reduction in the rate of vital organ deterioration in patients with relapsed or refractory systemic light chain amyloidosis would represent clinical benefit.

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Rationale for Stratification Factors

Much of the variability in outcomes in the literature is related to the different proportion of patients with advanced cardiac disease in each clinical trial. Additionally, the patient's response to the prior therapy is important. To maintain a balanced representation of the disease characteristics, patients enrolled in this study will be stratified by: 1) Cardiac Risk Stage: 1 versus 2 versus subgroup Cardiac Risk Stage 3 (ie, both NT-proBNP and troponin T over threshold [but NT-proBNP < 8000 pg/mL]); 2) relapsed versus refractory (relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy); and 3) proteasome inhibitor naïve versus exposed.

Because no approved therapy exists for patients with AL amyloidosis, experts, including the NCCN, recommend treatment of patients on clinical studies. At relapse, given the limited treatment options, patients seek subsequent treatment even if it means exposure to an agent from the same drug class.[4] MLN9708 is a modified peptide boronic acid analog similar to the first-in-class proteasome inhibitor VELCADE, which in some parts of the world, is used to treat relapsed AL amyloidosis and is also being evaluated in 2 frontline phase 3 trials comparing melphalan plus dexamethasone with or without VELCADE. It is unlikely that there will be significant differences in safety, based on the emerging safety data from ongoing phase 1 studies in patients with relapsed or refractory MM who have been previously treated with proteasome inhibitors; however, there may be differences in activity. Therefore, patients are eligible for this study regardless of prior exposure to proteasome inhibition therapy; however, patients will be stratified based on this past exposure (naïve versus exposed) in order to characterize the activity of oral MLN9708 as compared to other oral regimens routinely used in clinical practice.

Amyloid heart involvement is predominantly due to infiltration of the heart by amyloid aggregates. Patients with cardiac AL amyloidosis and evidence of active disease have a poor prognosis.[56] Cardiac biomarkers, such as cardiac troponins and NT-proBNP, are now validated as a sensitive, reliable, quantitative assessment of cardiac damage and cardiomyocyte stress; in the context of AL amyloidosis, are the most important predictors of outcome; and serve as the basis of a staging system used to stratify patients.[19, 26, 56] Cardiac troponin T is a highly specific and sensitive marker of cardiac injury, while NT-proBNP is considered a sensitive indicator of cardiac dysfunction.[88, 89] Baseline levels of cardiac biomarkers predict for OS.[56, 90, 91] As reported by the Mayo Clinic, median survival for

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three risks groups (as defined in Table 1-5) were 26.4 (1-low risk), 10.5 (2-intermediate risk), and 3.5 months (3-high risk) ($p < 0.0001$).[56] Additionally, the serum concentration of NT-proBNP drops if the reduction of circulating FLC is adequate (at least 50%)[26, 29, 45, 92] even without changes based on echocardiogram,[19] translating into improvement in cardiac symptoms,[19, 26, 93] and prolonged survival.[26, 28, 45, 94, 95, 96] Several reports confirm that the deeper the reduction in circulating amyloidogenic FLC by chemotherapy, the greater the improvement in cardiac function.[26, 81, 91] Together the troponin plus NT-proBNP risk staging system adds objective, reproducible, biochemical information beyond the clinical and echocardiographic diagnostic determination of presence or absence of cardiac involvement and divides patients into 3 groups with different outcomes.[97, 98, 99] These criteria provide a prognostic guide for staging and stratifying patients; therefore in order to balance patients between the 2 treatment groups, patients in this study will be stratified by Cardiac Risk Stage 1, 2, or a subgroup of Stage 3 based on the cardiac biomarkers NT-proBNP and troponin T. Most studies exclude patients with severe (Stage 3) cardiac disease, because these patients usually die quickly from cardiac failure, arrhythmias, and organ failure, often before they have had a chance to respond to therapy.[90, 100] According to Chee, et al patients with this worst outcome were characterized by NT-proBNP values greater than 9000 pg/mL.[100] This clinical trial proposes to include (and stratify) patients with Cardiac Risk Stage 3 disease with NT-proBNP levels less than 8000 ng/L as a means to include patients with a significant unmet medical need while ensuring the ability to comprehensively characterize of the safety and efficacy of MLN9708. This will allow for similarities between treatment arms and thus consistent and reliable comparisons of the therapeutic outcomes.

Table 1-5 Cardiac Risk Assessment Staging System

Stage	Criteria: Threshold levels NTpro-BNP > 332 pg/mL and troponin T < 0.035 ng/mL
1 (low risk)	Both troponin or NT-proBNP under threshold
2 (intermediate risk)	Either troponin or NT-proBNP [but not both] over threshold
3 (high risk)	Both troponin or NT-proBNP over threshold

Source: Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. Journal of Clinical Oncology 2004;22(18):3751-7.[97]

Abbreviations: NT-pro BNP = N-terminal pro-brain natriuretic peptide.

If troponin T not available at local institution, troponin I may be used, but threshold is < 0.1 µg/mL.

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Given the lack of randomized trials, this study proposes to include both patients whose disease has not responded to prior therapy as well as those whose disease has relapsed based on hematologic criteria. Treatment of AL amyloidosis is not curative and the pathophysiology of AL amyloidosis is complex. Patients with refractory disease, defined as no improvement in FLC and NT-proBNP after 3 cycles of therapy, are at high risk of early death from cardiac failure, arrhythmias, and organ failure.[26, 100] Patients may develop a late relapse in organ reserve even though there has been a reduction in measurable FLC prompting the need for subsequent therapy.[26, 39, 101] The depth of free light chain reduction (hematologic response) along with the tempo of organ improvement or failure influence the need for further treatment and depending on adequacy of organ function may reduce the therapeutic choices and have an effect on response to subsequent therapy.[26, 39, 101] Therefore, in order to balance patients between the 2 treatment groups, patients will be stratified by based on whether they are refractory to their prior therapy or if they have relapsed disease.

1.5 Rationale for MLN9708 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. 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. In clinical studies, single-agent weekly MLN9708 has been administered to patients with RRMM and to patients with RRAL. Study C16004, a phase 1 study in adult patients with RRMM, was the first trial to investigate single-agent MLN9708 in this weekly schedule. In this study, the estimated MTD is 2.97 mg/m^2 with DLTs of transient rash, nausea, vomiting, and diarrhea. The most common related > Grade 3 AEs included thrombocytopenia, diarrhea, nausea, neutropenia, and fatigue. Current data suggest weekly administration of oral MLN9708 is generally well tolerated with infrequent PN, and shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden and prolonged disease stabilization in some heavily pretreated patients with RRMM.[83] See Section 1.3 for additional details.

At initiation of clinical development of MLN9708, early phase 1 clinical studies empirically used a body surface area-based (BSA) 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 5 early trials (Studies C16001, C16002, C16003, C16004, and C16005). However, the clearance of small molecule drugs is typically not a linear function of BSA and the appropriateness of traditional BSA-scaled

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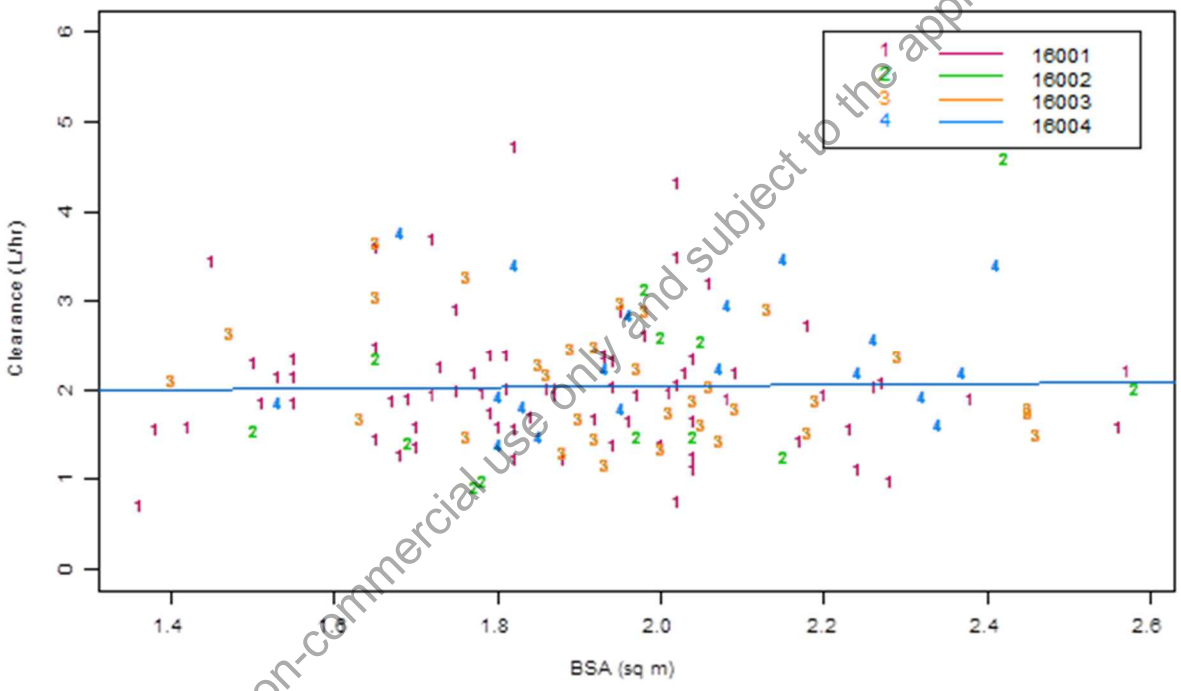
approaches for dosing anticancer agents has been questioned. Based on PK modeling of MLN9708 as shown in Figure 1-1 and described in Section 1.3 it was determined that BSA did not affect single-dose maximum (peak) concentration (C_{max}) or area under the plasma concentration versus time curve (AUC), and thus fixed dosing was appropriate. The clinical development of MLN9708 therefore transitioned from use of BSA-based dosing to fixed dosing in all subsequent studies, including the phase 1 trial C16007 that serves as the basis for the dose in this phase 3 trial.

Figure 1-1 No Apparent Relationship Between MLN9708 Clearance and Body Surface Area



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 the linear regression line.

Study C16007: Phase 1 Study in Relapsed or Refractory AL Amyloidosis: Dose, Schedule, Safety, and Early Activity

Study C16007 also evaluated single-agent oral MLN9708 weekly in patients with RRAL on Days 1, 8, and 15 of a 28-day cycle. Based on the data from the RRMM study C16004, there were 2 planned dose escalations in Study C16007: fixed doses of 4.0 mg (equivalent to 2.23 mg/m^2 dosing, 1 dose level below the MTD in C16004) and 5.5 mg (equivalent to 2.97 mg/m^2 dosing, the MTD in C16004). As of 30 April 2012, 14 patients have been treated. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which delayed the start of

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Cycle 2 and thus met the criteria for DLT). At the next dose level of 5.5 mg, 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram at study entry, but did have substantial renal involvement; however, the differential diagnoses at the time of the DLT included cardiac amyloid involvement and CHF. This patient discontinued therapy due to this AE. As per protocol, with 2/5 patients experiencing DLTs at the 5.5 mg dose level, the MTD of weekly oral MLN9708 was determined to be 1 dose level lower (ie, a fixed dose of 4.0 mg). With the MTD now established, patients are being enrolled to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed.[(84)]

Early signs of activity were documented with single agent MLN9708 in these patients. Eleven patients received at least 1 cycle of therapy and had completed response assessments (9 in the 4.0 mg [MTD] cohort and 2 in the 5.5 mg cohort). The overall hematologic response rate at the 4.0 mg dose level is 56% (5 achieved a hematologic response [4 VGPR and 1 PR]); 3 patients showed no change, and 1 patient had an early progression. Notably, the hematologic and organ response criteria used in Study C16007 is the same criteria to be used in Study C16011. More data will be gained from the 2 MTD expansion cohorts of Study C16007, in which up to an additional 25 patients will receive MLN9708 at dose of 4.0 mg administered weekly Days 1, 8, and 15 of a 28-day cycle.

There is a similarity and consistency among the type of AEs reported with weekly oral MLN9708, regardless of whether the patient population is MM or systemic light chain amyloidosis. Millennium considers the MM safety data clinically relevant as MM and AL amyloidosis are related plasma cell disorders. As of 30 April 2012, 6 clinical studies using the oral formulation as outlined in Table 1-1 have enrolled 220 patients with MM or AL amyloidosis. It is important to note that the doses used in the MM trials and the current and proposed AL amyloidosis trials are similar. Therefore, based on the available clinical data, including data from Study C16007 in a patient population similar to that eligible for this study (C16011), the recommended dose of MLN9708 in this study is a fixed dose of 4.0 mg.

VELCADE: First-in-Class Proteasome Inhibitor in AL amyloidosis

In addition to the clinical trials of weekly MLN9708, the weekly schedule used in this trial was based on a trial reported by Reece and colleagues. [(78)];[(79)] The CAN-2007 study, the first prospective phase 1/ 2 study of single-agent VELCADE, enrolled 70 patients with previously treated (relapsed) systemic AL amyloidosis who required further treatment (a

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population similar to that for Study C16011 with MLN9708). The primary objectives of the study were to determine the MTD and safety of single-agent VELCADE in this patient population; the secondary objectives were to determine the hematologic response rate (CR and PR) and the duration of response at the MTD. The MTD was not defined for either schedule, rather the maximum planned doses of 1.6 mg/m^2 (once weekly) and 1.3 mg/m^2 (twice weekly) were used in phase 2 evaluation.[102] It is important to note that these doses/schedules represent the same dose and schedule as used to treat patients with MM: 1.6 mg/m^2 once weekly (Days 1, 8, 15, and 22 in a 35-day cycle) and 1.3 mg/m^2 twice weekly (Days 1, 4, 8, and 11 in a 21-day cycle). Hematologic response rates were similar between the weekly and twice weekly treatment groups (68.8% and 66.7% [37.5% and 24.3% complete responses]), respectively (Table 1-6). Response durations of > 1 year were achieved in 78.8% and 75.5% of patients, respectively. Organ responses, across all 70 patients treated, were reported in 29% of those with renal involvement and 13% of those with cardiac involvement. The weekly dose schedule was better tolerated than the twice weekly when considering rates of Grade ≥ 3 toxicities (50% vs 79%) and discontinuation/dose reductions (28/22% vs 38/53%). The hematologic CR rate and organ response rates were better with the weekly dose schedule than the twice weekly schedule; thus, the results of this study were also used to guide the dose and weekly schedule planned in Study C16011 with MLN9708.

Table 1-6 Best Confirmed Hematologic Response to VELCADE in Patients at the Recommended Dose on Each Schedule or at Lower Doses on Either Schedule

	Recommended Dose Groups		
	1.6 mg/m^2 QW	**1.3 mg/m^2 BIW**	**Lower Doses**
Best confirmed hematologic response, n (%) (95% CI)	N = 16	N = 33	N = 18
Overall Response Rate (CR + PR)	11 (68.8) (41.3, 89.0)	22 (66.7) (48.2, 82.0)	7 (38.9) (17.3,64.3)
CR	6 (37.5) (15.2, 64.6)	8 (24.2) (11.1,42.3)	2 (11.1) (1.4, 34.7)
SD	4 (25.0) (7.3, 52.4)	10 (30.3) (15.6, 48.7)	11 (61.1) (35.7, 82.7)
PD	1 (6.3) (0.2,30.2)	1 (3.0) (0.1, 15.8)	0

Source: Reece et al., 2011[78]; VELCADE, IND 56,515, Sep. 2, 2010, Serial No. 1416.
Abbreviations: BIW = twice weekly; QW = once weekly.

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In summary and as outlined above, Millennium believes that the dose of MLN9708 to be used in the proposed Study C16011 is supported by several key data sets. The dose and schedule for MLN9708 proposed for Study C16011 has been derived from the MTD in a phase 1 trial in patients with relapsed and/or refractory MM using the same schedule as the proposed clinical trial. Millennium considers the MM clinical safety data relevant as MM and AL amyloidosis are related plasma cell disorders. Importantly, the applicability of the clinical data in a MM patient population to the AL amyloidosis setting is supported by clinical data from a phase 1/2 trial of another boronic acid proteasome inhibitor, VELCADE, where the dose and schedule in AL amyloidosis was the same as the approved clinical dose and schedule in MM.

1.6 Potential Risks and Benefits

As of the clinical cut-off date of 30 April 2012, 242 patients across 7 ongoing sponsor-led studies have been treated with oral MLN9708. Clinical safety data includes experience from patients who received multiple cycles followed by treatment-free periods and from patients who reduced or discontinued treatment. The emerging safety profile (as noted in Section 1.3, the MLN9708 IB, and the SMA) indicates that the adverse events reported with MLN9708 are generally consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with bortezomib though the frequency may slightly differ. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention. It is possible that MLN9708 will have toxicities that were not previously observed in or predicted from its evaluation in nonclinical studies and from ongoing clinical studies given the current human experience with MLN9708. To mitigate the inherent risks in clinical studies of MLN9708, patients are monitored closely for anticipated toxicities. Guidance for the management of AEs and procedures for reducing doses are provided in the protocols, and drug dosage can be reduced by either reducing the dose administered or by interruption of the scheduled treatment within a cycle. MLN9708 shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. Weekly dosing appears to enable delivery of higher MLN9708 doses. VELCADE's proven utility in the treatment of MM and mantle cell lymphoma and MLN9708's increased tissue distribution and activity in several xenograft models against the same components of the ubiquitin proteasome system support the further clinical investigation of MLN9708. The emerging data also support the expanded development of MLN9708 for the treatment of patients with plasma cell dyscrasias such as AL amyloidosis. See the MLN9708 Investigator's Brochure for more information. This trial will be

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conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonization (ICH) guidelines.

2. STUDY OBJECTIVES

As of this amendment, the objectives are to provide continued access of MLN9708 and/or other study medications and to continue collecting relevant safety data to monitor patient safety. All other study objectives will no longer be assessed. However, the complete list of objectives is retained below for reference.

2.1 Primary Objectives

The 2 primary objectives are:

- To determine whether dexamethasone plus MLN9708 improves hematologic response (PR + VGPR + CR) versus a physician's choice of a chemotherapy regimen as selected from the list of offered treatment options in patients diagnosed with relapsed or refractory AL amyloidosis.

- To determine whether dexamethasone plus MLN9708 improves 2-year vital organ (that is, heart or kidney) deterioration and mortality rate versus a physician's choice of a chemotherapy regimen as selected from the list of offered treatment options in patients diagnosed with relapsed or refractory AL amyloidosis. Cardiac deterioration is defined as the need for hospitalization for heart failure. Kidney deterioration is defined as progression to end-stage renal disease (ESRD) with the need for maintenance dialysis or renal transplantation.

2.2 Secondary Objectives

The key secondary objectives are:

- To determine OS.

- To determine the complete hematologic response rate (CR).

Other secondary objectives are:

- To determine progression-free survival (PFS).

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- To measure hematologic disease PFS.
- To determine best response in the vital organs allowed at study entry (heart and kidney).
- To determine time to vital organ deterioration or death.
- To measure vital organ PFS.
- To measure the duration of hematologic response (DOR).
- To evaluate safety.
- To measure time to treatment failure (TTF).
- To measure time to subsequent anticancer therapy.
- To describe the impact of treatment on quality of life (QOL) using the Medical Outcomes Study 36- item Short Form General Health Survey (SF-36 v2) (Section 15.3), FACT-neurotoxicity subscale (FACT/GOG-Ntx) (Section 15.4) and a symptom scale questionnaire (Section 15.5).
- To evaluate Health Utilization (HU) and to collect EuroQol 5-Dimensional (EQ-5D) (Section15.9) data.
- To collect PK data to contribute to population PK analyses.

3. STUDY ENDPOINTS

As of this amendment, evaluation of the safety profile of MLN9708 and/or other study medication is the only endpoint being assessed. All other study endpoints will no longer be assessed. However, the complete list of endpoints is retained below for reference.

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3.1 Primary Endpoints

The primary endpoints are:

- Overall hematologic (CR + VGPR + PR) response rate based on central laboratory results and the 2010 International Society of Amyloidosis (ISA) Consensus Criteria as evaluated by an Adjudication Committee (AC)

- 2-year vital organ (that is, heart or kidney) deterioration and mortality rate. Cardiac deterioration is defined as the need for hospitalization for heart failure. Kidney deterioration is defined as progression to end-stage renal disease (ESRD) with the need for maintenance dialysis or renal transplantation. Vital organ deterioration will be evaluated by an AC.

3.2 Secondary Endpoints

The key secondary endpoints are:

- Complete hematologic response rate (CR) according to central laboratory results and ISA criteria as evaluated by an AC.

- OS, measured as the time from randomization to the date of death.

Other secondary endpoints are:

- PFS, defined as the time from the date of randomization to the date of first documentation of disease progression (hematologic PD or major organ progression [specifically involvement of heart or kidney] whichever occurs first) according to central laboratory results and ISA criteria as evaluated by an AC, or death due to any cause, whichever occurs first.

- Hematologic disease PFS, defined as the time from the date of randomization to the date of first documented hematologic disease progression according to central laboratory results and ISA criteria, as evaluated by an AC, or death due to any cause, whichever occurs first.

- Time to vital organ (that is, heart or kidney) deterioration and mortality rate. Cardiac deterioration is defined as the need for hospitalization for heart failure. Kidney

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deterioration is defined as progression to ESRD with the need for maintenance dialysis or renal transplantation.

- Best response in the vital organs allowed at study entry (heart and kidney) according to central laboratory results and International Society of Amyloidosis criteria as evaluated by an AC.

- Vital organ PFS, defined as the time from the date of randomization to the date of first documentation of progression of vital organ (that is, heart or kidney) according to central laboratory results and ISA criteria, as evaluated by an AC, or death due to any cause, whichever occurs first.

- Duration of hematologic response, measured as the time from the date of first documentation of hematologic response to the date of first documented hematologic disease progression, respectively according to central laboratory results and ISA criteria as determined by an AC.

- Adverse events (AEs), serious adverse events (SAEs), and assessments of clinical laboratory values.

- TTF, defined as the time from the date of randomization to the date of first documented treatment failure. Treatment failure is defined as: 1) death due to any cause; 2) hematologic progression or major organ progression according to central laboratory results and ISA criteria as evaluated by an AC; 3) clinically morbid organ disease requiring additional therapy; or 4) withdrawn for any reason.

- Time to subsequent anticancer treatment, defined as the time from the date of randomization to the start date of subsequent anticancer treatment.

- QOL from patient-reported outcomes instruments (changes from baseline in health status based on SF-36 v2 survey, the FACT/GOG-Ntx, and a symptom scale questionnaire.

- Collection of Health Utilization (HU) related to the disease and the therapy in both treatment arms and the EQ-5D questionnaire data.

- Plasma concentration-time data to contribute to future population PK analysis.

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4. STUDY DESIGN

4.1 Overview of Study Design

This is a phase 3, randomized, controlled, open-label, multicenter study of the oral formulation of MLN9708 in combination with dexamethasone compared with treatment as chosen by the physician from a prespecified list of regimens available in clinical practice: dexamethasone alone, dexamethasone with an alkylating agent (melphalan or cyclophosphamide), or dexamethasone with an IMiD (thalidomide or lenalidomide) in patients with relapsed or refractory AL amyloidosis. Crossover to the investigational treatment arm is not permitted during participation in this study.

Patients must have biopsy-proven AL amyloidosis with relapsed or refractory disease despite 1 or 2 prior therapies and require further treatment. Patients cannot be refractory to proteasome inhibitor therapy. To be eligible for enrollment, patients must also have measurable disease as defined by dFLC and objective, measurable major organ involvement (ie, cardiac, renal), as defined by standard ISA criteria (Section 5.1). Patients may also have other organ involvement as outlined in Section 7.4.13.2.

The primary objectives of this study are hematologic response and 2-year vital organ (that is, heart or kidney) deterioration and mortality rate. Cardiac deterioration is defined as the need for hospitalization for heart failure. Kidney deterioration is defined as progression to end-stage renal disease (ESRD) with the need for maintenance dialysis or renal transplantation.

To maintain a balanced representation of the disease subtypes, enrollment to this study will be stratified by: 1) Cardiac Risk Stage: 1 versus 2 versus subgroup Cardiac Risk Stage 3 (ie, both NT-proBNP and troponin T over threshold [but NT-proBNP < 8000 pg/mL]); 2) relapsed versus refractory (relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy); and 3) proteasome inhibitor naïve versus exposed. In all treatment arms, each patient will continue to receive sequential cycles of therapy until disease progression, unacceptable toxicity, or termination of the study (See Section 6.4.2 for duration of treatment in the melphalan/dexamethasone group). Dose adjustments are possible based on toxicities experienced. Throughout the study, adverse events (AEs), laboratory values, and vital sign measurements will be collected and assessed to evaluate the safety of therapy. Clinical laboratory tests and clinically indicated disease assessments (to include but not limited to

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serum free light chain, cardiac biomarkers, 24-hour urine analyses, echocardiograms, and CT scan/MRIs) will be analyzed at the appropriate central laboratory/imaging center.

Response to therapy will be evaluated by an AC assessment, which will include the assessment of hematologic response and organ response according to the criteria outlined in the Revised Consensus Response Criteria of the International Society of Amyloidosis (ISA).[36] Hematologic and organ disease assessments will be done within 28 days before the first dose. Hematologic response will be assessed every cycle from the date of first dose until end of treatment, and every 6 weeks thereafter until documented progression or initiation of subsequent therapy. Organ response will be assessed after the completion of Cycles 3, 6, 9, and 12 and then every 3 cycles thereafter until disease progression or the initiation of subsequent therapy. Vital organ deterioration will be evaluated by an AC to provide a determination of the events of this composite endpoint. Vital organ deterioration is characterized as cardiac deterioration, that is the need for hospitalization for heart failure, and kidney deterioration, that is progression to ESRD with the need for maintenance dialysis or renal transplantation. Quality of life questionnaires will be administered to patients before each cycle, at the end of treatment, and every 6 weeks until disease progression or initiation of subsequent therapy. After disease progression, the patients will be followed for survival and subsequent therapy at least every 12 weeks.

The sponsor will designate the central laboratory and independent central safety and efficacy review, including the IDMC and AC.

Prior to randomization, the physician will choose a treatment regimen from the list of options provided by the sponsor for each screened patient. The physician's choice will be collected and recorded in the database. Eligible patients will be randomized to 1 of 2 study arms in a 1:1 ratio. Once randomized, patients should start therapy within 7 business days.

Arm A: Patients will receive MLN9708 (4.0 mg) PO on Days 1, 8, and 15 plus dexamethasone 20 mg/day PO weekly on Days 1, 8, 15, and 22 of each 28-day cycle; dexamethasone may be increased up to 40 mg/day after 4 weeks, if tolerated. Patients may continue to receive treatment until PD or unacceptable toxicity, whichever comes first.

Arm B: Patients will receive **one** of the following treatment options as selected by the physician:

- **Dexamethasone:** Dexamethasone 20 mg/day PO on Days 1 through 4, 9 through 12, and 17 through 20 of each 28-day cycle; dexamethasone may be increased up to

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40 mg/day after 4 weeks, if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities. Dose adjustments are possible based on toxicities experienced.

- **Dexamethasone plus melphalan:** Dexamethasone 20 mg/day PO on Days 1 through 4 of each 28-day cycle dexamethasone may be increased up to 40 mg/day after 4 weeks if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities, plus melphalan 0.22 mg/kg PO on Days 1 through 4 every 28 days. Melphalan has to be dose adjusted in patients with renal function impairment (see Section 6.4.2). Dose adjustments are possible based on toxicities experienced.

- **Dexamethasone plus cyclophosphamide:** Dexamethasone 20 mg/day PO weekly on Days 1, 8, 15, and 22 of each 28-day cycle; dexamethasone may be increased up to 40 mg/day after 4 weeks, if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities, plus cyclophosphamide 500 mg PO Days 1, 8, and 15 every 28 days. Dose adjustments are possible based on toxicities experienced.

- **Dexamethasone plus thalidomide**: Dexamethasone 20 mg/day PO weekly Days 1, 8, 15, and 22 of each 28-day cycle; dexamethasone may be increased up to 40 mg/day after 4 weeks, if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities, plus thalidomide total dose 200 mg/day PO (starting dose 50 mg/day, increased as tolerated to a maximum of 200 mg/day). Dose adjustments are possible based on toxicities experienced.

- **Dexamethasone plus lenalidomide**: Dexamethasone 20 mg/day PO weekly on Days 1, 8, 15, and 22 of each 28-day cycle; dexamethasone may be increased up to 40 mg/day after 4 weeks, if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities, plus lenalidomide 15 mg/day for 21 days every 28 days. Dose adjustments are possible based on toxicities experienced.

Patients may continue to receive treatment until PD or unacceptable toxicity.

The study includes 2 primary endpoints: assessment of hematologic response (PR + VGPR + CR), and 2-year vital organ deterioration and mortality rate; each of these endpoints will be assessed by an AC. Two formal interim analyses (IAs) have been planned for this study, the first to occur when approximately 176 patients enrolled have had an opportunity to complete 6 cycles of treatment. An independent statistician will perform the IAs. An IDMC

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will meet regularly to evaluate safety results, and at the appropriate IAs to evaluate efficacy results.

Health-related QOL will also be evaluated using the patient self-reported symptom scale questionnaire, FACT/GOG-Ntx, SF-36 v2, the symptom scale questionnaire, and EQ-5D. In addition to assessing selected symptoms, these instruments elucidate the effects of disease on physical, social, psychological/emotional, and cognitive functioning.

As of Amendment 6, the first IA has been conducted (data cut-off: 20 February 2019) and the primary endpoint of overall hematologic response rate (CR + VGPR + PR) did not reach statistical significance. However, patients in both treatment arms appeared to receive benefit. In light of the primary endpoint not being met, the sponsor has decided to remove the planned second IA and final analysis (FA) and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients. Ixazomib (MLN9708) and control drugs (if Takeda has been supplying them) will continue to be provided for patients who continue to derive benefit. Upon implementation of this amendment, data collection requirements will be limited to the following safety assessments: all SAEs (regardless of causality, including all deaths), any AE resulting in dose modification or discontinuation of any study drug, Grade ≥3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no longer required. All central laboratory and investigator assessments of response and progression for protocol purposes are discontinued—AC review of response data and IDMC review of efficacy and safety data will no longer be performed. Patients will not be followed for the PFS or OS follow-up periods, as PFS and OS are no longer being collected. Patients should otherwise be treated by the investigator according to standard of care.

4.2 Number of Patients

Approximately 176 patients are anticipated to be enrolled into this study at approximately 75 centers in North America, Europe, and the rest of the world.

4.3 Duration of Study

The duration of the study will be approximately 120 months (ie, 10 years), including 84 months of enrollment and 36 months of follow-up after the last patient is enrolled.

Delayed treatment-related AEs will be followed for 30 days after last dose of study drug.

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The first IA was conducted when 168 patients enrolled had the opportunity to receive at least 6 cycles of treatment or discontinue study. The planned second IA will no longer be conducted. The analyses from the first IA will be used to write the clinical study report. Minimal descriptive analyses will be done on patient data collected after the first IA.

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5. STUDY POPULATION

Adult patients with biopsy-proven systemic AL amyloidosis with relapsed or refractory disease will be enrolled.

5.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.

2. Biopsy-proven diagnosis of AL amyloidosis according to the following standard criteria:

    a. Histochemical diagnosis of amyloidosis, as based on tissue specimens with Congo red staining with exhibition of an apple-green birefringence.

    b. If clinical and laboratory parameters insufficient to establish AL amyloidosis or in cases of doubt, amyloid typing may be necessary (see Section 15.1).

3. Measurable disease as defined by serum differential free light chain concentration (dFLC, difference between amyloid forming [involved] and nonamyloid forming [uninvolved] free light chain [FLC]) ≥ 50 mg/L.

4. Objective, measurable major (cardiac or renal) organ amyloid involvement as defined as follows (amyloid involvement of at least 1 required).[20]

    a. Cardiac involvement is defined as the presence of a mean left ventricular wall thickness on echocardiogram greater than 12 mm in the absence of other potential causes of left ventricular hypertrophy (controlled hypertension is allowed) with a noncardiac biopsy showing amyloid, or a positive cardiac biopsy in the presence of clinical or laboratory evidence of involvement. If there is isolated cardiac involvement, then typing of amyloid deposits is recommended.

b. Renal involvement is defined as proteinuria (predominantly albumin) >0.5 g/day in a 24-hour urine collection.

Note: Amyloid involvement of other organ systems is allowed, but not required.

5. Must be relapsed or refractory after 1 or 2 prior therapies.

   For this protocol, relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy.

   a. Patient must not have been previously treated with proteasome inhibitors. (The sponsor reserves the right to open the study to proteasome inhibitor-exposed patients in the future, at some time point after the first IA. In that case, the patient may not be refractory to proteasome inhibitor therapy.)

   b. Given that the physician may select from an offered list of regimens to treat a specific patient, the patient may be refractory to an agent/s listed within the list of offered treatment choices.

   c. Must have recovered (ie, Grade ≤1 toxicity or patient's baseline status) from the reversible effects of prior therapy.

   d. If a patient has received a transplant as his/her first-line therapy, he/she must be at least 3 months posttransplantation and recovered from the side effects of the stem cell transplant.

6. Patient must meet criteria for 1 of the following AL Amyloidosis Risk Stages (as defined by NT-proBNP cut-off of < 332 pg/mL and troponin T cut-off of 0.035 ng/mL as thresholds):

   a. Stage 1: both NT-proBNP and troponin T under threshold.

   b. Stage 2: either NT-proBNP or troponin T (but not both) over threshold.

   c. Stage 3: both NT-proBNP and troponin T over threshold (but NT-proBNP < 8000 pg/mL).

7. ECOG Performance Status ≤ 2.

8. Clinical laboratory values:

   a. Absolute neutrophil count ≥ 1000/μL.

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b. Platelet count ≥ 75,000/µL.

c. Total bilirubin ≤ 1.5 × ULN, except for patients with Gilbert's syndrome as defined by > 80% unconjugated bilirubin and total bilirubin ≤ 6 mg/dL.

d. Alkaline phosphatase ≤ 5 × ULN.

e. ALT or AST ≤3 × ULN.

f. Calculated creatinine clearance ≥ 30 mL/min.

9. Female patients who:

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

   b. Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR

   c. Agree to practice true abstinence when this is line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)[(103)]

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

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

   b. Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR

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

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

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withdrawn by the patient at any time without prejudice to future medical care.

5.2 Exclusion Criteria

Prospective patients will be excluded from this study if they meet ANY of the following criteria:

1. Amyloidosis due to mutations of the transthyretin gene or presence of other non-AL amyloidosis.
2. Female patients who are lactating, breastfeeding, or pregnant.
3. Medically documented cardiac syncope, uncompensated NYHA Class 3 or 4 congestive heart failure (Section 15.6), myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive ventricular arrhythmias despite anti-arrhythmic treatment, or severe orthostatic hypotension or clinically important autonomic disease.
4. Clinically overt multiple myeloma, according to the IMWG criteria[103] with at least 1 of the following:
    a. Bone lesions.
    b. Hypercalcemia, defined as a calcium of > 11 mg/dL.
5. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or GI procedure that could interfere with the oral absorption or tolerance of treatment.
6. Requirement for other concomitant chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered to be investigational or which would be considered as a treatment of AL amyloidosis. However, patients may be on chronic steroids (maximum dose 20 mg/day prednisone or equivalent [Section 15.7]) if they are being given for disorders other than amyloidosis (eg, adrenal insufficiency, rheumatoid arthritis, etc.).
7. 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.
8. Ongoing or active infection, known HIV positive, active hepatitis B or C infection.

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9. Psychiatric illness/social situations that would limit compliance with study requirements.

10. Known allergy to boron, MLN9708, any of the study treatments, their analogues, or excipients.

11. Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment.

12. Diagnosed or treated for another malignancy within 3 years (or 5 years for patients in France) before study enrollment 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. DESCRIPTION OF TREATMENT

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

All doses must be taken as outlined in the Schedule of Events. Dosing should be performed on schedule, but occasional changes in patient scheduling are allowable (± 3 days) for holidays and other administrative reasons and (± 1 week) for patient vacations. See Section 7.4 for information about corresponding study procedures if dosing is delayed for reasons as noted. Refer to the Study Manual for additional instructions regarding study drug administration.

Patients will be given a diary to record study drug dosing. If a dose is missed entirely, the missed dose will be recorded as "not taken."

Study drug compliance will be calculated for each patient by taking into account whether a patient takes all study drug as instructed. Patients will be instructed to bring study drug to each patient visit for reconciliation. The number of tablets taken will be calculated by

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subtracting the number of tablets returned from the number of tablets dispensed. The dosing diary will provide supporting information if necessary.

6.1 MLN9708 and Dexamethasone

Patients randomized to Arm A will receive dexamethasone plus MLN9708. The investigator should refer to the current package insert/summary of product characteristics (SmPC) where available, for the most recent instructions on the handling, administration, and risks and potential side-effects of dexamethasone.

6.2 MLN9708 Administration

MLN9708 will be given as a once-daily oral dose. The study drug should be taken at approximately the same time each day, on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. The capsules should not be chewed, broken, or opened for administration. Each dose of MLN9708 will be taken orally with approximately 8 ounces (ie, 240 mL) total of water consumed.

MLN9708 will be administered on Days 1, 8, and 15 of a 28-day cycle. Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. Patients who vomit after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose. Dosing windows of ± 3 days are allowed occasionally (unless otherwise specified) as are occasional changes for holidays, vacations, and other administrative reasons (see Section 6).

6.3 Dexamethasone Administration

When used in the MLN9708 combination treatment arm, dexamethasone will be given as a single, oral dose of 20 mg/day PO weekly on Days 1, 8, 15, and 22 of each 28-day cycle; dexamethasone may be increased by 20 mg/day (up to 40 mg/day) after 4 weeks if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities.

Dexamethasone should be taken at approximately the same time each day. Each dose of dexamethasone should be taken with food or milk, and should be taken after MLN9708 unless an alternative timing is needed to maximize patient tolerance (refer to Section 6.5.3).

If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers it. 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

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dosing at the time of the next scheduled dose. Dosing windows of ± 3 days are allowed occasionally (unless otherwise specified) as are occasional changes for holidays, vacations, and other administrative reasons (see Section 6 and 6.5.3).

6.4 Physician's Choice

Before randomization, physicians will declare which treatment regimen from the list of options they plan to select for each patient. The selection will be collected and recorded in the database. Patients will then be randomized in a 1:1 ratio to 1 of 2 treatment arms: Arm A) dexamethasone plus MLN9708; or Arm B) the physician's preselected choice of treatment. Dosing windows of ± 3 days are allowed occasionally (unless otherwise specified) as are occasional changes for holidays, vacations, and other administrative reasons (see Section 6). The investigator should refer to the current package insert/SmPC, where available, for the most recent instructions on the handling, administration, and risks and potential side-effects of each drug.

6.4.1 Dexamethasone

Dexamethasone 20 mg/day PO on Days 1 through 4, 9 through 12, 17 through 20 every 28 days; dexamethasone may be increased by 20 mg/day (up to 40 mg/day) after 4 weeks if the lower is tolerated without any > Grade 2 dexamethasone-related toxicities. Dose adjustments are possible based on toxicities experienced.

6.4.2 Dexamethasone Plus Melphalan

Dexamethasone 20 mg/day PO on Days 1 through 4 of each 28-day cycle; dexamethasone may be increased by 20 mg/day (up to 40 mg/day) after 4 weeks, if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities, plus melphalan 0.22 mg/kg PO on Days 1 through 4 every 28 days. Melphalan can be dose adjusted for renal function:

- Creatinine clearance 20 to 40 mL/min: 0.18 mg/ kg of melphalan;
- Creatinine clearance < 20 mL/min: 0.15 mg/kg melphalan.

Note that at study entry, calculated creatinine clearance must be ≥ 30 mL/min; patients are not eligible if the results are lower. However, if renal function is lower during treatment, the melphalan dose may be adjusted as noted.

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Treatment cycles continue until best response plus 2 additional cycles or to a maximum of 18 months of therapy or 600 mg total dose given increased risk of second primary malignancies with prolonged melphalan use as noted in the melphalan package insert/ SmPC. Best response would be defined as a plateau in deepest response achieved (eg, an achievement of PR which did not improve over 3 cycles total [the onset of PR plus 2 additional cycles]).

6.4.3 Dexamethasone Plus Cyclophosphamide

Dexamethasone 20 mg/day PO weekly on Days 1, 8, 15, and 22; dexamethasone may be increased by 20 mg/day (up to 40 mg/day) after 4 weeks if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities, plus cyclophosphamide 500 mg PO on Days 1, 8, and 15 of each 28-day cycle.

6.4.4 Dexamethasone Plus Thalidomide

Dexamethasone 20 mg/day PO weekly Days 1, 8, 15, and 22 of each 28-day cycle; dexamethasone may be increased by 20 mg/day (up to 40 mg/day) after 4 weeks, if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities, plus thalidomide total dose 200 mg/day PO (starting dose 50 mg/day, increased as tolerated to a maximum of 200 mg/day).

6.4.5 Dexamethasone Plus Lenalidomide

Dexamethasone 20 mg/day PO weekly on Days 1, 8, 15, and 22 of each 28-day cycle; dexamethasone may be increased by 20 mg/day (up to 40 mg/day) after 4 weeks, if the lower dose is tolerated without any > Grade 2 dexamethasone-related toxicities, plus lenalidomide 15 mg/day for 21 days every 28 days.

6.5 Dose Modification Guidelines

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010.[(104)]

Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of treatment. Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Reduction or discontinuation of 1 agent and not the other is appropriate if toxicity is related primarily to 1 of the agents. If multiple toxicities are noted, the dose adjustments and/or delays should be made once per cycle according to the most severe toxicity guidelines. Further clarification can be obtained

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in consultation with the Millennium project clinician (or designee). Guidelines for dosing modifications and handling dexamethasone, melphalan, cyclophosphamide, thalidomide, and lenalidomide are provided here; however, it is recommended that the investigator refer to the most current prescribing information/SmPC for these therapies.

To manage excessive toxicity, reduction of the total drug dose can be done by reducing the daily dose administered and/or by interruption of the scheduled treatment within a cycle. A dose reduction to a lower dose level will be made either based on criteria within a cycle or at the start of the subsequent cycle, but not for both. For example, if a dose was reduced during a cycle, that lower dose would be carried forward into the next cycle; the dose would not be lowered again for the same toxicity at the beginning of the subsequent cycle. If medically appropriate, additional hematology and clinical assessment may be considered to determine if the dosing period should be interrupted for the remainder of that cycle or if additional monitoring is needed.

6.5.1 Criteria for Toxicity Recovery for a New Cycle of Therapy to Begin: All Treatment Regimens

- Absolute neutrophil count (ANC) must be $\geq 1 \times 10^9$/L
- Platelet count must be $\geq 75 \times 10^9$/L
- All other nonhematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for retreatment, hold treatment. The patient should be re-evaluated weekly or more frequently to determine whether the criteria for retreatment have been met and a new cycle can begin. If the criteria for retreatment have been met refer to appropriate drug modification guidelines to resume therapy. The maximum delay before treatment should be discontinued will be 3 weeks (except in the case of investigator-determined clinical benefit and discussion with the Millennium project clinician or designee). After 2 dose reductions due to toxicity in prior cycles, should treatment need to be again delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, treatment may need to be discontinued.

6.5.2 Dose-Modification Guidelines for MLN9708

Patients experiencing adverse events attributed to MLN9708 may continue in the study but will have doses of MLN9708 reduced by at least 1 dose level as shown in Table 6-1.

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Grade 4 nonhematologic toxicities will, in general, require that treatment with MLN9708 be permanently discontinued. If, in the opinion of the investigator and the Millennium clinician, it is in the patient's best interest to continue treatment with MLN9708, then the dose of MLN9708 will be reduced by at least 1 dose level in subsequent cycles of treatment after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values. When a dose reduction of MLN9708 is required due to toxicity, no dose re-escalation will be permitted. The investigator and project clinician (or designee) may discuss considerations for dose modifications.

Table 6-1 MLN9708 Dose Adjustments

Dose Level	Dose (mg)
Starting Dose	4.0 mg
-1	3.0 mg
-2	2.3 mg
-3	Discontinue

6.5.2.1 MLN9708 Dose Adjustments for Hematologic Toxicity

Dosage adjustments for hematologic toxicity are outlined in Table 6-2. Note: Dose level reductions should be made in accordance with those outlined in Table 6-1.

Table 6-2 MLN9708 Dose Adjustments for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
If platelet count $\leq 30 \times 10^9$/L or ANC $\leq 0.75 \times 10^9$/L on a MLN9708 dosing day (other than Day 1).	MLN9708 dose should be withheld. Complete blood count (CBC) with differential should be repeated at least weekly or more frequently until the ANC and/or platelet counts have exceeded the prespecified values (see Section 6.5.2). Upon recovery, MLN9708 may be reinitiated and reduced by 1 dose level in accordance with reductions outlined in Table 6-1.
Dose Modifications for Subsequent Treatment Cycles	
Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.5.1: • ANC < 1.0×10^9/L, platelet count < 75×10^9/L. • Or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition.	Hold MLN9708 until resolution per criteria Section 6.5.1. Reduce MLN9708 by 1 dose level as outlined in Table 6-1. The maximum delay before treatment should be discontinued (except in the case of investigator-determined clinical benefit and discussion with the project clinician/designee) should be 3 weeks.
Dose Modifications for Subsequent Treatment	

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Table 6-2 MLN9708 Dose Adjustments for Hematologic Toxicities

Criteria	Action
Cycles	
All hematologic toxicities.	If dose reduced within a cycle and toxicity recovers to meet criteria in Section 6.4.1 at the planned start of the next cycle, maintain that dose at the start of the cycle. If dose was not reduced within a cycle and the next cycle was delayed because of criteria in Section 6.4.1, upon recovery, decrease the dose of MLN9708 by 1 dose level as outlined in Table 6-1 at the start of the cycle.

Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count.

6.5.2.2 MLN9708 Dose Adjustments for Nonhematologic Toxicity

Dosage adjustments for nonhematologic toxicity are outlined in Table 6-3. Note: Dose level reductions should be made in accordance with those outlined in Table 6-1.

Table 6-3 MLN9708 Dose Adjustments for Nonhematologic Toxicities

Criteria	Action	
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	No action	Grade 1 signs & symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only[104]
Worsening Grade 1 peripheral neuropathy (ie, Grade 1 with pain) or Grade 2	Hold study drug until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs & symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)[104]
New or worsening 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 as outlined in Table 6-1	Grade 3 signs & symptoms: severe symptoms; limiting self care ADL; assistive device indicated[104]
New or worsening Grade 4 peripheral neuropathy	Discontinue study drug	
Grade 2 Rash	Symptomatic recommendations as per section 6.10. The investigator and project clinician may discuss considerations for dose modifications and symptom management.	
All Other Grade ≥ 3 Nonhematological Toxicities:	Hold MLN9708 until resolution to Grade < 1 or baseline. Reduce MLN9708 by 1 dose level as outlined in Table 6-1. Note: A dose level reduction will be made either based on within-cycle criteria or for a subsequent cycle criteria, but not for	

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Table 6-3 MLN9708 Dose Adjustments for Nonhematologic Toxicities

Criteria	Action
	both for a same cycle.
Grade 4 Nonhematologic Toxicities (except alopecia)	Consider permanently discontinuing MLN9708. Exception, in the case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee.
Criteria for Retreatment and Cycle Delays	
Both hematologic & nonhematologic recovery required.	Delay therapy × 1 week. Re-evaluate patient; if still not resolved, delay therapy × 1 additional week.
If not resolved:	If initiation of subsequent therapy needs to be delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, the dose of MLN9708 will be reduced by 1 dose level as outlined in Table 6-1 when treatment resumes. The maximum delay before treatment should be discontinued (except in the case of investigator-determined clinical benefit and discussion with the project clinician or designee) will be 3 weeks.

6.5.3 Dexamethasone–Related Treatment Modification

Dosage adjustments for dexamethasone are outlined in Table 6-4. Dexamethasone dose modifications are outlined in Table 6-5. The investigator and project clinician (or designee) may discuss considerations for dose modifications.

Table 6-4 Dose Reduction Steps for Dexamethasone

Permitted Dose Increase +1	Starting Dose 1	Dose Level -1	Dose Level -2	Dose Level -3
40 mg QD	20 mg QD	8 mg QD	4 mg	Discontinue dexamethasone

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Table 6-5 Dexamethasone–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events

Adverse Event (Severity)	Action on Study Drug
Gastrointestinal	
Dyspepsia, gastric, or duodenal ulcer, gastritis Grades 1-2 (requiring medical management)	Treat with histamine-2 blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, decrease dexamethasone by 1 dose reduction as outlined in Table 6-4.
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 as outlined in Table 6-4. 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 as outlined in Table 6-4. 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 as outlined in Table 6-4. If weakness persists despite these measures, decrease dose by 1 dose level as outlined in Table 6-4. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	
Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite these measures, decrease dose by 1 dose level as outlined in Table 6-4 until levels are satisfactory. The investigator and project clinician may discuss considerations for dose modifications.

Source: Package insert for DEXAMETHASONE Tablets USP, DEXAMETHASONE Oral Solution September 2007, Roxane Laboratories, Inc, a division of Boehringer Ingelheim.(105)

6.5.4 Dose Modification for Melphalan

After initiation of melphalan therapy, melphalan dose modification should be based on individual patient treatment tolerance as described in the package insert/SmPC. The investigator and project clinician (or designee) may discuss considerations for dose modifications.

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Table 6-6 Dose Reduction Steps for Melphalan

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3	Dose Level -4
0.22 mg/kg	0.20 mg/kg	0.18 mg/kg	0.15 mg/kg	Discontinue

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

Adverse Event (Severity)		Action on Melphalan
Hematologic: > Grade 3 ANC associated with fever (temperature ≥ 38.5°C) or Grade 4 neutropenia lasting for 7 days	Days 2-14 of cycle	Follow CBC weekly. Next cycle, decrease 1 dose level as outlined in Table 6-6
	Days 15-28 of cycle	Begin melphalan next cycle on schedule at 1 dose level as outlined in Table 6-6 once ANC has recovered to Grade 1 or better.
Thrombocytopenia > Grade 3 (platelet count < 50,000/mm^3) lasting for 7 days	Days 2-14 of cycle	Follow CBC weekly. Next cycle, decrease 1 dose level as outlined in Table 6-6.
	Days 15-28 of cycle	Begin melphalan next cycle on schedule at 1 dose level as outlined in Table 6-6 once platelets have recovered to Grade 2 or better.
Renal function:		
Creatinine clearance 20-40 mL/min after start of treatment		Reduce dose to 0.18-mg/kg of melphalan.
Creatinine clearance < 20 mL/min after start of treatment		Reduce dose to 0.15-mg/kg melphalan.
Nonhematologic > Grade 3, attributable	Days 2-14 of cycle	Next cycle, decrease 1 dose level.
	Days 15-28 of cycle	Begin melphalan next cycle on schedule at 1 dose level lower once recovered to Grade 1 or better.

Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count.

6.5.5 Dose Modification for Cyclophosphamide

After initiation of cyclophosphamide therapy, cyclophosphamide dose modification should be based on individual patient treatment tolerance, as described in the package insert/SmPC.

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Table 6-8 Dose Reduction Steps for Cyclophosphamide

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
500 mg	300 mg	100 mg	Discontinue

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

Adverse Event (Severity)		Action on Cyclophosphamide
Hematologic : > Grade 3 ANC associated with fever (temperature ≥ 38.5°C) or Grade 4 neutropenia lasting for 7 days	Days 2-14 of cycle	Hold. Follow CBC weekly. Next cycle, decrease 1 dose level as outlined in Table 6-8
	Days 15-28 of cycle	Hold. Begin next cycle at 1 dose level lower (giving consideration to any reductions already done within the previous cycle) as outlined in Table 6-6 once ANC has recovered to Grade 1 or better.
Thrombocytopenia > Grade 3 (platelet count < 50,000/mm^3) lasting for 7 days	Days 2-14 of cycle	Hold. Follow CBC weekly. Next cycle, decrease 1 dose level as outlined in Table 6-6.
	Days 15-28 of cycle	Hold. Begin next cycle at 1 dose level lower (giving consideration to any reductions already done within the previous cycle) as outlined in Table 6-6 once platelets recovered to Grade 2 or better.
Genitourinary	Cystitis Grade 1-2	Decrease cyclophosphamide by 1 dose level.
	Cystitis ≥ Grade 3	Discontinue cyclophosphamide for remainder of study cycle.
Nonhematologic > Grade 3, attributable	Days 2-14 of cycle	Hold. Next cycle, decrease by 1 dose level as outlined in Table 6-6.
	Days 15-28 of cycle	Hold. Begin next cycle at 1 dose level lower (giving consideration to any reductions already done within the previous cycle) as outlined in Table 6-6 once recovered to Grade 1 or better.

Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count.

6.5.6 Dose Modification for Thalidomide

After initiation of thalidomide therapy, thalidomide dose modification should be based on individual patient treatment tolerance, as described in the package insert/SmPC. The investigator and project clinician (or designee) may discuss considerations for dose modifications.

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Table 6-10 Thalidomide–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events

Adverse Event (Severity)		Action on Thalidomide
Hematologic: Grade 3 ANC associated with fever (temperature ≥ 38.5°C) or Grade 3 neutropenia (ANC < 750/mcL)	Days 2-14 of cycle	Hold. Follow CBC weekly. Restart within cycle with a decrease by 50 mg/day once ANC recovered to Grade 1 or better. Continue this dose into next cycle.
	Days 15-28 of cycle	Hold. Begin next cycle on schedule and decrease dose by 50 mg/day once ANC has recovered to Grade 1 or better giving consideration to any reductions already done within the cycle.
Thrombocytopenia > Grade 3 (platelet count < 50,000/mm^3)	Days 2-14 of cycle	Hold. Follow CBC weekly. Restart within cycle with a dose decrease of 50 mg/day once ANC recovered to Grade 1 or better. Continue this dose into next cycle.
	Days 15-28 of cycle	Hold. Begin next cycle on schedule and decrease dose by 50 mg/day once platelets recovered to Grade 2 or better, giving consideration to any reductions already done within the cycle.
Other hematologic toxicity, attributable		Hold treatment and restart at a dose 50 mg/day below previous one when toxicity has resolved to ≤Grade 2.
Grade 4		Consider discontinuing.
Hypersensitivity (eg, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis)	Grade 2-3 skin rash	Interrupt until resolved.
	Grade 4 rash, angioedema, exfoliative or bullous rash or SJS or TEN	Discontinue thalidomide.
Drowsiness/somnolence ≥ Grade 2		Hold treatment and restart at a dose 50 mg/day below previous when toxicity has resolved to ≤ Grade 1 or to patient's baseline.
Dizziness, syncope, or orthostatic hypotension ≥ Grade 3		Hold treatment and restart at a dose 50 mg/day below previous when toxicity has resolved to ≤ Grade 1 or to patient's baseline.
Constipation ≥ Grade 2		Hold treatment and restart at a dose 50 mg/day below previous when toxicity has resolved to ≤ Grade 1 or to patient's baseline.
Peripheral Neuropathy ≥ Grade 2		Hold treatment and restart at a dose 50 mg/day below previous when toxicity has resolved to ≤Grade 1 or to patient's baseline.
Nonhematologic Grade 3, attributable	Days 2-14 of cycle	Hold treatment until recovery to ≤ Grade 1 or baseline, and restart at a dose 50 mg/day below previous.
Grade 4, attributable	Days 15-28 of cycle	Hold treatment. Begin next cycle on schedule at a dose of 50 mg/day below previous once recovered to Grade 1 or better.
		Consider discontinuing thalidomide.

Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

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6.5.7 Dose Modification for Lenalidomide

After initiation of lenalidomide therapy, lenalidomide dose modification should be based on individual patient treatment tolerance, as described in the package insert/SmPC. The investigator and project clinician (or designee) may discuss considerations for dose modifications.

Table 6-11 Dose Reduction Steps for Lenalidomide

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
15 mg	10 mg	5 mg	Discontinue

Because lenalidomide is primarily excreted unchanged by the kidney, adjustments to the initial dose of lenalidomide are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. See package insert/SmPC for details.

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Table 6-12 Lenalidomide–Related Treatment Modification (Delays, Reductions, and Discontinuations) Guidelines Due to Adverse Events

Adverse Event (Severity)		Action on Lenalidomide
Hematologic: Platelets	Fall to < 30,000/mcL	Interrupt lenalidomide; Follow CBC weekly.
	Return to ≥ 30,000/mcL	Restart lenalidomide, decrease 5 mg less than previous dose. Do not dose below 5 mg daily.
	For each subsequent drop < 30,000/mcL	Interrupt lenalidomide treat; upon recovery to ≥ 30,000/mcL. Resume at 5 mg less than previous dose. Do not dose below 5 mg daily.
Hematologic: ANC	Fall to < 1000/mcL lasting for 7 days	Interrupt lenalidomide treatment, add G-CSF, follow CBC weekly. With return to ≥ 1000/mcL and neutropenia is the only toxicity: resume lenalidomide at previous dose.
	Return to ≥ 1000/mcL and if other toxicity	Resume lenalidomide at 5 mg less than previous dose. Do not dose below 5 mg daily.
	For each subsequent drop < 1000/mcL	Interrupt lenalidomide treatment. Return to ≥ 1000/mcL. Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily.
Other Grade 3/4 hematologic toxicity		Hold treatment and restart at next lower dose level as outlined in Table 6-11 when toxicity has resolved to ≤Grade 2.
Hypersensitivity (eg, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis)	Grade 2-3 skin rash	Interrupt until resolved
	Grade 4 rash, angioedema, exfoliative or bullous rash or SJS or TEN	Discontinue lenalidomide
Nonhematologic ≥ Grade 3	Days 2-14 of cycle	Next cycle, decrease 1 dose level as outlined in Table 6-11.
	Days 15-28 of cycle	Begin next cycle on schedule at 1 dose level lower as outlined in Table 6-11 once recovered to Grade 1 or better.

Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

6.6 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Angiotensin converting enzyme (ACE) inhibitors should be used with caution and their use requires consultation with the Millennium clinician or designee. Patients with AL amyloidosis usually poorly tolerate ACE inhibitors not due to possible interaction with MLN9708, but because of symptomatic hypotension due to an

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underlying involvement of the autonomic nervous system. Therefore, ACE inhibitors should be excluded in patients with eGFR < 60 mL/min and in those whom orthostatic systolic blood pressure is < 100 mmHg.

- 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. The rationale for this (unlike with inhibitors) is that in the event of a drug-drug interaction with a strong inducer, MLN9708 exposure would be decreased.

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

    - Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba

The following procedures are prohibited during the study:

- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)

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

6.7 Permitted Concomitant Medications and Procedures

All necessary supportive care consistent with optimal patient care shall be available to patients as necessary. All blood products and concomitant medications received from the first day of study treatment administration until 30 days after the final dose will be recorded in the CRFs.

The following are examples of those permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.

- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.

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- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Millennium project clinician or designee. Granulocyte stimulating factors should be used in this patient population with caution given risk for fluid retention.

- Patients should be transfused with red cells and platelets as clinically indicated according to institutional guidelines.

- Antiviral therapy such as acyclovir may be administered if medically appropriate.

- DVT/pulmonary embolism (for patients receiving thalidomide or lenalidomide). Prophylactic anticoagulation is permitted according to published guidelines. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

- Concomitant treatment with bisphosphonates will be permitted.

- Patients who experience worsening neuropathy from baseline may be observed for recovery, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

Standard amyloid supportive guidelines that should be considered include:

- Patients who experience fluid retention or CHF may be treated with intravenous diuretics.

- Patients who experience life-threatening ventricular arrhythmias or atrial arrhythmias with hemodynamic instability should be treated according to standard clinical practice guidelines.

- Compression garments and midodrine for patients with symptomatic orthostasis.

6.8 Precautions and Restrictions

- Fluid deficits should be corrected before initiation of treatment.

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- Nonsteroidal anti-inflammatory drugs (NSAIDs) induced prevalence of nephrotoxicity is relatively low; however, given the wide use of these agents many persons are at risk, including for example, patients with cardio-renal disease, dehydration, and the aging kidney. NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

6.9 Contraception Requirements

Patients treated with IMiDs must adhere to the contraceptive and pregnancy testing guidelines of the appropriate IMiD (thalidomide or lenalidomide) safety management program (eg, pregnancy testing in female patients of child-bearing age prior to each cycle).

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

Female patients must meet 1 of the following criteria:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, AND
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

6.10 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with MLN9708 treatment. Management guidelines regarding these events are outlined below. Further details of management of MLN9708 AEs are described in Section 6 of the MLN9708 IB. Please refer to the appropriate package insert/SmPC for information relating to adverse events related to melphalan, cyclophosphamide, thalidomide, lenalidomide, and dexamethasone.

Prophylaxis Against Risk of Reactivation of Herpes Infection

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

Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once

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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

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

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 $\leq$ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of MLN9708 (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

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

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. MLN9708 administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 6.5). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form

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in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. MLN9708 administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Section 6.5). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

Fluid Deficit

Dehydration should be avoided since MLN9708 may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with MLN9708, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration (see Section 6.5).

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 anorexia. 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, 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-

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directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study patient, at a dose above that which is assigned to that individual patient 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

This is an open-label study; investigators and patients will know the individual treatment assignments.

6.12 Description of Investigational Agents

MLN9708 Capsules

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

The 3 different dose strengths are differentiated by both capsule size and color as described in Table 6-13:

Table 6-13 MLN9708 Capsules

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light Gray
2.3 mg	Size 2	Light Pink

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

6.12.1 MLN9708 Preparation, Reconstitution, and Dispensation

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

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

6.12.2 MLN9708 Packaging and Labeling

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

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

6.12.3 MLN9708 Storage, Handling, and Accountability

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

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

Because MLN9708 is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken

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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 MLN9708, including that MLN9708 is to be taken as intact capsules.

Please refer to the Pharmacy Manual for additional instructions.

6.12.3.1 Dexamethasone

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

6.12.3.2 Melphalan

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

6.12.3.3 Cyclophosphamide

Cyclophosphamide is a standard agent. Cyclophosphamide may be supplied by the sponsor or sourced locally by the clinical sites when arrangements have been made and agreed to by Millennium and the clinical site and when regulations allow for clinical site sourcing,

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appropriate labeling, and compliance with local and regional regulations. Additional details are provided in the package insert/SmPC.

6.12.3.4 Thalidomide

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

6.12.3.5 Lenalidomide

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

6.12.4 Other Protocol-Specified Materials

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

7. STUDY CONDUCT

7.1 Study Personnel and Organizations

The contact information for the Millennium clinician or designee for this study, the central laboratory(ies) and any additional laboratories, the coordinating investigator for each member state/country, and a full list of investigators will be available in the sponsor's or designee's database.

7.2 Arrangements for Recruitment of Patients

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

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7.3 Treatment Group Assignments

All patients who meet the inclusion and exclusion criteria will be stratified (as detailed in Section 4.1) and then randomized in a 1:1 ratio. Before randomization, physicians will declare which standard available regimen from the list of options they would select for each enrolling patient. The physician's selection will be collected and recorded in the database. Patients will then be randomized between dexamethasone plus MLN9708 (Arm A) or the Physician's Choice arm (Arm B) in a 1:1 fashion. If the patient is randomized to the Physician's Choice arm, the patient should receive the regimen initially selected by the physician. The procedures for enrollment using the IVRS system are described in the Study Manual. Patients should begin therapy within 7 business days after randomization.

7.4 Study Procedures

Patients are being evaluated at scheduled visits over 4 study periods: Screening, Treatment, End of Treatment (EOT), and Follow-Up (PFS and OS). The first IA was conducted (data cut-off date 20 February 2019) and the primary endpoint of overall hematologic response rate (complete response [CR] + very good partial response [VGPR] + partial response [PR]) did not reach statistical significance. However, the primary endpoint of hematologic response was not met at the first IA. However, patients in both treatment arms appeared to receive benefit. In light of the primary endpoint not being met, the sponsor has decided to remove the planned second IA and FA and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients. Ixazomib (MLN9708) and control drugs (if Takeda has been supplying them) will continue to be provided for patients who continue to derive benefit. Patients will not be followed for the PFS or OS follow-up periods, as PFS and OS are no longer being collected. Ixazomib (MLN9708) and control drugs (if Takeda has been supplying them) will continue to be provided for patients who continue to derive benefit.

Refer to the Schedule of Events for the timing of study procedures. (Note that for Amendment 6, for ease of study conduct, the Schedule of Events has been simplified to apply only to the remainder of the study. The full Schedule of Events as of global Amendment 4 has been moved to Section 15.11.) Tests and procedures should be done on schedule, but visit windows are allowed as follows: All baseline evaluations/procedures are to be conducted at Cycle 1, Day 1 (C1D1) before dosing or within 3 days before the first dose of drug unless otherwise specified. Evaluations/procedures for subsequent cycles (CXD1) are to be conducted within 3 days before the drug dosing unless otherwise

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specified. Occasional changes are allowable (± 3 days) for holidays and other administrative reasons and (± 1 week) for vacations. If the study schedule is shifted, then both assessment and dosing schedules should be shifted accordingly to ensure that collection of assessments is completed prior to dosing. The cycle of therapy begins with the first dose of study drug. See Section 6.1 for corresponding dosing schedule.

Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Informed consent must be obtained before any study-specific procedures for research purposes are performed.

7.4.2 Patient Demographics

The age, 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. A complete medical history is to be obtained, including AL amyloidosis diagnosis, staging (cardiac biomarkers and NYHA classification), AL amyloidosis organ involvement, treatment history, neurologic medical history, and cardiac medical history. The history should include a review of all current medications and the patient's 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. A neurologic exam is to be conducted as part of the symptom-directed physical exam. Assessment of AL amyloidosis symptoms will be conducted at the time points specified in the Schedule of Events.

7.4.5 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (see Section 15.8) at the time points specified in the Schedule of Events.

7.4.6 Vital Signs, Body Weight and Height

Measurement of vital signs will include temperature, blood pressure, and heart rate. Consideration should be given to determining orthostatic hypotension in patients with

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amyloid nerve involvement or those who might have become volume depleted or experienced dizziness or syncope.

Body weight and height will be determined at the Screening visit and the time points specified in the Schedule of Events. Height will be measured at the Screening visit only.

7.4.7 Pregnancy Test

A serum pregnancy test will be performed for all women of childbearing potential at the Screening visit and the time points specified in the Schedule of Events and as required by any treatment-specific pregnancy prevention programs, if applicable. Patients treated with IMiDs must adhere to the contraceptive and pregnancy testing guidelines of the appropriate IMiD (thalidomide or lenalidomide) safety management program (eg, pregnancy testing in female patients of child-bearing age prior to each cycle).

The Cycle 1, Day 1 pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the first dose.

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 Schedule of Events. It may be repeated as clinically indicated during the study at the discretion of the investigator. ECG data to be obtain include intervals RR, PR, QRS, QT, and QTc and waveforms.

7.4.9 Clinical Laboratory Evaluations

Handling of central clinical laboratory samples will be outlined in the Study Manual. For dosing decisions, local hematology and chemistry laboratory results may be used. Hematology and chemistry panels may be collected up to 3 days before Day 1 dosing, and 24 hours before Day 15 dosing (see Schedule of Events for details). Laboratory tests may be done more frequently at the investigator's discretion. Criteria for retreatment are provided in Section 6.5.1.

Per Amendment 6, centralized clinical laboratory evaluations of efficacy and safety will no longer be performed. Local laboratory evaluations should be entered into the eCRF only if required to understand a TEAE. For dosing decisions, response assessment, and all other

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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.

Clinical Chemistry and Hematology

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

Hematology

- Hemoglobin
- Hematocrit
- Platelet count
- WBC count with differential

Serum Chemistry

- Blood Urea Nitrogen (BUN)
- Creatinine
- Total bilirubin
- Uric acid
- Lactate dehydrogenase
- Alkaline phosphatase
- AST
- ALT
- Albumin
- Glucose
- Sodium
- Potassium
- Chloride
- CO_2
- Magnesium
- Calcium
- Phosphate
- PT

Urinalysis

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

24-Hour Urine Collection

- Total protein
- Creatinine

Other

- Cardiac Markers:
  BNP, NT-ProBNP, and troponin T (site may perform troponin I locally, but troponin T is required for the protocol)
- β2-Microglobulin

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7.4.10 Quality of Life Assessments

The FACT/GOG-Ntx (Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity [FACT/GOG-Ntx]; Section 15.4) comprises 11 individual items evaluating symptoms of neurotoxicity on a scale of 0 (not at all) to 4 (very much). It will be completed by the patient at screening and at the time points specified in the Schedule of Events.

SF-36 v2 is a multipurpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. Physical component summary (PCS) is mostly contributed by physical function (PF), role physical (RP), bodily pain (BP), and general health (GH). Mental component summary (MCS) is mostly contributed by mental health (MH), role emotional (RE), social function (SF), and vitality (VT). It will be completed by the patient at screening and at the time points specified in the Schedule of Events.

The symptom scale questionnaire contains 3 items, each rated on an 11-point numerical rating scale of symptom severity. Items were generated from published literature, clinical experts, and amyloidosis patients. The psychometric properties of the measure will be evaluated using the clinical trial data. The questionnaire yields individual symptom scores.

The patient-reported symptom questionnaire (see Section 15.5) will be completed by the patient at screening and the time points specified in the Schedule of Events. The symptom questionnaire is to be completed before other assessments are performed or study drug is administered.

Upon implementation of Amendment 6, QOL assessments will no longer be collected.

7.4.11 Health Utilization

During the treatment and the follow-up portions of the study, 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 of medical care encounters, such as inpatient/outpatient admissions, homecare, time of work loss, etc.

Upon implementation of Amendment 6, Health Utilization assessments will no longer be collected.

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7.4.12 EQ-5D

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, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ visual analogue scale (VAS) records the respondent's self-rated health on a 20-cm vertical VAS that ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

The EQ-5D will be completed by the patient at screening and at the time points specified in the Schedule of Events.

Upon implementation of Amendment 6, the EQ-5D will no longer be collected.

7.4.13 Disease Assessments

Patients with AL amyloidosis not only have a hematologic malignancy, but also progressive dysfunction of 1 or more organs. The primary determinant of response for continuing treatment is the hematologic response as defined by dFLC according to published criteria.[20, 34, 36] A bone marrow aspirate and/or core biopsy are to be obtained at the Screening visit, and may be repeated at the discretion of the investigator as clinically indicated. Immunohistochemistry of dominant clonal plasma cells is recommended.

The clinical laboratory tests and imaging for hematologic and organ response/progression will be analyzed/read at a central laboratory. The investigator will evaluate each patient for response to therapy according to the response criteria presented in Section 15.10 (only 1 parameter is required to satisfy the organ response criteria). At each staging evaluation, response will be assessed relative to baseline.

Upon implementation of Amendment 6, disease assessment for progressive disease will no longer be confirmed by the CRO Medical Monitor or Takeda Medical Monitor designee. Disease assessment will be performed and assessed by the investigator, according to standard of care treatment.

7.4.13.1 Hematologic Disease Assessments

The response assessments will be performed at screening and at the time points specified in the Schedule of Events. The tests for hematologic response/progression will be conducted at

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a central laboratory. Upon implementation of Amendment 6, the tests for hematologic response/progression will be conducted at a local laboratory.

Quantitative Immunoglobulins, Serum M-protein, Urine M-protein, and Serum Free Light Chains

Serum specimens will be analyzed for quantitative immunoglobulins at screening, and if needed at the time points specified in the Schedule of Events.

Analysis for serum and urine M-protein and immunofixation is to be performed at screening and at the time points specified in the Schedule of Events. Serum and urine immunofixation must be repeated if CR is documented by other criteria.

Serum free light chain assay, ratio, and difference between involved and uninvolved (dFLC) is to be performed at screening and at the time points specified in the Schedule of Events. If the patient comes off treatment, but has not yet progressed, the dFLC assay should be conducted every 6 weeks until disease progression. An abnormal kappa-lambda FLC ratio (normal range 0.26-1.65) indicates an excess of 1 light chain type versus the other, and thus indicating clonal expansion. The excess monoclonal light chain isotype is considered the involved FLC isotype and the opposite light chain type as the uninvolved FLC type. The definition of hematologic response to treatment is based on the difference between the concentration of amyloid forming light chains (involved) and uninvolved free light chain (dFLC). To be measurable, dFLC must be at least 50 mg/L.[68]

Upon implementation of Amendment 6, all central laboratory and investigator assessments of response and progression for protocol purposes are discontinued. Disease assessment will be performed and assessed by the investigator, according to standard of care treatment.

7.4.13.2 Amyloid-Related Organ Assessments

The extent of amyloid-related organ involvement according to standard criteria (see Section 15.10) is to be performed for all patients at screening and at the time points specified in the Schedule of Events. Eligible patients must have objective measurable involvement of at least 1 major (heart or kidney) organ. Organ involvement of additional organ system is allowed, as defined in Section 15.10.

The clinical laboratory tests and imaging for major (heart or kidney) organ response/progression will be analyzed/read at a central laboratory/imaging center. At each staging evaluation, the organ involvement will be assessed according to standard criteria

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(see Section 15.10) as response, no change, or progressed based on the characteristics of their disease at study entry.[20, 34, 36]

Disease assessments include relevant AEs and patient-reported symptoms, physical findings, and special laboratory tests for individual organ sites. In addition, radiographic, CT, MRI, and ultrasound techniques may be performed as indicated to assess organ involvement. In some cases, tissue sampling may be necessary.

The following procedures/tests should be included at a minimum to assess amyloid-related organ involvement. If clinically indicated, additional assessments may be performed at the discretion of the investigator.[18, 20, 34, 36, 68]

Heart: NT-proBNP, troponin-T, echocardiography, physical examination

- Echocardiogram to estimate mean left ventricular wall thickness and LVEF
- NYHA criteria assessment (Section 15.6)
- Cardiac troponin T is required and will be conducted at the central laboratory; however, troponin I may be done at the site at the physician's discretion
- BNP may be analyzed but is not specific to the organ response criteria.

Kidney: 24-hour urine proteinuria, serum creatinine, serum albumin, and calculated creatinine clearance. eGFR will also be calculated.

Evaluation and special testing based on other organ system involvement (see Section 15.10) may include:

Liver: alkaline phosphatase, CT scan/MRI (ultrasound if indicated). Serum albumin, prothrombin time, and ALT will be assessed as part of overall organ function, but are not specific to the organ response criteria.

Peripheral nervous system: patient reported symptoms, physical examination and neurologic assessment by an investigator, nerve conduction studies or EMG (if indicated for clinically significant peripheral neuropathy)

Autonomic nervous system: patient reported symptoms, determination of postural hypotension

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Soft tissue: physical examination, imaging as indicated

GI tract: physical findings, stool guaiacs or other special testing based on patient symptomatology as needed.

Lung: physical examination and radiographic changes usually by CT scan

Cardiac Assessments

Cardiac assessments are to be performed for all patients as outlined in the Schedule of Events.

Detailed cardiac evaluations are planned. The assessments include, but are not limited to:

- Relevant AEs and clinical findings, such as dyspnea, fluid retention, fatigue, and CHF
- Hospitalization
- Cardiac markers (NT-proBNP and troponin T [required; central laboratory]). Cardiac troponin I may be done at local hospital for investigator information
- Blood pressure
- NYHA classification determination (see Section 15.6)
- Cardiac Risk Assessment Staging

Table 7-1 Cardiac Risk Assessment Staging System

Stage	Criteria: Threshold Levels NTpro-BNP < 332 pg/mL and Troponin T< 0.035 ng/mL
1	Both troponin or NT-proBNP under threshold
2	Either troponin or NT-proBNP (but not both)over threshold
3	Both troponin or NT-proBNP over threshold NOTE: To be eligible NT-proBNP must be < 8000 pg/mL at study entry

Source: Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. Journal of Clinical Oncology 2004;22(18):3751-7. [97]

Abbreviations: NT-pro BNP = N-terminal pro-brain natriuretic peptide.

If troponin T is not available at local institution, troponin I may be used, but threshold is < 0.1 µg/mL.

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- In the setting of sustained hematologic response, but with an increase in NT-proBNP that is both >30% and >300 pg/mL, the following criteria will be used to confirm heart progression:

    - Echo: interventricular septal thickness increased by 2 mm over baseline, or

    - An increase in NYHA class by 1 grade with decreasing LVEF of >10%

- Echocardiogram at screening and at the time points specified in the Schedule of Events. The following data may be collected: 2D-guided M-Mode (wall thickness and chamber diameters), short-axis, long-axis, apical 4-chamber and 2-chamber video clips (5 beats each), transmitral, transaortic, transtricuspidal, and pulmonary vein Doppler studies, mitral and tricuspidal annulus longitudinal excursion, and tissue Doppler imaging for systolic and diastolic wall velocities. Strain and strain rate analyses may also be analyzed off-line from the short-axis and 4-chamber video clips at the discretion of the investigator.

Note: Mean left ventricular wall thickness is derived as the mean of the end diastolic ventricular septal wall (IVS) thickness + end diastolic posterior wall (PW) thickness.

Note: If CT or MRI cardiac assessments are clinically indicated, then a record of the findings will be made.

Renal Assessments

- 24-hour urine collection (total protein, calculated creatinine clearance, M-protein quantification, and immunofixation)
- eGFR assessment
- Serum creatinine
- Serum albumin
- Hospitalization
- Dialysis

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- Transplant

Renal assessments are to be performed in all patients as outlined in the Schedule of Events.

Special Testing Based on Patient's Other Organ System Involvement at Study Entry:

Hepatic Assessments

- Alkaline phosphatase
- CT or MRI scan
- Clinical examination, or
- Abdominal ultrasound at the discretion of the investigator if clinically indicated
- Assessment of hepatomegaly according to standard criteria if clinically indicated
- Hepatic assessments are to be performed in all patients as outlined in the Schedule of Events. The same evaluation (physical examination or radiography [and the same imaging modality]) must be used consistently in individual patients throughout the study for all follow-up assessments.

Neurologic Assessments

Assessments are to be performed as outlined in the Schedule of Events based on the involvement and characteristics of the patient's disease at study entry.

- Patient-reported gastrointestinal and neurologic symptoms
- Clinical examination
- Neurologic examination by the patient's investigator, including sensory and/or motor findings
- Detection and measures of postural hypotension
- Nerve conduction studies, if indicated (including EMG, if necessary)

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Soft Tissue or Lymph Node Assessments

Assessments are to be performed as outlined in the Schedule of Events based on the involvement and characteristics of the patient's disease at study entry.

- CT or MRI scans at the discretion of the investigator as clinically indicated. The same imaging modality used at screening (CT/MRI) should be used for all follow-up assessments
- Recording of any abnormalities on physical examination
- Patient reported symptoms

Gastrointestinal Tract Assessments

- Assessments are to be performed as outlined in the Schedule of Events based on the involvement and characteristics of the patient's disease at study entry.
- Recording of any abnormalities on physical examination
- Patient reported symptoms, ie, reduction of diarrhea

Upon implementation of Amendment 6, all amyloid-related organ assessments for protocol purposes are discontinued.

7.4.14 Pharmacokinetic Measurements (Arm A Only)

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 PK samples are provided in the Study Manual. The sampling scheme is indicated in the Pharmacokinetic Sampling Schedule immediately following the Schedule of Events.

Blood samples (3 mL) for the determination of plasma concentrations of MLN2238 will be collected during Cycles 1 through 10. Blood samples are to be collected at the time points specified in the Schedule of Events aligning with the dosing schedule if an occasional change has been made for holidays, vacations, and other administrative reasons (see Section 6).

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Upon implementation of Amendment 6, blood samples for PK measurements will no longer be collected.

7.4.15 Concomitant Medications and Procedures

Concomitant medications and therapy will be recorded as specified in 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.

Upon implementation of Amendment 6, concomitant medications and procedures will not be recorded in the eCRF.

7.4.16 Adverse Events

Monitoring of AEs, both nonserious and serious, will be conducted throughout the study as specified in the Schedule of Events. Upon implementation of this amendment, data collection requirements will be limited to the following safety assessments: all SAEs (regardless of causality, including all deaths), any AE resulting in dose modification or discontinuation of any study drug, Grade ≥3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose).

See Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

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

7.4.17 Follow-Up Assessments (PFS and OS)

Patients who do not develop PD will continue to have progression-free follow-up visits. The hematologic PFS follow-up should occur every 6 weeks from the EOT visit until the occurrence of progression or the start of subsequent anticancer therapy. The amyloid-organ PFS follow up should occur every 12 weeks from the EOT visit until the occurrence of progression or the start of subsequent anticancer therapy. During these follow-up periods, data will be collected regarding hospitalizations, development of CHF, and progression to

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ESRD requiring maintenance dialysis or renal transplantation. Refer to the Schedule of Events and Section 7.4.13 for appropriate assessments.

After the occurrence of PD or the initiation of subsequent anticancer therapy, patients will continue to have OS follow-up visits. The OS follow-up visits should be conducted every 12 weeks after documented PD. Data may be collected by methods that include, but are not limited to, telephone, e-mail, mail, and social security indexes. During these follow-up periods, data will be collected regarding hospitalizations, development of CHF, and progression to ESRD requiring maintenance dialysis or renal transplantation. See the Schedule of Events for appropriate assessments. The duration of follow-up for OS will be at least 2 years after the last patient enters OS follow-up.

Upon implementation of Amendment 6, patients will no longer be followed during any of the follow-up periods, as PFS and OS are not being collected.

7.5 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients will be given a diary to record study drug dosing. The appropriate study personnel will maintain records of study drug receipt and dispensing. The dosing diary will provide supporting information, if necessary.

Compliance regarding adherence to study visit schedule and sharing of medical information is important throughout the duration of the study. Various measures of contact utilized will include but are not limited to clinic visits, telephone calls, e-mail contact, contact of family/significant other, and contact with referring physicians will be utilized by site staff to obtain medical information important to the study endpoints. The sponsor and/or its designees will work with site investigators and study staff to manage follow-up visit reminders, to stress the importance of patient retention and to obtain data points key to the study endpoints.

7.6 Discontinuation of Treatment With Study Drug, and Patient Replacement

Treatment with study drug must be discontinued for pregnancy. Treatment may be discontinued permanently if any of the other following criteria are met:

- AE (including SAE)
- Protocol violation

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- Study terminated by sponsor
- Withdrawal by patient
- Lost to follow-up
- PD
- Initiation of subsequent therapies (including initiation of hematopoietic stem cell transplant)
- Symptomatic deterioration
- Pregnancy (patient must be discontinued)
- Other

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

7.7 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
- Initiation of hematopoietic stem cell transplant
- Other

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

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8. STATISTICAL AND QUANTITATIVE ANALYSES

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.

The SAP will be written by Millennium and will be finalized before any formal 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.

The first IA has been performed (data cut-off date: 20 February 2019) and the primary endpoint of hematologic response was not met. Therefore, the sponsor has decided not to conduct any subsequent formal statistical analyses. The analysis of efficacy and safety has been completed on data from the first IA. As of this decision, no additional patients will be enrolled in the study and the number of study patients is reduced from 248 to 176 (note that 8 patients had not completed a minimum of 6 cycles of treatment or discontinued before the data cut-off date required for inclusion in the IA). Minimal descriptive analyses will be done on patient data collected after the first IA. The description of statistical methods presented below reflects the original design of the study so to retain the statistical considerations up to the first IA.

8.1.1 Determination of Sample Size

Two primary endpoints, hematological response and 2-year vital organ deterioration and mortality rate, along with key secondary endpoints of OS and complete hematologic response rate, will be sequentially tested in this study.

The total sample size was calculated based on maintaining 80% power to test the OS key secondary endpoint. There are 2 planned IAs and 1 FA. The study is also adequately powered to test both primary endpoints: hematologic response rate and 2-year vital organ deterioration and mortality rate.

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Assuming a hazard ratio of 0.625 (median survival of 26 months in control arm versus 41.6 months in the active arm), the number of events needed was 145 (80% power and 2-sided alpha of 0.05). A total of approximately 248 patients will need to be randomized in a 1:1 ratio into those 2 arms, assuming an average enrollment rate of 3 patients for the first 5 months, approximately 3 to 5 patients per month thereafter, and an additional 28 months follow up for all patients after last patient is enrolled, and approximately 10% drop out rate. The FA of OS is estimated to occur approximately 112 months from the enrollment of first patient. This period includes an approximate 84 months accrual period and 28 months follow-up period.

The first IA was performed when 168 patients enrolled had the opportunity to complete 6 cycles of treatment or discontinue treatment before receiving 6 cycles of treatment. This was the FA for hematological response. To maintain the overall strong control of Type I error rate at a 2-sided alpha level of 0.05, hematological response and organ deterioration and mortality rate was tested sequentially at the first and second IA using the fall-back approach to adjust for multiple testing. At the first IA, hematologic response was tested at a 2-sided alpha level of 0.04. With 176 patients as the planned sample size for the first IA, the hematological response endpoint was powered at 90% at a 2-sided alpha level of 0.04 with the assumption of 40% response rate in the control arm and 65% response rate in the MLN9708 arm. If the test was statistically significant, the study was to continue to test 2-year vital organ deterioration and mortality rate at a 2-sided alpha of 0.05; otherwise 2-year vital organ deterioration and mortality rate will be tested at the second IA with a 2-sided alpha of 0.01. The primary endpoint was not met at the first IA and the sponsor has decided not to conduct the second IA. If the second IA had been conducted, below would have been the steps for the IA and the justification for the sample size for the second IA.

The second IA was originally planned to be performed when approximately 218 patients enrolled have had the opportunity to complete 2 years of treatment or to be followed up for at least 2 years if discontinuing treatment before receiving 2 years of treatment. This will be the FA for 2-year vital organ deterioration and mortality rate. With a statistically significant response for the primary endpoint at the first IA, the endpoint of 2-year vital organ deterioration and mortality rate is powered at 90% at a 2-sided alpha level of 0.05 with the assumption of 80% deterioration and mortality rate in the control arm and 60% rate in the MLN9708 arm. If the test for the primary endpoint at the first IA is not significant, the endpoint of 2-year vital organ deterioration and mortality rate is powered at 74% at a 2-sided alpha level of 0.01. If the test for 2-year vital organ deterioration and mortality rate is not

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significant, the study will continue to FA without any formal testing; otherwise, OS will be tested with the total alpha to be the same as testing the 2-year vital organ deterioration and mortality rate. If the test for OS is statistically significant, the complete hematologic response rate will be tested at the same alpha level as that for OS and the study may be stopped for evidence of efficacy; if the test for OS is not statistically significant, the study will continue to the FA to test OS again.

The O'Brien and Fleming stopping boundary (the Lan-DeMets method) will be used to assign alpha level to the second IA and FA on OS.

8.1.2 Randomization and Stratification

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

Eligible patients will be randomized in a 1:1 ratio into 1 of the 2 two treatment arms, stratified by: 1) Cardiac Risk Stage: 1 versus 2 versus subgroup Cardiac Risk Stage 3 (ie, both NT-proBNP and troponin T over threshold [but NT-proBNP < 8000 pg/mL]); 2) relapsed versus refractory; and 3: proteasome inhibitor naïve versus exposed.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

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.

Hematologic Response-Evaluable population: The hematologic response-evaluable population is defined as patients who have measurable disease at baseline, who receive at least 1 dose of any study treatment, and have at least 1 postbaseline hematologic response assessed by an AC.

Safety population: The safety population is defined as all patients who receive at least 1 dose of any study treatment. Patients will be analyzed according to the treatment actually received.

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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. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified. For patient reported outcomes data, primarily missing data imputation will be based on published instrument specific methods. Other missing data imputation method such as Last Observation Carry Forward (LOCF), random slope model, and pattern mixture model may be explored as sensitivity analyses for patient reported outcomes data.

For the hematologic response rate, a missing value is defined as no post-baseline hematologic response assessment due to either lost to follow-up or withdrawal by patient. In the primary analysis, if the hematologic response assessment in either arm is missing upon comparison of hematologic response rates, it will be counted as a failure (non-responder) instead of a missing value.

For the 2-year organ deterioration and mortality rate, a missing value is defined as no documented vital organ deterioration or death event within the first 2 years and no further information available regarding vital organ deterioration or death event on or after 2-years from the date of first dosing of the study drug [Arm A] or standard drug [Arm B]. If there is any vital organ (heart or kidney) deterioration or death event within the first 2 years during the study, whichever occurred first, this event will be counted as one event at 2-year time point. In addition, at the time for the analysis, all patients will have the opportunity to be followed up for a minimum of 2-years. In the primary analysis, if the 2-year vital organ deterioration assessment or death information is missing in either arm, it will be counted as a failure instead of a missing value; that is, patient who has a missing event will be counted as an event towards vital organ deterioration or death.

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, sex, race, weight, baseline disease characteristics, and other parameters, as appropriate.

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8.1.6 Efficacy Analysis

8.1.6.1 Analyses of Primary Efficacy Endpoints

There are 2 primary efficacy endpoints: hematologic response and 2-year vital organ deterioration and mortality rate.

Hematologic Response

Hematologic response rate is defined as the proportion of patients who achieved PR or better relative to ITT population according to central laboratory results and ISA criteria as evaluated by an AC. The unstratified Cochran-Mantel-Haenszel (CMH) test will be used to compare hematologic response rate 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.

2-year Vital Organ Deterioration and Mortality Rate

Cardiac deterioration is defined as the need for hospitalization for heart failure. Kidney deterioration is defined as progression to ESRD with the need for maintenance dialysis or renal transplantation. Vital organ deterioration will be assessed by an AC.

A patient enrolled in either arm of the study will be counted as a failure instead of a missing value if the 2-year vital organ deterioration assessment or death information is missing for the primary analysis upon comparison 2-year vital organ deterioration and mortality rates.

The unstratified CMH test will be used to make comparisons between the 2 treatment arms when approximately 218 patients enrolled have had the opportunity to complete 2 years of treatment or to be followed up for at least 2 years if discontinuing treatment before receiving 2 years of treatment. If the 2-year organ deterioration and mortality rate is statistically significantly lower in the dexamethasone plus MLN9708 arm (Arm A) by using the 2-sided CMH test, null hypothesis will be rejected.

A logistic regression model will be used to estimate the treatment effect in terms of odds ratio. The odds ratio and its associated 95% confidence intervals (CIs) will be presented.

Sensitivity Analyses for Primary Endpoints

It is expected that the missing values will be limited and therefore, the primary analysis on both primary endpoints will not be driven by the handling of the missing data. To further

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assess the impact of missing values and potential other factors, a range of sensitivity analyses are proposed as below:

1. Hematologic response and vital organ deterioration assessed by investigator will be analyzed in the ITT population.

2. Stratified CMH method

3. Binomial test with the standard error for the estimated difference in rates adjusted by the number of missing values in each arm (further elaborated in the SAP)

4. Subgroup analyses including the stratification factors, and other baseline prognostic factors to be determined before database lock

In addition, hematologic response assessed by an AC will be analyzed in the hematologic response-evaluable population.

8.1.6.2 Analyses of Key Secondary Efficacy Endpoints

In addition to the primary comparison of hematologic response and 2-year vital organ deterioration and mortality rate, there are 2 key secondary endpoints: OS ; complete hematologic response rate. Key secondary endpoints will be tested sequentially. That is, complete hematologic response rate will be tested at the same alpha level as the OS analysis when the test of OS is statistically significant either at the IA or at the FA. The secondary endpoints will be tested on the ITT population, and the response data will be based on central laboratory results and ISA criteria by an AC. Investigator-assessed response data will be used as sensitivity analysis.

Overall Survival

Overall survival 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. Overall survival 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 second IA and FA is decided by the O'Brien and Fleming alpha spending function. 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

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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.

Complete Hematologic Response Rate

Complete hematologic response rate is defined as the proportion of patients who achieved CR in the ITT population. Complete hematologic response will be assessed by an AC using central laboratory results and ISA criteria.

The complete hematologic response rate will be analyzed using the similar method as hematological response rate.

8.1.6.3 Analyses of Other Secondary Efficacy Endpoints

Other secondary efficacy parameters include PFS, duration of hematologic response, hematologic disease PFS, time to vital organ deterioration or death, vital organ response, vital organ PFS, TTF, and time to subsequent anticancer therapy. These endpoints will be tested on the ITT population and the data will be based on central laboratory results and ISA criteria by an AC.

PFS

Progression-free disease is defined as the time from the date of randomization to the date of first documentation of hematologic disease progression, or organ (cardiac or renal) progression, or death due to any cause, whichever occurs first.

Patients without documentation of hematologic PD and organ progression will be censored at the date of last hematologic response assessment that is SD or better, or the date of last organ assessment SD or better, whichever occurs last. Progression-free survival will be analyzed using a method similar to that used for the analysis of OS.

Hematologic Disease PFS

Hematologic disease PFS is defined as the time from the date of randomization to the date of first documentation of hematologic PD, or death due to any cause, whichever occurs first.

Patients without documentation of hematologic PD will be censored at the date of last hematologic response assessment that is SD or better. Hematologic disease PFS will be analyzed based on the ITT population using a method similar to that used for the analysis of OS.

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Time to Vital Organ Deterioration or Death

Time to vital organ deterioration or death defined as the time from randomization to vital organ (heart or kidney) deterioration or death, whichever occurs first.

Patients without documentation of organ deterioration or death will be censored at the date of the last assessment. Time to vital organ deterioration or death will be analyzed based on the ITT population using a method similar to that used for the analysis of OS.

Vital Organ Response Rate

Vital organ (heart and kidney) response rate is defined as the proportion of patients who achieved vital organ response in the ITT population. Changes from baseline in the vital organs will be documented as "response", "no change", or "progressed". An overall determination of vital organ response will then be documented for the given time point:

- Progression of 1 of the 2 vital organs will equate to organ progression
- Response of 1 or 2 of the involved vital organs with no change from baseline in the rest of involved vital organs will equate to vital organ response
- No change from baseline in any involved vital organs will equate to stable organ disease

Vital organ PFS

Vital organ PFS is defined as the time from the date of randomization to the date of first documentation of progression of these two vital organs (heart or kidney), or death due to any cause, whichever occurs first.

Patients without documentation of vital organ progression will be censored at the date of last vital organ assessment SD or better. Vital organ PFS will be analyzed using the similar method as OS.

Duration of Hematologic Response

Duration of hematologic response (DOR) is defined as the time from the date of first documentation of a hematologic PR or better to the date of first documentation of hematologic PD for hematologic responders.

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Hematologic responders without documentation of hematologic PD will be censored at the date of last hematologic response assessment that is SD or better. DOR will be summarized descriptively using the Kaplan-Meier method.

Time to Treatment Failure

Time to treatment failure (TTF) is defined as the time from randomization to the date of first documented treatment failure. Treatment failure is defined as: 1) death due to any cause; 2) hematologic progression or major organ progression according to central laboratory results and ISA criteria as evaluated by an AC; 3) a hematologic response with stable but clinically morbid organ disease requiring additional therapy; or 4) or withdrawn for any reason.

Patients without documentation of treatment failure will be censored at the date of last response assessment. Time to treatment failure will be analyzed based on the ITT population using a method similar to that used for the analysis of OS.

Time to Subsequent Anticancer Therapy

Time to subsequent anticancer therapy is defined as the time from randomization to the first date of subsequent anticancer therapy.

Patients without subsequent anticancer therapy will be censored at the date of death or last known to be alive. Time to subsequent anticancer therapy will be analyzed based on the ITT population using a method similar to that used for the analysis of OS.

8.1.7 Analyses of Patient-Reported Outcomes and Health Economics

8.1.7.1 Patient-reported Outcomes Analysis

Patient-reported outcome assessments using FACT/GOG-NTX, the symptom scale questionnaire, and SF-36 v2, will be analyzed to determine if response to therapy and side effects of therapy are accompanied by measurable changes in the PROs. The analysis will be performed on summary scores as well as on subscales and individual symptoms.

To compare the 2 treatment groups with respect to maximum improvement from baseline in SF-36 v2, as well as the symptom scale questionnaire, an analysis of covariance (ANCOVA) model will be fitted. Summaries from ANCOVA with baseline and other relevant clinical or demographic variables as covariates will include F-test p values, mean change scores, and 95% CI for the differences between the treatment groups.

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Per the recommendations outlined in the FDA Guidance (2009), it will be informative to examine the cumulative distribution function (CDF) of responses between treatment groups to characterize the treatment effects. A graphical display of this cumulative distribution, showing a continuous plot of the change from baseline on the X-axis and the percent of patients experiencing that change on the Y axis, will be presented. The CDF will be performed on the PCS and MCS for the SF-36 v2, FACT/GOG-NTx, and individual and total symptom score on the symptom scale questionnaire.

Missing items in a scale will be handled by the individual scales or subscales on the basis of each individual assessment and according to the developer's guidelines. Investigation of missing patterns and details of imputation will be discussed in the SAP.

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.

8.1.8 Pharmacokinetics, Pharmacodynamics, and Biomarkers

Pharmacokinetic Analysis

PK data collected will be used to perform population PK analysis using a nonlinear mixed effects modeling approach and to assess the effect of various covariates on PK after including data from other studies, if possible.

8.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs will be tabulated. Treatment-emergent AEs are AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs

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- 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 patients in any treatment group)
- SAEs

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

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, weight, ECOG scores will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst 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 screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN9708. Additional safety analyses may be done at a time as requested by health care authorities.

Upon implementation of this amendment, safety assessments will be limited to the following: all SAEs (regardless of causality, including all deaths), any AE resulting in dose modification or discontinuation of any study drug, Grade ≥3 AEs, AEs of new primary

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malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose).

8.1.10 Interim Analyses

There were 2 planned IAs. The first IA was performed when 168 patients enrolled had the opportunity to complete 6 cycles of treatment or discontinued study treatment before receiving 6 cycles of treatment. At that time, relevant safety and efficacy data from those patients was queried and cleaned; all analyses at this IA will be based on these patients whose data have been cleaned. This will be the FA for hematologic response. At the first IA, hematologic response was tested at a 2-sided alpha level of 0.04. If the test was statistically significant, the study would have continued to test organ deterioration and mortality rate at a 2-sided alpha of 0.05 at the second IA; otherwise organ deterioration and mortality rate would have been tested at the second IA with a 2-sided alpha of 0.01. Therefore, by using this fall-back approach[106], the type I error would have been strongly controlled for 2 primary endpoints: hematologic response and 2-year vital organ deterioration and mortality rate. This first IA has occurred (data cut-off date: 20 February 2019) and the primary endpoint of hematologic response was not met. Therefore, the sponsor has decided not to conduct the second IA. The text below describes the sample size and steps originally planned for the second IA.

The second IA will be performed when approximately 218 patients enrolled have had the opportunity to complete 2 years of treatment or followed up for at least 2 years if discontinuing treatment before receiving 2 years of treatment. This IA is expected to occur approximately 98 months from the first patient is enrolled. At that time, relevant safety and efficacy data from those patients will be queried and cleaned; all analyses at this IA will be based on these patients whose data have been cleaned.

If the test for 2-year vital organ deterioration and mortality rate is significant at the second IA, the analyses on OS will be performed and the test for significance on OS for the second IA and FA will be determined using O'Brien-Fleming boundaries.[107] If the alpha allocated to OS is 0.05, the trial will be stopped for overwhelming efficacy if the observed p value is less than 0.027 at the second IA assuming there are exactly 120 death events. The FA will be tested at 2-sided alpha level of 0.0423 (corresponding to nominal alpha of 0.023). If the alpha allocated to OS is 0.01, OS will be tested using a similar approach as above.

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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 advise on the conduct of the study and development of publications and presentations (see also Section 12).

9.2 Independent Data Monitoring Committee

An IDMC will monitor safety and efficacy and perform the interim analyses. As part of the IDMC safety monitoring, this committee will receive reports of all cases of new primary malignancies occurring during the trial.

As of Amendment 6, the primary efficacy and safety analyses have been completed for this study, and no further independent data monitoring committee reviews of safety and efficacy data will take place for patients still receiving study therapy. The sponsor will continue to monitor all cases of new primary malignancies occurring during the trial.

9.3 Adjudication Committee

Response to therapy will be assessed by an AC. Assessment of hematologic response and organ response will be based central laboratory results and will follow the criteria outlined in the Revised Consensus Response Criteria of the International Society of Amyloidosis (ISA).[20, 34, 36] Vital organ deterioration will be evaluated in a blinded manner by the AC to provide a determination of the events of this composite endpoint. The AC will also review specific data elements and corresponding data documentation to support criteria of vital organ (that is heart or kidney) deterioration. Vital organ deterioration is characterized as cardiac deterioration, that is the need for hospitalization for heart failure, and kidney deterioration, that is progression to ESRD with the need for maintenance dialysis or renal transplantation). Such criteria will be applied consistently to both treatment arms.

Upon implementation of Amendment 6, AC review of response data will no longer be performed.

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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.)

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- 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.[104] 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.

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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). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

The paper SAE forms should be submitted via fax (see fax numbers below) within 24 hours of awareness. In case of fax, site personnel need to 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 need to 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, EDC/RAVE must be updated as soon as possible with the appropriate information

SAE Reporting Contact Information*

Cognizant
US and Canada
Toll-Free Fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

All other countries (Rest of World)
Fax #: 1 202 315-3560
E-mail: takedaoncocases@cognizant.com

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

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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.[104] 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?

Upon implementation of this amendment, data collection requirements will be limited to the following safety assessments: all SAEs (regardless of causality, including all deaths), any AE resulting in dose modification or discontinuation of any study drug, Grade ≥3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose).

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 or the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs. That is, if a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Upon implementation of Amendment 6, only AEs resulting in dose modification or discontinuation of any study drug, Grade ≥3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose) are to be reported.

- Serious pretreatment events will be reported to Millennium Department of 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 and recorded in the eCRF. All SAEs should be monitored

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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, all new primary malignancies that occur during the follow-up periods must be reported, irrespective of causality to study regimen, starting from the first dose of study drug. All cases of new primary malignancy will be immediately reported to the appropriate regional pharmacovigilance system according to the governing regulations. The IDMC will also receive reports of all cases of new primary malignancies occurring during the trial. (Upon implementation of Amendment 6, the IDMC will no longer review safety data from the study; the sponsor will review all cases of new primary malignancy.)

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance (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 MLN9708 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,

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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 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

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regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

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, 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.

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 study 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

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

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

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 MedComm Solutions (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 Overdose for MLN9708), Call PPD at Phone: 1-877-TAKEDA7 (1-877-825-3327)

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E-mail: medicalinformation@tpna.com
FAX: 1-800-247-8860
Hours: Mon-Fri, 8 a.m. to 6 p.m. ET
(US and International)

Product complaints in and of themselves are not AEs. If a product complaint is an SAE, an SAE form should be completed and sent to PPD (refer to section 10.2).

11.12 Closure of the Study

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

Within 1 year of the end of the study, a summary of the clinical 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.

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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.

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13. INVESTIGATOR AGREEMENT

I have read Protocol C16011, Amendment 6: A Phase 3, Randomized, Controlled, Open-Label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physician's Choice of Treatment Administered to Patients With Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

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

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

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

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15. APPENDICES

15.1 Amyloid Typing

Because clinical presentations are similar for the common types of systemic amyloidosis, the stigmata of organ involvement do not enable one to deduce the type of amyloid in a given patient.[108]

Two potential precursor proteins can coexist in a patient, making it perplexing as to which type the patient has, a happenstance particularly relevant to 3 situations:

1. African-Americans who have higher rates of monoclonal gammopathies and a 4% incidence of an hereditary ATTR variant (Val122Ile);[108, 109]
2. Patients presenting with peripheral neuropathy as the only clinical feature of organ involvement and a monoclonal gammopathy; peripheral nervous system involvement is a common presentation of hereditary disease;[109]
3. Elderly men who also have higher rates of both monoclonal gammopathies and wild-type ATTR.[109]

For diagnosis, tissue biopsy, either of an involved organ or a surrogate site (eg, abdominal fat), must demonstrate amyloid deposition by classic Congo red staining or electron microscopy.

For typing, immunohistochemical staining is frequently unreliable and inaccurate, and immunogold electron microscopy (IEM) reliable but limited by serologic dependence.[109] DNA sequencing of genes related to hereditary variants is useful for typing, particularly in African-Americans and patients with peripheral neuropathy as above (situations 1 and 2 where sequencing the transthyretin gene is indicated), or if adequate biopsy material for proteomic studies cannot be obtained. DNA sequencing is also useful for confirming proteomic findings and for subsequent screening of kin.[109]

Proteomics employing mass spectrometry with customized bioinformatic assessment of the constituents of the Congophilic deposits is now the gold standard for typing amyloid, enabling precise identification of type. It is specifically indicated for typing in cases where 2 potential amyloid precursor proteins may be present in a patient as in situation 3 above. Given the population in this study has relapsed or refractory AL amyloidosis, the sponsor believes that if needed amyloid typing would have been done at initial diagnosis and thus is

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not required for entry to this study. However, amyloid typing may be repeated at the investigators discretion if there is a question.

15.2 Equation to Estimate Glomerular Filtration Rate (eGFR)

Race and Sex	Serum Creatinine Level μmol/L (mg/dL)	Equation
Black		
Female	≤ 62 (≤ 0.7)	GFR = 166 × (SCR/0.7) - 0.329 × (0.993)age
	> 62 (> 0.7)	GFR = 166 × (SCR/0.7) - 1.209 × (0.993)age
Male	≤ 80 (≤ 0.9)	GFR = 163 × (SCR/0.9) - 0.411 × (0.993)age
	> 80 (> 0.9)	GFR = 163 × (SCR/0.9) - 1.209 × (0.993)age
White or Other		
Female	≤ 62 (≤ 0.7)	GFR = 144 × (Scr/0.7) - 0.329 × (0.993)age
	> 62 (> 0.7)	GFR = 144 × (Scr/0.7) - 1.209 × (0.993)age
Male	≤ 80 (≤ 0.9)	GFR = 141 × (Scr/0.9) - 0.411 × (0.993)age
	> 80 (> 0.9)	GFR = 141 × (Scr/0.9) - 1.209 × (0.993)age

Source: Levey et al, 2009.[110]

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR – glomerular filtration rate.

Expressed for specified race, sex, and serum creatinine level. To convert GFR from mL/min/1.73 m^2 to mL/sec/1.73 m^2, multiply by 0.0167. The equation coefficients were derived from pooled development and internal validation sets. The CKD-EPI equation, expressed as a single equation, is GFR = 141 × $\min(Scr/\kappa,1)^{\alpha}$ × $\max(Scr/\kappa,1)^{-1.209}$ × 0.993^{age} × 1.018 (if female) × 1.159 (if black), where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, and min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.

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15.3 Short Form General Health Survey (SF-36 v2™)

Subject ID: _____/_____ Site #_____ Study Day_____ Date: _____/_____/_____
Initials/Number m m / d d / y y y y

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

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Subject ID: _____/_____Site #_____Study Day_____ Date: _____/_____/_____
Initials/Number m m / d d / y y y y

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c Lifting or carrying groceries	☐1	☐2	☐3
d Climbing several flights of stairs	☐1	☐2	☐3
e Climbing one flight of stairs	☐1	☐2	☐3
f Bending, kneeling, or stooping	☐1	☐2	☐3
g Walking more than a mile	☐1	☐2	☐3
h Walking several hundred yards	☐1	☐2	☐3
i Walking one hundred yards	☐1	☐2	☐3
j Bathing or dressing yourself	☐1	☐2	☐3

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Subject ID: _____/_____Site #_____Study Day_____ Date: _____/_____/_____
Initials/Number m m / d d / y y y y

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

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Subject ID: _____/_____Site #_____Study Day_____ Date: _____/_____/_____
Initials/Number m m / d d / y y y y

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

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Subject ID: _____/_____Site #_____Study Day_____ Date: _____/_____/_____
Initials/Number m m / d d / y y y y

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Se
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

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Subject ID: _____/_____Site #_____Study Day_____ Date: _____/_____/_____
Initials/Number m m / d d / y y y y

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

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Subject ID: _____/_____Site #_____Study Day_____ Date: _____/_____/_____
Initials/Number m m / d d / y y y y

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

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15.4 FACT/GOG-Ntx

FACT/GOG-Ntx (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

US English
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SAMPLE
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15.5 Amyloidosis Symptom Scale

Amyloidosis Symptom Scale

For each symptom below, please circle the one number that best describes how severe that symptom was for you **AT ITS WORST IN THE LAST 24 HOURS**

1. How severe was the **swelling** in your lower body (feet, ankles, or legs) **at its worst in the last 24 hours**?

No swelling	0	1	2	3	4	5	6	7	8	9	10 Very severe swelling

2. How severe was your **shortness of breath at its worst in the last 24 hours**?

No shortness of breath	0	1	2	3	4	5	6	7	8	9	10 Very severe shortness of breath

3. How severe was your **dizziness or lightheadedness at its worst in the last 24 hours**?

No dizziness or lightheadedness	0	1	2	3	4	5	6	7	8	9	10 Very severe dizziness or lightheadedness

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15.6 New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac diseases.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Note: A classification of 0 will be assigned to patients without cardiac disease or no evidence thereof.

15.7 Steroid Equivalent Doses

Approximately equivalent doses:

Steroid	Glucocorticoid Anti-inflammatory (mg)	Mineralocorticoid (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.[111]

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15.8 Eastern Cooperative Oncology Group 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.[112]

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15.9 EuroQol 5-Dimensional (EQ-5D)

Health Questionnaire

(English version for the US)

© EuroQoL Group 1990

SAMPLE
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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	❑

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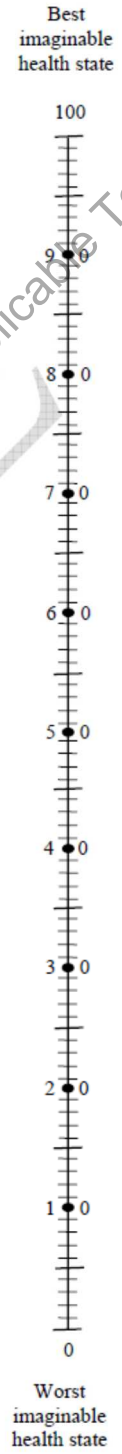
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

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



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15.10 Amyloid-Related Hematologic and Organ Criteria for Involvement, Stabilization, Response, and Progression

Organ System	Involvement	Stable[a]	Response	Progression
Hematologic	Measurable disease defined as serum differential free light chain concentration (dFLC) ≥ 50mg/L dFLC is the difference between the amyloid forming (involved) and nonamyloid forming (uninvolved) free light chain. A nephelometric assay measures both kappa and lambda light chains and identifies an excess production of FLC isotype produced from the clonal plasma cell. This FLC isotype is involved in the pathogenic process of misfolding into the amyloid fibrils.	No CR, VGPR, PR, no progression	**Complete Response (CR):** Negative serum & urine immunofixation, normal kappa:lambda FLC ratio **Very Good Partial Response (VGPR)**: dFLC <40 mg/L **Partial Response (PR)**: dFLC decrease ≥ 50%	Progression from CR: any detectable monoclonal protein or abnormal FLC ratio; involved free light chain must double. Progression from VGPR, PR or stable disease: Involved free light chain increase of 50% to > 10 mg/dL (100 mg/L) from its lowest measured level 50% increase in serum M-protein to > 0.5 g/dL from nadir/baseline, or 50% increase in urine M-protein to > 200 mg/24 hours with a visible peak present;
Involvement of Heart or Kidney (at least one) required for study entry				
Cardiac	Echo: mean interventricular septal wall thickness >12mm, no other cardiac cause with a non-cardiac biopsy showing amyloid, or positive cardiac biopsy in the presence of clinical or laboratory evidence of involvment, e.g. NT-proBNP > 332 pg/mL in the absence of renal failure. Note: a baseline NT-proBNP ≥650 pg/mL was required for NT-proBNP response to be evaluable	Stable disease is defined when none of the criteria for response or for worsening disease are met.	NT-proBNP >30% and >300 pg/mL decrease if baseline NT-proBNP ≥650 pg/mL) Echo: mean interventricular septal wall thickness decrease by 2mm, or 20% improvement in LVEF, or Improvement by ≥ 2 NYHA classes without an increase in diuretic use and no increase wall thickness	Increase in NT-proBNP that is both >30% and >300 pg/mL, or Echo: interventricular septal thickness increased by 2mm over baseline, or An increase in NYHA class by 1 grade with decreasing LVEF of ≥10%,
Renal	24- hour protein > 0.5 g/day, predominantly albumin	Stable disease is defined when none of the criteria for response or for worsening disease are met.	At least a 50% reduction in 24-hour urine protein (must be at least 0.5 g/day) without worsening of creatinine or creatinine clearance by 25% compared to baseline	50% increase in urinary protein loss (at least 1 g/24 hours) or 25% worsening of creatinine or creatinine clearance

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Organ System	Involvement	Stable[a]	Response	Progression
Involvement of any of the below allowed in addition to the requirement for involvement of one or more of the above organs				
Liver	Alkaline phosphatase value > 1.5 × ULN, or liver span > 15 cm radiographically in the absence of heart failure,.	Stable disease is defined when none of the criteria for response or for worsening disease are met.	≥50% decrease in alkaline phosphatase from baseline Decrease in liver size by at least 2 cm (radiographic determination	≥50% increase of alkaline phosphatase above lowest level.
Gastro-intestinal	Direct biopsy verification with symptoms such as diarrhea, frank bleeding, early satiety, malabsorption, GI motility disturbances, and weight loss (BJH 2004)	Stable disease is defined when none of the criteria for response or for worsening disease are met. Clinical changes based on NCI CTC Version 4.02 criteria may be useful	Reliable, quantitative methods for defining response do not to exist. Improvement in clinical findings such as diarrhea, motility disturbances and weight loss may be useful[b]	Progression of signs and symptoms not attributable to therapy under study
Nerve, Peripheral	Evidence of amyloid involvement alternative site plus clinical symptoms such as symmetric lower extremity sensory peripheral neuropathy (often with pain) on neurologic examination, parasthesiae, numbness or muscle weakness. Motor neuropathy is rare. (BJH 2004) Note: EMG and nerve conduction velocity are relatively insensitive in detecting involvement.	Stable disease is defined when none of the criteria for response or for worsening disease are met. Clinical changes based on NCI CTC Version 4.02 criteria may be useful.	Reliable, quantitative methods for defining response do not to exist.. Improvement in clinical findings with decrease in the Ntx score, signs and/or symptoms of peripheral neuropathy, and decrease in neuropathic pain may be useful[b]	Progressive neuropathy not attributable to therapy under study. Progressive neuropathy by EMG or nerve conduction velocity may show progression.
Nerve, Autonomic	Based on clinical history of autonomic dysfunction and symptoms such orthostasis, gastric emptying disorder, early satiety, impotence/ erectile dysfunction, bowel or bladder dysfunction not related to direct organ infiltrate, anhidrosis or gustatory sweating (BJH 2004)	Stable disease is defined when none of the criteria for response or for worsening disease are met. Clinical changes based on NCI CTC Version 4.02 criteria may be useful	Reliable, quantitative methods for defining response do not to exist. Improvement in clinical examination findings including such symptoms as improvement in orthostasis and other signs and/or symptoms related to autonomic dysfunction[b]	Progression neuropathy not attributable to therapy under study
Soft tissue and lymphatic	Based on classic physical findings such as: • Macroglossia (enlarged tongue), • Arthropathy, • Claudication, presumed vascular amyloid • Shoulder pad sign, • Periorbital purpura (Raccoon eyes), • Carpal tunnel	Stable disease is defined when none of the criteria for response or for worsening disease are met. Clinical changes based on NCI CTC Version 4.02 criteria may be useful	Reliable, quantitative methods for defining response do not to exist. Clinical changes based on NCI CTC Version 4.02 criteria may be useful	Progression of signs and symptoms not attributable to therapy under study

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Organ System	Involvement	Stable[a]	Response	Progression
	syndrome, • Synovial enlargement, • Lymphadenopathy, biopsy verification. • Skin thickening • Myopathy by biopsy or pseudohypertrophy			
Lung	Direct biopsy verification with symptoms. Diffuse interstitial radiographic pattern usually by CT scan	Stable disease is defined when none of the criteria for response or for worsening disease are met. Clinical changes based on NCI CTC Version 4.02 criteria may be useful	Reliable, quantitative methods for defining response do not to exist. Radiographic improvement	Progression of radiographic findings not attributable to therapy under study

Sources: (4, 19, 20, 34, 36, 38)

a Unless clinically indicated to check sooner, stabilization of organ function must be confirmed visit in the absence of worsening of any other organs unless worsening is considered a treatment-emergent adverse event.

b Based on NCI CTC Version 4.02 criteria.(113)

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15.11 Full Schedule of Events (Prior to Amendment 6)

This full Schedule of Events is no longer in effect, as of Amendment 6, because the first IA has been conducted and the primary endpoint of overall hematologic response rate (CR + VGPR + PR) did not reach statistical significance. As such, the sponsor has decided to discontinue the majority of study assessments for protocol purposes; study drug will continue to be provided

Study Procedures	Screening	Treatment Period 28-Day Cycles							End of Treatment[n]	Follow-up		
										PFS	PFS Organ Assessment	OS
Cycle		C1	C1	C2	C2	C3	C3	After C3 until PD				
Days	-28 to -1	1	14	1	14	1	14	1		Every 6 weeks	Every 12 weeks	Every 12 weeks
Window		± 3 days							+ 10 days	± 1 wk		
Informed Consent[a]	X											
Inclusion/Exclusion Criteria	X											
Demographics	X											
Complete Medical History, including AL amyloidosis treatment history, neurologic history and cardiac medical history	X											
12-lead ECG	X			X					X			
Complete Physical Examination	X					X		Q3C	X	X		
Symptom-Directed Physical Exam		X		X				X				
Assessment of AL Amyloidosis Symptoms[b]	X	X		X		X		X	X	X		
ECOG Performance Status	X	X		X		X		X	X	X		

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Study Procedures	**Screening**	**Treatment Period 28-Day Cycles**							**End of Treatment[n]**	**Follow-up**		
										PFS	**PFS Organ Assessment**	**OS**
Cycle		**C1**	**C1**	**C2**	**C2**	**C3**	**C3**	**After C3 until PD**				
Days	**-28 to -1**	**1**	**14**	**1**	**14**	**1**	**14**	**1**		**Every 6 weeks**	**Every 12 weeks**	**Every 12 weeks**
Window		**± 3 days**							**+10 days**	**± 1 wk**		
Vital Signs	X	X		X		X		X	X			
Height (cm)	X											
Weight (kg)	X	X		X		X		X	X	X		
Pregnancy Test[c]	X	X							X			
Hematology[d]	X	X	X	X	X	X	X	X	X			
Prothrombin Time	X					X		X	X			
Clinical Chemistry[d]	X	X		X		X		X	X			
Urinalysis[e]	X								X			
24-hour Urine Collection for Creatinine[f]	X	X[f]							X			
Select Physician's Choice Treatment	X											
SF-36 v2[g]	X	X				X		Q3C	X	X		
Symptom Scale Questionnaire[g]	X	X		X		X		X	X	X		
EQ-5D[g]	X	X		X		X		X	X	X		X
HU Assessment[g]				X		X		X	X	X		X
FACT/GOG-Ntx[g]	X	X		X		X		X	X	X		
Bone marrow core biopsy and/or aspirate[h]	X											
Hematologic Disease Response												
β2-microglobulin	X											
M-protein measurements (SPEP)	X	X		X		X		X	X	X		

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Study Procedures	Screening	Treatment Period 28-Day Cycles							End of Treatment[n]	Follow-up		
										PFS	PFS Organ Assessment	OS
Cycle		C1	C1	C2	C2	C3	C3	After C3 until PD				
Days	-28 to -1	1	14	1	14	1	14	1		Every 6 weeks	Every 12 weeks	Every 12 weeks
Window		± 3 days							+ 10 days	± 1 wk		
M-protein Measurements (UPEP [24-hour urine collection][i,j]	X	X[e]							X		X[e]	
Serum Free Light Chain Assay[i]	X			X		X		X	X	X		
Immunofixation - Serum and Urine [e,i,j]	X								X			
Quantification of Ig[i,j]	X								X			
Skeletal Survey[e,k]	X											
Amyloid-related Organ Assessment												
24-hour Urine Collection for Total Protein	X					X		Q3C	X		X	
Serum Albumin, calculated creatinine clearance, and eGFR	X					X		Q3C	X		X	
CT or MRI Scans, alkaline phosphatase, and ALT as indicated to assess organ involvement (eg, liver)[l]	X					X		Q3C	X		X	
Echocardiogram	X					X		Q3C	X		X	
Serum Cardiac Markers (NT-proBNP, BNP, troponin T)	X			X		X		X	X	X		
NYHA Classification	X			X		X		X	X		X	
Concomitant Medications/Procedures		Recorded from the first dose of study drug through 30 days after last dose of any study drug										

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Study Procedures	**Screening**	**Treatment Period 28-Day Cycles**							**End of Treatment[n]**	**Follow-up**		
										PFS	**PFS Organ Assessment**	**OS**
Cycle		**C1**	**C1**	**C2**	**C2**	**C3**	**C3**	**After C3 until PD**				
Days	**-28 to -1**	**1**	**14**	**1**	**14**	**1**	**14**	**1**		**Every 6 weeks**	**Every 12 weeks**	**Every 12 weeks**
Window		**± 3 days**							**+10 days**	**± 1 wk**		
Adverse Event Reporting		Recorded from the first dose of study drug through 30 days after last dose of study drug										
		Serious adverse events[m] will be reported from signing of the informed consent form through 30 days after the last dose of study drug.										
Survival												X
Drug Administration												
MLN9708		MLN9708 on Days 1, 8, and 15										
Dexamethasone		Dexamethasone on Days 1, 8, 15, and 22										
Comparator Administration:												
Dexamethasone Alone		Daily on Days 1-4, 9-12, & 17-20										
Dexamethasone and Melphalan		Days 1-4										
Dexamethasone and Cyclophosphamide		Cyclophosphamide Days 1, 8, and 15 and dexamethasone Day 1, 8, 15, and 22										
Dexamethasone and Thalidomide		Thalidomide daily and dexamethasone Days 1, 8, 15, and 22										
Dexamethasone and Lenalidomide		Lenalidomide Days 1-21 and dexamethasone Day 1, 8, 15, and 22										

Abbreviations: ALT = alanine aminotransferase; β = Beta; BNP = B-type natriuretic peptide; C = Cycle; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGRR = estimated glomerular filtration rate; Ig = immunoglobulin; MRI = magnetic resonance imaging; NT-pro BNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OS = overall survival; PD=progressive disease; PFS = progression-free survival; QOL = quality of life; Q3C = every 3 cycles; SPEP = serum protein

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Study Procedures	Screening	Treatment Period 28-Day Cycles							End of Treatment[n]	Follow-up		
										PFS	PFS Organ Assessment	OS
Cycle		C1	C1	C2	C2	C3	C3	After C3 until PD				
Days	-28 to -1	1	14	1	14	1	14	1		Every 6 weeks	Every 12 weeks	Every 12 weeks
Window		± 3 days							+10 days	± 1 wk		

electrophoresis; UPEP = urine protein electrophoresis.

a Informed consent must be obtained before any study-specific procedures for research purposes are performed. Evaluations during the Screening period are to be conducted within 28 days prior to randomization, unless otherwise noted or with permission from the MPI clinician /designee in extenuating circumstances. Bone marrow examinations may be performed within 42 days of randomization. One complete cycle is 28 days. Occasional changes are allowable for holidays, vacations, and other administrative reasons (see Sections 6 and 7.4).

b The Cardiac Assessment (CA) and Neurological Assessment (NA) forms can be used, or should serve as a guide for to the level of detail required for these assessments in the medical note. The CA and NA forms must be used if the medical notes do not document the level of detail specified in these forms.

c Treatment with IMiDs requires pregnancy testing in female patients of child-bearing age prior to each cycle. A serum pregnancy test will be performed for all women of childbearing potential. The Cycle 1, Day 1 pregnancy test may be collected up to 3 days before dosing and the results must be available and negative before the first dose.

d Hematology and chemistry panels may be collected up to 3 days before dosing on Day 1. Day 14 hematology (Cycle 1-3) can be done locally to make a dosing decision, but a central hematology also needs to be drawn. Criteria for retreatment are provided in Section 6.5.1.

e Repeat as clinically indicated.

f Repeat as clinically indicated by change in serum creatinine.

g All questionnaires should be completed before any other study procedures are performed. The SF-36 v2, FACT/GOG-Ntx and the symptom scale questionnaire must be completed at PD and PFS follow up. The EQ-5D and HU questionnaires may be collected by phone during the OS follow-up period.

h Bone marrow biopsy and/or aspirate should be repeated at the discretion of the investigator as clinically indicated. Immunohistochemistry of dominant clonal plasma cells is recommended.

i Serum and urine immunofixation required in patients suspected of CR based on FLC criteria of complete response.

j Must be obtained at PD. Serum and urine immunofixation to be obtained at the end-of-treatment visit.

k Skeletal surveys may be performed within 8 weeks of randomization. To be performed at screening and at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions. If results are interpreted as abnormal, then repeat at the discretion of the investigator

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Study Procedures	Screening	Treatment Period 28-Day Cycles							End of Treatment[n]	Follow-up		
										PFS	PFS Organ Assessment	OS
Cycle		C1	C1	C2	C2	C3	C3	After C3 until PD				
Days	-28 to -1	1	14	1	14	1	14	1		Every 6 weeks	Every 12 weeks	Every 12 weeks
Window		± 3 days							+ 10 days	± 1 wk		

as clinically indicated. The same imaging modality used at screening should be used for all follow-up assessments.

l If results are interpreted as abnormal, then repeat at the discretion of the investigator as clinically indicated. The same imaging modality used at screening (CT/MRI) should be used for all follow-up assessments.

m Including serious pretreatment events; see Section 11.2.

n Patients who do not continue treatment must complete the EOT assessments, which should occur at least 30 days after the last dose of study drug or prior to the initiation of subsequent antineoplastic therapy.

15.12 Pharmacokinetic Sampling Schedule (Prior to Amendment 6)

Cycle	1			2		3-10
Days	1		14	1	14	1
Window	1 hour postdose (± 0.25)	4 hours postdose (± 0.75)	At any time during clinic visit	Predose	At any time during clinic visit	Predose
	X	X	X[a]	X	X[a]	X

a PK samples will be collected from patients visiting the clinic for other study-related activities. PK samples are optional for patients who do not have an onsite visit on Cycle 1 Day 14 or Cycle 2 Day 14.

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15.13 Amendment 1 Rationale and Purposes

Rationale for Amendment 1

The primary purpose of this amendment is to revise the second primary endpoint, key secondary endpoints, and regular secondary endpoints.

Consideration has been given to the fact that the current treatment paradigm of patients with systemic light chain (AL) amyloidosis is complex and presents unique challenges. As such, while overall survival (OS) is a standard regulatory endpoint, it may be difficult to demonstrate in this patient population, particularly because physicians change treatment regimens in an effort to obtain more robust clinical benefits than those achieved with the previous treatment that the patient received. This change in treatment makes it difficult to determine which therapy has the greatest impact on survival. As is standard in nononcology settings when investigating agents for conditions such as congestive heart failure (CHF) or diabetic nephropathy, deterioration of vital organs (heart and kidney, respectively) and mortality is an acceptable regulatory endpoint to demonstrate clinical benefit. The 2 organs most commonly involved in AL amyloidosis are heart and kidney; thus, congestive heart failure and renal nephropathy are conditions that frequently affect patients with light chain amyloid involvement of the heart and kidney, respectively.

Originally, the second primary endpoint in this study was OS. However, considering the methods by which patients are treated and the intention to demonstrate a meaningful measure of clinical benefit, this endpoint has been replaced by 2-year vital organ (that is, heart and kidney) deterioration and mortality rate. The definitions of heart and kidney deterioration are in alignment with those used in nononcology settings (ie, cardiac deterioration is defined as hospitalization for CHF, and kidney deterioration is defined as progression to end-stage renal disease [ESRD] with the need for maintenance dialysis or renal transplantation). In and of itself, OS remains an important endpoint and has therefore been included as a key secondary endpoint. Also, the key secondary endpoint of organ response and stabilization rate is now revised to vital organ response and is included as a regular secondary endpoint.

Purposes for Amendment 1

The purposes of this amendment are to:

- Change the second primary endpoint from overall survival (OS) to 2-year vital organ (that is, heart or kidney) deterioration and mortality rate
- Include OS as a key secondary endpoint
- Change the key secondary endpoint of organ response and stabilization rate to a regular secondary endpoint
- Remove liver from the list of vital organs with amyloid involvement required at study entry
- Revise definitions of relapsed and refractory disease
- Update the Study Schema to accurately reflect the study design
- Update Schedule of Events to more accurately reflect conduct of study procedures

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- Replace reference to Medical Resource Utilization (MRU) with Health Utilization (HU) to reflect the Sponsor's updated terminology
- Replace reference to Independent Review Committee with Adjudication Committee to accurately reflect how hematologic and organ response and vital organ deterioration will be assessed
- Update Section 1.3, Clinical Experience to provide data as of 30 April 2012
- Update Section 1.5, Rationale for MLN9708 Dose and Schedule Selection
- Revise the duration of study from 7.6 years to 6.7 years
- Update the Management of Clinical Events section to include Stevens-Johnson Syndrome and hypotension
- Revise Table 6-2, MLN9708 Dose Adjustments for Hematologic Toxicities to reflect sponsor's current dose adjustment recommendations
- Revise Table 6.3, MLN9708 Dose Adjustments for Nonhematologic Toxicities to reflect sponsor's current dose adjustment recommendations
- Revise Sections 6.12.3, Dexamethasone, 6.12.3.2, Melphalan, and 6.12.3.3, Cyclophosphamide, to clarify that these drugs may be supplied by the sponsor
- Add note to Section 7.4.17, Adverse Events, to indicate that related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee
- Update the description of the investigational agents
- Add paragraph to Section 7.5, Compliance, to describe the methods of contact the sponsor or sponsor designee may utilize to obtain follow-up information on patients
- Revise Section 8, Statistical and Quantitative Analyses, to reflect changes to the statistical analysis plan
- Revise the Amyloid Symptom Scale (Section 15.5) to replace diarrhea with dizziness/lightheadedness
- Correct typographical errors, punctuation, grammar, and formatting

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15.14 Amendment 2 Rationale and Purposes

The primary reason for this protocol amendment is to address regulatory feedback received from several competent authorities and to clarify inconsistencies identified in the protocol.

Additionally, the sponsor has decided not to collect or test any gene polymorphism samples. Of the numerous signaling pathways constitutively activated in primary multiple myeloma cells, the nuclear factor-κB (NF-κB) pathway has recently emerged as one of the most important drivers of the tumor-promoting machinery, ie, cell proliferation, metastasis, tumor promotion, inflammation, and suppression of apoptosis. In multiple myeloma, many studies have suggested the link between activation of NF-kB and response to bortezomib. This has not been tested in AL amyloidosis. The original protocol was designed to evaluate this hypothesis in patients with AL amyloidosis given it is a similar plasma cell dyscrasia; however, given that the assessment was exploratory in addition to other business reasons,

references to collection and testing of this sample have been removed from the protocol. Protocol-specified samples given by the patients in this study will not be used for genetic testing.

- Remove the screening blood sample for assessment of gene polymorphism
- Add the definition of cardiac deterioration to the primary objective to be consistent with other sections of the protocol
- Clarify the definition of abstinence "to be in line with the preferred and usual lifestyle of the patient" per country-specific regulations
- Update the duration of contraception to 90 days following last dose of study treatment
- Exclude patients diagnosed with another malignancy or with a history of malignancy from participating in the study
- Clarify reference to hepatitis B and C virus infections in the exclusion criteria
- Outline conditions for the dosing schedule changes for holidays, administrative reasons, vacations, and extenuating circumstances
- Clarify dose modification procedures
- Clarify the precautions and restrictions section regarding nonsteroidal anti-inflammatory drugs (NSAIDs)
- Update the management of clinical events section to add information on thrombotic thrombocytopenic purpura (TTP), neutropenia, and posterior reversible encephalopathy syndrome (PRES)
- Add SAE and pregnancy to the criteria for discontinuation of treatment
- Update the independent data monitoring committee section to include reporting of all cases of new primary malignancies
- Delete redundant serious adverse event reporting language
- Modify the reporting period for SAEs to Millennium Department of Pharmacovigilance or designee from 1 working day to 24 hours per current company standards
- Update language regarding follow-up of AEs to current company standards
- Add reporting requirements for all new primary malignances
- Clarify that initiation of hematopoietic stem cell transplant is a reason for discontinuation from the study
- Update MedComm Solutions contact information for reporting product complaints
- Correct typographical errors, punctuation, grammar, and formatting

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15.15 Amendment 3 Rationale and Purposes

Rationale for Amendment 3

The primary reason for this protocol amendment is to clarify details regarding the duration

of treatment in the melphalan/dexamethasone group given the risk of second malignancy with prolonged use as noted in the melphalan package insert/summary of product characteristics (SmPC). Additionally, further clarification has been added to the definition of cardiac involvement in the setting of a cardiac biopsy.

This amendment also provides additional revisions and corrections made to clarify the initial intent of sections as detailed in the following.

Purposes for Amendment 3

The purposes of this amendment are to:

- Clarify the guidelines regarding the duration of treatment in the melphalan/dexamethasone group given the published risk of second malignancy with prolonged use
- Clarify language regarding the definition of cardiac involvement in the setting of a positive cardiac biopsy
- Revise the timing of the bone marrow screening window to 42 days
- Revise the pharmacokinetic sampling schedule to eliminate the 2-hour predose requirement
- Provide clarification regarding dexamethasone dose modifications to maximize patient tolerance as initially intended
- Simplify wording regarding overt multiple myeloma as outlined in the exclusion criteria to align with published International Myeloma Working Group (IMWG) guidelines
- Clarify that informed consent must be obtained before performing any study-specific procedures for research purposes
- Update guidance regarding the management of prophylaxis against risk of reactivation of herpes infection, erythematous rash with or without pruritus, neutropenia, hypotension, fluid deficit, and posterior reversible encephalopathy syndrome to reflect the sponsor's current recommendations
- Clarify that the investigator's selection of a Physician's Choice regimen within Arm B only occurs prior to randomization
- Revise treatment window language to align with sponsor's current guidelines
- Clarify that in some instances, a patient may receive more than 1 cycle of take-home medication following approval of the Millennium clinician/designee
- Clarify that if the study schedule is shifted, then both assessment and dosing schedules should be shifted accordingly
- Clarify how mean ventricular wall thickness is calculated on echocardiogram
- Update all units of measurement for NT-proBNP (pg/mL) and troponin T (ng/mL) for consistency throughout the protocol
- Correct typographical errors, punctuation, grammar, and formatting

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15.16 Rationale for Amendment 4

The rationale for Amendment 4 is: 1) to enrich the study population for proteasome inhibitor-naïve patients so that it will better reflect the global population of patients with relapsed or refractory amyloidosis; 2) to delay the first interim analysis (IA), which is also the final analysis (FA) for hematologic response, to allow time for proteasome inhibitor-naïve patients to enroll; and 3) instead of using the closed sequential approach for the first primary endpoint of hematologic response and second primary endpoint of 2-year organ deterioration and mortality rate, the fall-back approach is used to strongly control type I error.

Purposes for Amendment 4

The purposes of this amendment are to:

- Revise inclusion criterion #5 to allow enrichment of proteasome inhibitor-naïve patients by holding enrollment of proteasome inhibitor-exposed patients.
- Delay the timing of the first interim analysis (IA) to allow time for proteasome inhibitor-naïve patients to enroll and increase the number of patients in the analysis.
- Extend the duration of the study as a result of enriching for proteasome inhibitor-naïve patients and delaying the timing of the first IA.
- Revise the statistical analysis to allow splitting of alpha at the first IA and second IA for the 2 primary endpoints by using the fall-back alpha spending approach, and remove the requirement to terminate the study at the second IA if the test for the primary endpoint is not statistically significant.
- Clarify the analysis of the second primary efficacy endpoint.
- Revise inclusion criterion #8 to allow patients with Gilbert's syndrome to be eligible for enrollment despite a total bilirubin > 1.5 x ULN.
- Revise exclusion criterion #11 to remove the concomitant use of strong inhibitors of CYP1A2 and CYP3A.
- Revise exclusion criterion #12 to shorten the time period from previous diagnosis or treatment for another malignancy from 5 years to 3 years.
- Remove the requirement for bone marrow analysis to establish complete hematological response.
- Increase the flexibility around the timing of Day 14 PK sampling to ease patient burden.
- Clarify the requirement for assessment of AL amyloidosis symptoms.
- Clarify when the second IA will be performed.
- Clarify that 2-year follow-up refers to patients included in the analysis for the second primary endpoint.
- Remove details regarding the safety population analysis from the protocol, as the analysis will be clarified in the Statistical Analysis Plan (SAP).
- Update the background PK and drug metabolism text for the rationale for the revisions to exclusion criterion #11.

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- Update the number of study centers from 50 to 75.
- Add a reference for the statistical analysis fall-back approach.
- Clarify when the Independent Data Monitoring Committee (IDMC) will meet to evaluate safety and efficacy results.
- Clarify that additional safety analyses may be done at a time as requested by health authorities.
- Update the serious adverse event reporting contact information.
- Update the Product Complaint contact information to reflect that inquiries will now be handled by the Takeda US call center, run by Pharmaceutical Product Development (PPD).
- Make minor corrections to the amyloid-related hematologic and organ criteria for involvement, stabilization, response, and progression.
- Update the Global Clinical Lead for the study to [redacted], MD, PhD.
- Correct typographical errors, punctuation, grammar, and formatting.

15.17 Rationale for Amendment 5

(France-specific protocol Amendment 5 contains the same changes in global protocol Amendment 4, with the exception of the revision to exclusion #12.)

The rationale for Amendment 5 is: 1) to enrich the study population for proteasome inhibitor-naïve patients so that it will better reflect the global population of patients with relapsed or refractory amyloidosis; 2) to delay the first interim analysis (IA), which is also the final analysis (FA) for hematologic response, to allow time for proteasome inhibitor-naïve patients to enroll; and 3) instead of using the closed sequential approach for the first primary endpoint of hematologic response and second primary endpoint of 2-year organ deterioration and mortality rate, the fall-back approach is used to strongly control type I error.

Purposes for Amendment 5

The purposes of this amendment are to:

- Revise inclusion criterion #5 to allow enrichment of proteasome inhibitor-naïve patients by holding enrollment of proteasome inhibitor-exposed patients.
- Delay the timing of the first interim analysis (IA) to allow time for proteasome inhibitor-naïve patients to enroll and increase the number of patients in the analysis.
- Extend the duration of the study as a result of enriching for proteasome inhibitor-naïve patients and delaying the timing of the first IA.
- Revise the statistical analysis to allow splitting of alpha at the first IA and second IA for the 2 primary endpoints by using the fall-back alpha spending approach, and remove the requirement to terminate the study at the second IA if the test for the primary endpoint is not statistically significant.
- Clarify the analysis of the second primary efficacy endpoint.

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- Revise inclusion criterion #8 to allow patients with Gilbert's syndrome to be eligible for enrollment despite a total bilirubin > 1.5 × ULN.
- Revise exclusion criterion #11 to remove the concomitant use of strong inhibitors of CYP1A2 and CYP3A.
- Remove the requirement for bone marrow analysis to establish complete hematological response.
- Increase the flexibility around the timing of Day 14 PK sampling to ease patient burden.
- Clarify the requirement for assessment of AL amyloidosis symptoms.
- Clarify when the second IA will be performed.
- Clarify that 2-year follow-up refers to patients included in the analysis for the second primary endpoint.
- Remove details regarding the safety population analysis from the protocol, as the analysis will be clarified in the Statistical Analysis Plan (SAP).
- Update the background PK and drug metabolism text for the rationale for the revisions to exclusion criterion #11.
- Update the number of study centers from 50 to 75.
- Add a reference for the statistical analysis fall-back approach.
- Clarify when the Independent Data Monitoring Committee (IDMC) will meet to evaluate safety and efficacy results.
- Clarify that additional safety analyses may be done at a time as requested by health authorities.
- Update the serious adverse event reporting contact information.
- Update the Product Complaint contact information to reflect that inquiries will now be handled by the Takeda US call center, run by Pharmaceutical Product Development (PPD).
- Make minor corrections to the amyloid-related hematologic and organ criteria for involvement, stabilization, response, and progression.
- Update the Global Clinical Lead for the study to [redacted], MD, PhD.
- Correct typographical errors, punctuation, grammar, and formatting.

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15.18 Amendment 6 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Amendment 6 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Add primary study results from the first interim analysis (IA) and clarify details about subsequent analyses.

The primary change occurs in Section 8.1 Statistical Methods.

Initial wording:	Details for the FA will be provided in the statistical analysis plan (SAP). The SAP will be written by Millennium and will be finalized before any formal 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.
Amended or new wording:	~~Details for the FA will be provided in the statistical analysis plan (SAP).~~ The SAP will be written by Millennium and will be finalized before any formal 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. **The first IA has been performed (data cut-off date: 20 February 2019) and the primary endpoint of hematologic response was not met. Therefore, the sponsor has decided not to conduct any subsequent formal statistical analyses. The analysis of efficacy and safety has been completed on data from the first IA. Minimal descriptive analyses will be done on patient data collected after the first IA. The description of statistical methods presented below reflects the original design of the study so to retain the statistical considerations up to the first IA.**

Rationale for Change:

The first IA was conducted and the primary endpoint of hematologic response rate (at the primary analysis) did not reach statistical significance. However, patients in both treatment arms appeared to receive benefit. In light of the primary endpoint not being met, the sponsor has decided to remove the planned second IA and FA and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients.

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The following sections also contain this change:

- Protocol Summary
- Schedule of Events
- Section 4.1 Overview of Study Design
- Section 4.3 Duration of Study
- Section 7.4 Study Procedures
- Section 8.1.10 Interim Analyses

Change 2: Clarify the study objectives as of Amendment 6.

The primary change occurs in Section 2 STUDY OBJECTIVES.

Added text:	**As of this amendment, the objectives are to provide continued access of MLN9708 and/or other study medications and to continue collecting relevant safety data to monitor patient safety. All other study objectives will no longer be assessed. However, the complete list of objectives is retained below for reference.**

Rationale for Change:

In light of the primary endpoint not being met, the sponsor has decided to remove the planned second IA and FA and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients.

The Protocol Summary also contains this change.

Change 3: Clarify the study endpoints as of Amendment 6.

The primary change occurs in Section 3 STUDY ENDPOINTS.

Added text:	**As of this amendment, evaluation of the safety profile of MLN9708 and/or other study medication is the only endpoint being assessed. All other study endpoints will no longer be assessed. However, the complete list of endpoints is retained below for reference.**

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Rationale for Change:

In light of the primary endpoint not being met, the sponsor has decided to remove the planned second IA and FA and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients.

The Protocol Summary also contains this change.

Change 4: Define the ongoing safety assessments as of Amendment 6.

The primary change occurs in Section 7.4.16 Adverse Events.

Added text:	Monitoring of AEs, both nonserious and serious, will be conducted throughout the study as specified in the Schedule of Events. **Upon implementation of this amendment, data collection requirements will be limited to the following safety assessments: all SAEs (regardless of causality, including all deaths), any AE resulting in dose modification or discontinuation of any study drug, Grade ≥3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose).**

Rationale for Change:

A comprehensive safety analysis was conducted using data from the first IA. As of Amendment 6, no further formal efficacy or safety analyses are planned and select safety assessments are retained to ensure patient safety.

The following sections also contain this change:

- Protocol Summary
- Schedule of Events
- Section 4.1 Overview of Study Design
- Section 7.4.9 Clinical Laboratory Evaluations
- Section 8.1.9 Safety Analysis
- Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

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Change 5: Discontinue all disease and efficacy response assessments, including central laboratory assessments of efficacy and safety, for protocol purposes because no further analyses will be performed.

The primary change occurs in Section 7.4.9 Clinical Laboratory Evaluations.

Added text:	**Per Amendment 6, centralized clinical laboratory evaluations of efficacy and safety will no longer be performed. Local laboratory evaluations should be entered into the eCRF only if required to understand a TEAE. For dosing decisions, response assessment, 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.**

Rationale for Change:

To clarify that no further efficacy or formal safety analyses will be performed for this study.

The following sections also contain this change:

- Protocol Summary
- Schedule of Events
- Section 4.1 Overview of Study Design
- Section 7.4.13 Disease Assessments
- Section 7.4.13.1 Hematologic Disease Assessments
- Section 7.4.13.2 Amyloid-Related Organ Assessments

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Change 6: Discontinue pharmacokinetic (PK) sampling for ongoing patients.

The primary change occurs in Section 7.4.14 Pharmacokinetic Measurements (Arm A Only).

Added text:	**Upon implementation of Amendment 6, blood samples for PK measurements will no longer be collected.**

Rationale for Change:

To clarify that no further PK sampling will be done for patients in the study.

The Pharmacokinetic Sampling Schedule (now moved to Section 15.12) also contains this change.

Change 7: Discontinue Quality of Life (QOL) and Health Utilization assessments for ongoing patients.

The primary change occurs in Section 7.4.10 Quality of Life Assessments.

Added text:	**Upon implementation of Amendment 6, QOL assessments will no longer be collected.**

Rationale for Change:

In light of the primary endpoint not being met, the sponsor has decided to discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients.

The following sections also contain this change:

- Section 7.4.11Health Utilization
- Section 7.4.12 EQ-5D

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Change 8: Discontinue collection of concomitant medications and procedures.

The primary change occurs in Section 7.4.15 Concomitant Medications and Procedures.

Added text:	**Upon implementation of Amendment 6, concomitant medications and procedures will not be recorded in the eCRF.**

Rationale for Change:

To reflect that no further analysis of concomitant medications or procedures will be performed for patients in the study.

Change 9: Specify that no further Adjudication Committee (AC) reviews are needed as of Amendment 6.

The primary change occurs in Section 9.3 Adjudication Committee.

Added text:	**Upon implementation of Amendment 6, AC review of response data will no longer be performed.**

Rationale for Change:

To reflect that no further efficacy or formal safety analyses will be performed for this study.

The following sections also contain this change:

- Protocol Summary
- Section 4.1 Overview of Study Design

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Change 10: Update the number of patients in the study.

The primary change occurs in Section 4.2 Number of Patients Duration of Study,

Initial wording:	Approximately 248 patients are anticipated to be enrolled into this study at approximately 75 centers in North America, Europe, and the rest of the world.
Amended or new wording:	Approximately ~~248~~**176** patients are anticipated to be enrolled into this study at approximately 75 centers in North America, Europe, and the rest of the world.

Rationale for Change:

To reflect that no new patients will be enrolled in the study after analysis of patient data from the first IA.

The following sections also contain this change:

- Protocol Summary
- Section 4.3 Duration of Study
- Section 8.1.1 Determination of Sample Size
- Section 8.1.10 Interim Analyses

Change 11: Update the estimated study duration.

The primary change occurs in Section 4.3 Duration of Study.

Initial wording:	The duration of the study will be approximately 112 months (ie, 9.3 years), including 84 months of enrollment and 28 months of follow-up after the last patient is enrolled. All patients included in the analysis for the second primary endpoint will have the opportunity to be followed for a minimum of 2 years.
Amended or new wording:	The duration of the study will be approximately ~~112~~**120** months (ie, ~~9.3~~**10** years), including 84 months of enrollment and ~~28~~**36** months of follow-up after the last patient is enrolled. ~~All patients included in the analysis for the second primary endpoint will have the opportunity to be followed for a minimum of 2 years.~~

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Rationale for Change:

To reflect the new planned duration of follow-up after the last patient was enrolled.

The Protocol Summary also contains this change.

Change 12: Discontinue the PFS and OS follow-up periods.

The primary change occurs in Section 7.4.17 Follow-Up Assessments (PFS and OS).

Added text:	**As of Amendment 6, patients will no longer be followed during any of the follow-up periods, as PFS and OS are not being collected.**

Rationale for Change:

To clarify that patients no longer need to be followed once they come off study treatment, as no further efficacy or formal safety analyses will be performed for this study.

The following sections also contain this change:

- Protocol Summary
- Schedule of Events
- Section 4.1 Overview of Study Design
- Section 7.4 Study Procedures
- Section 7.6 Discontinuation of Treatment With Study Drug, and Patient Replacement

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Change 13: Clarify the exclusion criterion for patients diagnosed with or treated for another malignancy.

The primary change occurs in Section 5.2 Exclusion Criteria.

Added text:	12. Diagnosed or treated for another malignancy within 3 years **(or 5 years for patients in France)** before study enrollment 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.

Rationale for Change:

To incorporate the France-specific requirement for prior malignancies.

Change 14: Define overdose.

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

Added text:	**Overdose** **An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study patient, at a dose above that which is assigned to that individual patient 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.**

Rationale for Change:

To define overdose and outline the clinical management of overdose should it occur.

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Change 15: Clarify the procedures for management of medication errors, including overdose.

The primary change occurs in Section 11.11 Product Complaints **and Medication Errors (Including Overdose)**.

Added text:	11.11 Product Complaints Product Complaints **and Medication Errors (Including Overdose)** ….. **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.** *[Added 'Medication Errors including Overdose for MLN9708' to contact table]*

Rationale for Change:

To provide an update to the procedures for product complaints, including instruction for medication errors and overdose.

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Change 16: Remove mention of the Safety Management Attachment (SMA).

The primary change occurs in Section 1.1.3 MLN9708, A Next-Generation Proteasome Inhibitor.

Deleted text:	As Millennium's next-generation proteasome inhibitor, MLN9708 was designed to build upon the attributes of VELCADE while also providing an option for oral administration and increased activity in tumor types where VELCADE has shown activity, and improving the safety profile (refer to the MLN9708 Investigator's Brochure ~~and Safety Management Attachment [SMA]~~).

Rationale for Change:

To remove reference to the SMA, as this document no longer exists. All applicable safety data are included in the MLN9708 IB.

Change 17: 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 should be submitted via fax (please see fax numbers below) within 24 hours of awareness. In case of fax, site personnel need to 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 need to 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, EDC/RAVE must be updated as soon as possible with the appropriate information.**

Rationale for Change:

To provide an update to the procedures for SAE reporting.

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Change 18: Specify that no further independent data monitoring committee reviews of safety and efficacy are needed as of Amendment 6.

The primary change occurs in Section 9.2 Independent Data Monitoring Committee.

Added text:	**As of Amendment 6, the primary efficacy and safety analyses have been completed for this study, and no further independent data monitoring committee reviews of safety and efficacy data will take place for patients still receiving study therapy. The sponsor will continue to monitor all cases of new primary malignancies occurring during the trial.**

Rationale for Change:

To provide an update to the procedures for monitoring efficacy and safety.

Section 10.3 Monitoring of Adverse Events and Period of Observation also contains this change.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	13-Jan-2020 20:08 UTC
[redacted]	Biostatistics Approval	14-Jan-2020 02:31 UTC
[redacted]	Clinical Science Approval	14-Jan-2020 04:54 UTC

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