MM 42

Open-Label Study to Determine the Feasibility of MLN9708 as Maintenance after Allogeneic Stem Cell Transplant for Multiple Myeloma, Followed by an Expansion Phase at the Maximum-Tolerated Dose (MTD)

SCRI INNOVATIONS STUDY NUMBER:	MM 42
STUDY DRUG:	MLN9708
SPONSOR:	SCRI Development Innovations, LLC (SCRI Innovations) 3322 West End Avenue , Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@scresearch.net
STUDY CHAIR:	Carlos Bachier, MD Program Director, Blood and Marrow Transplant Sarah Cannon Center for Blood Cancer 250 25th Ave North Nashville, TN 37203 615-342-4914 Office 210-364-3897 Cell
DATE FINAL:	11 April 2014
AMENDMENT NUMBER 1:	Date Final: 13 May 2014
AMENDMENT NUMBER 2:	Date Final: 07 May 2015
AMENDMENT NUMBER 3:	Date Final: 11 February 2016

Clinical Study Statement of Compliance

Open-Label Study to Determine the Feasibility of MLN9708 as Maintenance after Allogeneic Stem Cell Transplant for Multiple Myeloma, Followed by an Expansion Phase at the Maximum-Tolerated Dose (MTD)

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **US Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

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INNOVATIONS

Clinical Study Signature Approval Page

Open-Label Study to Determine the Feasibility of MLN9708 as Maintenance after Allogeneic Stem Cell Transplant for Multiple Myeloma, Followed by an Expansion Phase at the Maximum-Tolerated Dose (MTD)

SCRI INNOVATIONS STUDY NUMBER:		MM 42	
STUDY DRUG:		MLN9708	
DATE FINAL:		11 APRIL 2014	
Amendment Number:	1	**Amendment Date:**	13 May 2014
Amendment Number:	2	**Amendment Date:**	07 May 2015
Amendment Number:	3	**Amendment Date:**	11 February 2016

Carlos Bachier

Study Chair
Carlos Bachier, MD
Program Director
Blood and Marrow Transplant
Sarah Cannon Center for Blood Cancer

Carlos Bachier
DIGITALLY SIGNED
I am approving this document.

Study Chair Signature

02/11/2016
07:03 PM EST

Date

Sheetal Khedkar

Sponsor Representative
Sheetal Khedkar, MD MSPH
Director, Pharmacovigilance, Medical Writing, and Regulatory
SCRI Innovations

Sheetal Khedkar
DIGITALLY SIGNED
I am approving this document.

Sponsor Representative Signature

02/14/2016
08:20 PM EST

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SCRI DEVELOPMENT INNOVATIONS

Clinical Study Principal Investigator Signature Form

Open-Label Study to Determine the Feasibility of MLN9708 as Maintenance after Allogeneic Stem Cell Transplant for Multiple Myeloma, Followed by an Expansion Phase at the Maximum-Tolerated Dose (MTD)

SCRI INNOVATIONS STUDY NUMBER:		MM 42	
DATE FINAL:		11 APRIL 2014	
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Amendment Number:	3	**Amendment Date:**	11 February 2016

By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

Principal Investigator Name	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

SCRI Development Innovations
3322 West End Avenue, Suite 900
10th Floor MM 42 Study
Nashville, TN 37203

SCRI DEVELOPMENT INNOVATIONS

MM 42 Protocol Summary of Changes

AMENDMENT NUMBER:	3	AMENDMENT DATE:	11 February 2016

Additions are noted by **bolding**. Deletions are noted by ~~cross-outs~~.

Exclusion Criteria

2. Umbilical cord blood ~~or haploidentical allogeneic stem cell~~ transplant

Section 1.2.8

Allogeneic stem cell transplant can achieve better control of multiple myeloma, but carries a higher mortality as a consequence of complications related to graft-versus-host disease (GVHD) (Kumar et al. 2011). In GVHD, donor cells recognize the recipient as a foreign object and mount an immune reaction. **Haploidentical blood or marrow stem cell transplantation has historically been limited by unacceptable rates of GVHD, graft failure, and nonrelapse mortality. As a result, patients with this type of transplantation were previously excluded from this protocol. However, modern transplant techniques have remarkably reduced GVHD and have led to the increasing utilization of haploidentical donors. The feasibility of haploidentical transplantation has dramatically expanded the donor pool, making allogeneic transplantation available for the vast majority of patients (McCurdy and Fuchs 2015, Kanate et al 2015). With the introduction of Protocol Amendment 3, haploidentical allogeneic transplantion is allowed.**

MM 42 PROTOCOL SYNOPSIS

Title of Study:	Open-Label Study to Determine the Feasibility of MLN9708 as Maintenance after Allogeneic Stem Cell Transplant for Multiple Myeloma, Followed by an Expansion Phase at the Maximum-Tolerated Dose (MTD)
SCRI Innovations Study Number:	MM 42
Sponsor:	SCRI Development Innovations, LLC, Nashville, TN
Study Duration:	The total duration of the study from first patient in to last patient out is planned to be ~3 years.
Study Centers:	This study will be conducted at up to 5 centers in the United States (US).
Number of Patients:	Up to 38 patients are planned to be enrolled in this study.
Objectives:	**Primary Objectives** The primary objectives of this study are to assess the: • Maximum-tolerated dose (MTD) of MLN9708 in this patient population • Safety of MLN9708 when used as maintenance after allogeneic stem cell transplant for multiple myeloma. **Secondary Objectives** The secondary objectives of this study are to determine the: • Progression-free survival (PFS) at 2 years after initiation of maintenance therapy. • Overall survival (OS) at 2 years after allogeneic stem cell transplant. • Incidence of graft-versus-host disease (GVHD) in patients receiving allogeneic stem cell transplant and maintenance with MLN9708. • Effect of MLN9708 on immune effector cells after allogeneic stem cell transplant.
Study Design:	This is a Phase II, open-label, multicenter, non-randomized study to determine the feasibility of MLN9708 as maintenance after allogeneic stem cell transplant for multiple myeloma. Patients will be enrolled between Days 45 and 120 after allogeneic transplant and will receive MLN9708 on Days 1, 8, and 15 of each 28-day cycle for 6 cycles. Up to 18 patients will be enrolled in the dose-escalation phase to define the MTD of MLN9708. An additional 20 patients will be enrolled in the expansion phase at the MTD.
Study Drugs, Doses, and Modes of Administration:	MLN9708 will be administered orally as monotherapy. Dosing will start at 2.3 mg. If acceptable tolerability is demonstrated, escalations will be made to 3 mg and to a maximum-planned dose (MPD) of 4 mg. Once the MTD is determined, enrollment into the expansion phase will proceed at that dose.
Inclusion Criteria	Patients must meet the following criteria in order to be included in this research study: 1. Symptomatic multiple myeloma or asymptomatic myeloma with myeloma-related organ damage diagnosed according to standard criteria in patients who received allogeneic transplant due to high-risk prognostic features, such as, but not limited to: • Chromosome 17p, partial deletion [del(17p)], t(4;14), t(14;16), t(14;20) • Plasma cell leukemia • PFS of less than 2 years after autologous stem cell transplant 2. Evidence of engraftment of neutrophils (absolute neutrophil count [ANC] >1000 cells/mm^3) and platelets (platelets >60,000 cells/mm^3 [dose escalation phase] and >50,000 cells/mm^3 [dose expansion phase]) 3. Achievement of at least a PR prior to allogeneic stem cell transplant.

Inclusion Criteria (continued):	4. Adequate liver function defined as: • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 x the upper limit of normal (ULN) • Total bilirubin ≤2.0 x ULN 5. Adequate renal function defined as creatinine clearance ≥30 mL/min, estimated or calculated. 6. Age ≥18 years and ≤70 years, at time of enrollment 7. Ability to swallow oral medication 8. Absence of gastrointestinal symptoms that precludes oral intake and absorption of MLN9708 (nausea, vomiting, diarrhea, malabsorption) 9. Off antibiotics and amphotericin B formulations, voriconazole or other anti-fungal therapy for the treatment of proven, probable or possible infections (defined in accordance with the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [EORTC/MSG] criteria) 10. Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤ 2 (Appendix A). 11. Life expectancy ≥3 months 12. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 90 days following last dose of study drug. Male patients must also refrain from donating sperm during their participation in the study (Appendix C). 13. Ability to understand the nature of this study and give written informed consent before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
Exclusion Criteria:	Patients who meet any of the following criteria will be excluded from study entry: 1. Patients who have progressive disease when compared to pre-transplant staging as defined by IMWG Uniform Response criteria for Multiple Myeloma (see Appendix E). 2. Umbilical cord blood transplant 3. Patients with > Grade 2 peripheral neuropathy with pain, or ≥ Grade 3 peripheral neuropathy per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 4. Patients with uncontrolled bacterial, viral, or fungal infections 5. New York Heart Association (NYHA) Class III or IV heart failure uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities (see Appendix B). Prior to study entry, any electrocardiogram (ECG) abnormality at Screening has to be documented by the Investigator as not medically relevant. 6. Patients who are pregnant (positive beta-human chorionic gonadotropin [β-HCG]) or breastfeeding 7. Most recent chemotherapy ≤21 days and ≤ Grade 1 chemotherapy-related side effects, with the exception of alopecia 8. Use of a study drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of MLN9708. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of MLN9708 is required.

Exclusion Criteria (continued):	9. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤14 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy 10. Major surgical procedures ≤14 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement. 11. Ongoing or active systemic infection. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C 12. Central nervous system involvement 13. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. 14. Systemic treatment with strong inhibitors of cytochrome P450 (CYP) 1A2 (CYP1A2) (fluvoxamine, enoxacin, ciprofloxacin), moderate inhibitors of CYP1A2 (mexiletine, propafenone, and zileuton), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, posaconazole, and nefazodone), moderate CYP3A inhibitors (amprenavir, aprepitant, diltiazem, erythromycin, fosamprenavir, grapefruit-containing products including grapefruit juice, and verapamil), or clinically significant CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, oxcarbazepine, primidone, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before study drug administration in the study. 15. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer. 16. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 17. Graft versus host disease > Grade 2; or GVHD grade 1 or Grade 2 which requires >0.5 mg/kg methylprednisolone, or equivalent.
Correlative Testing:	Immune analysis from the peripheral blood will include: • CD3+, CD4+, CD8+, CD45+, CD19+ and CD56+/CD16+ cells by fluorescence-activated cell sorting • Regulatory T cells by intracellular staining of FoxP3 and surface staining of CD4+ and CD25+ cells • Inflammatory cytokines including IL-1β, IL-6, IL-8, IL-10 and TNF-α Participating sites will process the samples, analyse and report data for the flow cytometric analysis. Samples for cytokine analysis will be shipped to a central laboratory for analysis. Samples will be collected on Days 1 (pre-dose), 4, 8, and 15 of Cycle 1 and Day 1 (pre-dose) of Cycle 2 from 3 patients at each dose level and from 5 patients at the MTD/MPD.

MM 42 PROTOCOL SYNOPSIS

Statistical Methodology:	Safety of MLN9708 when used in this indication (primary endpoint) will be evaluated as follows. Toxicity profile data will include adverse events (AEs), laboratory parameters, vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation. Safety data will be tabulated for all patients who receive any amount of study medication. Adverse events will be tabulated by system organ class, preferred term, severity, and relation to treatment. The tabulation of laboratory parameters will indicate the normal range of each parameter. Each analyte value will be classified as falling above, below, or within the normal range. Progression-free survival and OS (efficacy secondary endpoints) estimates will be generated using Kaplan-Meier methods, both for all patients enrolled and those patients receiving the MTD. Two-year PFS and OS estimates with 95% confidence intervals (CIs), and median PFS and OS with 95% CIs, will be generated and reported accordingly. Incidence of GVHD (safety secondary endpoint) will reported in a manner consistent with the AE reporting previously described. Demographic data and baseline disease characteristics will be summarized using descriptive statistics. All statistical analyses will be performed using SAS 9.3 or the current version of SAS available at the time of analysis.

MM 42 CONTACT INFORMATION

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
β-HCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CO_2	Carbon dioxide
CR	Complete remission
CYP	Cytochrome P450
del(17p)	Chromosome 17p, partial deletion
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC/MSG	European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft-versus-host disease
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Congress on Harmonisation
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MPD	Maximum-planned dose
MRD	Minimal residual disease
MTD	Maximum-tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OS	Overall survival
PD	Progressive disease
PHI	Protected health information
PFS	Progression-free survival
PR	Partial response

SAE	Serious adverse event
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SFLC	Serum free light chains
SPEP	Serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis

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1. INTRODUCTION

1.1 Background

Multiple myeloma is a clonal disease of plasma cells that is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and commonly results in bone marrow failure, bone destruction, hypercalcemia, and renal failure. Multiple myeloma accounts for approximately 1% of all reported neoplasms and approximately 13% of hematologic cancers worldwide (Palumbo and Anderson. 2011). In North and South America and Western European countries, an estimated 5-to-7 new cases of multiple myeloma are diagnosed per 100,000 people each year (Palumbo and Anderson. 2011, Landgren and Weiss. 2009, Harousseau et al. 2008). In the United States (US), approximately 20,000 cases of multiple myeloma are diagnosed each year and 10,650 deaths per year are due to the disease (~2% of all cancer deaths). Although generally less common in Asian countries, in those with larger populations, multiple myeloma is a growing health problem, with an incidence approaching that of Western countries (Huang et al. 2007, Qiu et al. 2008).

Although multiple myeloma is considered fatal, survival has dramatically improved over the last 2 decades with the introduction of more effective treatment options. Multiple myeloma is sensitive to a number of cytotoxic drugs (e.g., alkylating agents and anthracyclines) and corticosteroids that are commonly used for initial treatment and for relapsed disease. Between 1990 and 2007, the cancer death rate for people with multiple myeloma in the US decreased by approximately 9% for males and 13% for females owing to the introduction of stem cell transplant and novel agents VELCADE® (bortezomib) for Injection, thalidomide, and lenalidomide (Jemal et al. 2010). In addition, 5-year survival improved from 25% in 1975 to 39% in 2006 (National Comprehensive Cancer Network. 2010). Most patients receive multiple lines of therapy over the course of their disease; however, responses remain transient. Bortezomib, the first proteasome inhibitor, has shown marked response in the relapsed setting and is also an effective agent in the pretransplant setting (Kumar et al. 2008).

Despite an increasing number of therapeutic options, multiple myeloma is generally considered incurable and there is considerable need for better agents. In an effort to further target the proteasome with improved activity in multiple myeloma and other cancers, Millennium has developed MLN9708, a small molecule 20S proteasome inhibitor.

1.2 MLN9708

MLN9708 is an orally bioavailable, potent, reversible inhibitor of the 20S proteasome. In Phase I studies it has been shown to be very well tolerated with minimal peripheral neuropathy. It has also shown impressive anti-myeloma activity in both the relapsed/refractory setting and the upfront setting (Kumar et al. 2011, Berdeja et al. 2011, Richardson et al. 2011). These characteristics make MLN9708 an ideal proteasome inhibitor to use after allogeneic stem cell transplant.

1.2.1 Safety Pharmacology and Toxicology

A comprehensive set of nonclinical studies have been conducted to support development of MLN9708. Detailed information regarding the nonclinical pharmacology and toxicology of MLN9708 may be found in the current Investigator's Brochure (IB).

1.2.2 Preclinical Experience

Please refer to the current MLN9708 IB and its Safety Management Attachment (SMA) provided by Millennium.

1.2.3 Clinical Experience

MLN9708 is a peptide boronic acid that is structurally different from bortezomib. MLN9708 is the first investigational oral proteasome inhibitor to enter clinical trials. Phase I, Phase I/II, and Phase II trials are ongoing or being initiated in MM and lymphoma. Phase III trials in relapsed and/or refractory multiple myeloma (RRMM), newly diagnosed multiple myeloma (NDMM), and relapsed or refractory systemic light-chain amyloidosis (RRAL amyloidosis) are underway.

As of 27 March 2014, data are available from 637 patients who have received at least 1 dose of MLN9708 across the clinical development program. In addition, 817 patients have enrolled in Phase III clinical trials, either placebo-controlled Studies C16010 or C16014 (and received either MLN9708 or placebo in combination with lenalidomide and dexamethasone [LenDex]), or in Study C16011 (and received either MLN9708 and dexamethasone or physician's choice of a dexamethasone-containing regimen).

MLN9708 is available as an IV and oral formulation; however, only the oral formulation is currently being developed for commercialization. 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 MLN9708 is given on Days 1, 8, and 15 of a 28-day cycle. Schedules with longer cycles are being investigated in Study C16006.

The following oncology indications are being studied: RRMM, NDMM, RRAL amyloidosis, solid tumors, and lymphoma. Ongoing studies are investigating both single agent MLN9708 and MLN9708 in combination with standard treatments.

1.2.4 Pharmacokinetics and Drug Metabolism

The PK of MLN9708 after IV dosing is characterized by a multi-exponential disposition profile in plasma with the terminal half-life after multiple doses ranging from 2.8 to 12.2 days. Plasma exposures increase proportionally over the dose range of 0.5 to 3.11 mg/m^2 (0.8-6.8 mg actual administered dose range). Renal elimination appears to be a minor clearance pathway for MLN9708 as renal clearance is less than 5% of the total body clearance estimate from the population PK analysis. After both once- and twice-weekly oral dosing, MLN9708 is rapidly absorbed with a median T_{max} of 1 hour. The observed range for the terminal half-life after multiple doses is 2.1 to 11.3 days. Dose proportionality has been observed for doses between 0.48 and 3.95 mg/m^2 (0.8-8.9 mg actual administered dose range).

Pharmacokinetic parameters for MLN9708 coadministered with LenDex (Studies C16005 and C16008), or MP (Study C16006), appear to be similar to those observed when MLN9708 is administered as a single agent. This suggests that there is no readily apparent effect of

coadministration of LenDex, or MP, on the clinical PK of MLN9708. Likewise, no apparent differences in the PK of MLN9708 have been noted between patients with different malignancies.

After once-weekly dosing, Day 1 geometric mean dose-normalized MLN9708 exposures in Japanese and Asian patients receiving MLN9708 plus LenDex are similar to the observed values in Western patients (Studies C16004, C16005, and C16007). On Day 15, the geometric mean dose-normalized MLN9708 $AUC_{0\text{-}168}$ in Asian patients is approximately 45% higher than the observed values in Western patients. A high-fat meal decreased both the rate and extent of absorption of MLN9708. Therefore, MLN9708 will continue to be administered on an empty stomach (no food for 2 hours before and for 1 hour after dosing).

A population PK analysis has been performed using preliminary PK data from 137 patients treated with IV and PO MLN9708 as a single agent across 4 ongoing, Phase I studies (intensive PK sampling) in Western patient populations. Patients with solid tumors, lymphoma, or MM were administered MLN9708 via IV or PO routes using BSA-based dosing on a twice-weekly (Days 1, 4, 8, and 11; 21-day cycle) or weekly (Days 1, 8, and 15; 28-day cycle) schedule.

There is a lack of a discernible relationship between BSA and MLN9708 clearance over a relatively wide BSA range (1.4-2.6 m^2) indicating that total systemic exposure (AUC) following fixed dosing should be independent of the individual patient's BSA. Therefore, BSA is not expected to affect C_{max} or AUC after IV or oral dosing, and thus fixed dosing is appropriate for both oral and IV routes of administration. The clinical development of MLN9708 has therefore transitioned from the use of BSA-based dosing to fixed dosing.

Accordingly, the starting dose of MLN9708 in the Phase III study in RRMM (Study C16010) is a fixed dose of 4.0 mg, on the basis of the recommended dose of 2.23 mg/m^2 (using mean patient BSA of 1.86 m^2 from the 2208 patients with MM in bortezomib clinical studies for conversion to a fixed dose). Also, no relationship between creatinine clearance and CL was observed in patients with a wide range of renal function (creatinine clearance range: 21.9-236.1 mL/min), so starting dose adjustment is not required in patients with mild (60-90 mL/min) and moderate (30-60 mL/min) renal impairment in clinical studies (Gupta et al. 2011). Further details on these studies are provided in the IB.

1.2.5 Clinical Trial Experience Using the Oral Formulation of MLN9708

As of 27 March 2014, a total of 491 patients with differing malignancies (MM, systemic light-chain amyloidosis [AL amyloidosis], lymphoma, and nonhematologic cancers) have received at least 1 dose of MLN9708 in Phase I, Phase I/II, and Phase II studies evaluating the oral MLN9708 formulation. These patients have been treated with different doses of MLN9708 either as a single-agent treatment (241 patients) or in combination with currently clinically available treatments (250 patients). In addition, 817 patients have enrolled in Phase II Studies C16010 and C16014 (double-blind, placebo–controlled studies in MM) and Study C16011 (open–label study in AL amyloidosis). Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1.

Table 1 Overview of Clinical Studies of Oral MLN9708

Indication	Line	MLN9708 Schedule and Combination Therapies	Enrollment Status
Multiple Myeloma	Newly Diagnosed	Ph I/II QW + LenDex (C16005)	Closed
		Ph I/II TW + LenDex (C16008)	Closed
		Ph I/II QW or TW + MP (C16006)	Enrolling
		Ph III QW + LenDex vs placebo + LenDex (C16014)	Enrolling
		Ph II QW + CD (C16020)	Enrolling
	Relapsed/ Refractory	Ph I QW (C16004)	Closed
		Ph I TW (C16003)	Closed
		Ph III QW + LenDex vs placebo + LenDex (C16010)	Enrolling
		Ph I QW + LenDex in Asia (C16013)	Enrolling
		Ph I QW single agent or + LenDex in Japanese pts (TB-MC010034)	Closed
Amyloid		Ph I QW (C16007)	Closed
		Ph III QW + Dex vs physician's choice (C16011)	Enrolling
Lymphoma	Advanced Disease	Ph I QW (C16017)	Enrolling
Clin Pharm		DDI, FE, BA QW (C16009)	Enrolling
		Renal impairment pts (C16015)	Enrolling
		Hepatic impairment QW (C16018)	Enrolling
		ADME QW (C16016)	Enrolling

Abbreviations: ADME = absorption, distribution, metabolism, and excretaion; BA = bioavailability; CD = cyclophosphamide and dexamethasone; Clin Pharm = clinical pharmacology; DDI = drug-drug interaction; Dex = dexamethasone; FE = food effect; LenDex = lenalidomide and dexamethasone; MP = melphalan and prednisone; Ph = phase; pts = patients; QW = weekly; TW = twice weekly. Gray background = Phase III trial.

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

Most Frequent Adverse Events in the Overall Safety Population

The most frequent AEs (those reported in at least 10% of the total safety population, excluding ongoing Phase III Studies C16010, C16011, and C16014), regardless of study drug causality, are shown in Table 2. Adverse events (AEs) observed to date (as of 27 March 2014) are generally reversible, manageable with standard medical interventions, and are dose dependent. The type of AEs are generally consistent across the patient populations treated to date, though some AEs may be more common either due to the patient population or the regimen being studied (e.g., thrombocytopenia is more common with weekly single-agent MLN9708 in RRMM than in RRAL amyloidosis; in RRMM, thrombocytopenia is more common with weekly single agent MLN9708 than when given in combination with LenDex; nausea is common across studies; diarrhea is more common with weekly MLN9708 in combination with LenDex than with single-agent MLN9708). Such differences may illustrate effects of the disease or prior therapy on the body (e.g., on the bone marrow) as well as the side effect profile of the agents in a combination regimen.

The more commonly observed (≥ 30% incidence) treatment-emergent AEs (TEAEs) from pooled data across clinical studies with oral MLN9708 include nausea (47%), diarrhea (47%), fatigue (45%), rash (all terms; 40%), vomiting (37%), and thrombocytopenia (33%). The frequency of rash is noted in an aggregate because it is characterized in different ways; however, it is less common when considering individual preferred terms. 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. Therefore, Table 2 includes the number of patients experiencing a rash of any term, in addition to the most frequently reported preferred terms, for added clarity about frequency.

Table 2 Overall Safety Population: Treatment-Emergent Adverse Events Reported by ≥ 10% of Patients

Primary System Organ Class Preferred Term	IV Studiesa N = 146	Oral Studiesb N = 491	Total N = 637
Subjects with at Least One Adverse Event	145 (99)	482 (98)	627 (98)
Gastrointestinal disorders	**115 (79)**	**400 (81)**	**515 (81)**
Nausea	59 (40)	230 (47)	289 (45)
Diarrhea	51 (35)	230 (47)	281 (44)
Vomiting	60 (41)	181 (37)	241 (38)
Constipation	36 (25)	134 (27)	170 (27)
Abdominal pain	28 (19)	60 (12)	88 (14)
General disorders and administration site conditions	**118 (81)**	**363 (74)**	**481 (76)**
Fatigue	89 (61)	223 (45)	312 (49)
Pyrexia	45 (31)	112 (23)	157 (25)
Edema peripheral	31 (21)	122 (25)	153 (24)
Asthenia	10 (7)	74 (15)	84 (13)
Nervous system disorders	**87 (60)**	**272 (55)**	**359 (56)**
Headache	25 (17)	85 (17)	110 (17)
Dizziness	31 (21)	74 (15)	105 (16)
Neuropathy peripheral	17 (12)	81 (16)	98 (15)
Metabolism and nutrition disorders	**89 (61)**	**267 (54)**	**356 (56)**
Decreased appetite	56 (38)	120 (24)	176 (28)
Dehydration	25 (17)	61 (12)	86 (14)
Hypokalemia	11 (8)	57 (12)	68 (11)
Blood and lymphatic system disorders	**88 (60)**	**256 (52)**	**344 (54)**
Thrombocytopenia	65 (45)	161 (33)	226 (35)
Anemia	28 (19)	114 (23)	142 (22)
Neutropenia	16 (11)	103 (21)	119 (19)
Lymphopenia	16 (11)	61 (12)	77 (12)
Skin and subcutaneous tissue disorders	**84 (58)**	**255 (52)**	**339 (53)**
Rash (all terms)	73 (50)	197 (40)	270 (42)
Rash maculo-papular	21 (14)	60 (12)	81 (13)
Rash macular	15 (10)	56 (11)	71 (11)

Table 2 Overall Safety Population: Treatment-Emergent Adverse Events Reported by ≥ 10% of Patients

Primary System Organ Class Preferred Term	IV Studiesa N = 146	Oral Studiesb N = 491	Total N = 637
Musculoskeletal and connective tissue disorders	**78 (53)**	**249 (51)**	**327 (51)**
Back pain	27 (18)	88 (18)	115 (18)
Arthralgia	17 (12)	72 (15)	89 (14)
Pain in extremity	21 (14)	66 (13)	87 (14)
Respiratory, thoracic and mediastinal disorders	**87 (60)**	**228 (46)**	**315 (49)**
Cough	32 (22)	94 (19)	126 (20)
Dyspnea	31 (21)	80 (16)	111 (17)
Infections and infestations	**48 (33)**	**244 (50)**	**292 (46)**
Upper respiratory tract infection	12 (8)	94 (19)	106 (17)
Psychiatric disorders	**32 (22)**	**151 (31)**	**183 (29)**
Insomnia	14 (10)	89 (18)	103 (16)

Source: \biostatistics\MLNM9708\IB\2014\Tables\T14.1.3-TEAE_Pct10_Pooled and \biostatistics\MLNM9708\IB\2014\Tables\T14.6.2-TEAE_AESI_Rash; data cutoff 27 March 2014.

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug.

A subject counts once for each preferred term and system organ class. Percentages use the number of treated subjects as the denominator.

a Studies C16001 and C16002.
b Studies C16003, C16004, C16005, C16006, C16007, C16008, C16009, C16013, C16015, C16017, C16018, and TB-MC010034.

1.2.6 Relapsed and/or Refractory Multiple Myeloma

The development of MLN9708 in patients with RRMM includes 2 Phase 1 dose-escalation single-agent studies (Studies C16003 and C16004).

Across these studies, 120 patients were treated, 60 in each study (Study C16003 with the twice-weekly schedule and Study C16004 with the weekly schedule). The MTD in Study C16003 was 2 mg/m2 twice-weekly dosing based on DLTs of macular rash and thrombocytopenia (platelet count = 10 x 10^9/L). The MTD in Study C16004 was 2.97 mg/m^2 given weekly based on DLTs of diarrhea, nausea, vomiting, and erythema multiforme.

At the data cut-off, with 3 patients remaining on study, the median number of cycles administered in Study C16003 was 4 (range 1-61) with 33 (55%) patients treated for ≥4 cycles, 17 (28%) for ≥8 cycles, and 11 (18%) for ≥12 cycles. Across all patients treated, including above and below the MTD, dose reductions were needed once in 57% of patients, with ≥2 reductions needed in 20% of patients.

At the data cut-off, all patients in Study C16004 have discontinued treatment. The median number of cycles administered was 2 (range 1-24) with 19 (32%) patients treated for ≥4 cycles, 12 (20%) for ≥8 cycles, and 2 (3%) for ≥12 cycles. Across all patients treated including above and below the MTD, dose reductions were needed once in 33% of patients, with ≥2 reductions needed in 13% of patients.

Final study results suggest that single-agent MLN9708 has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated(Richardson et al. 2014, Kumar et al. 2014).

1.2.7 Newly Diagnosed Multiple Myeloma (NDMM)

Three Phase I/II studies are being conducted with MLN9708 in combination with standard anti-myeloma regimens; 2 in combination with LenDex (Studies C16005 [Berdeja et al. 2011, Richardson et al. 2012 (a), Richardson et al. 2012 (b), Kumar et al. 2013] and C16008 [Richardson et al. 2012 (a)]) and 1 in combination with MP (Study C16006 [San Miguel et al. 2012]). Study C16014 is a randomized, placebo-controlled Phase III study of MLN9708 or placebo in combination with LenDex. Please refer to the MLN9708 IB and SMA for further information.

1.2.8 Rationale for the Study

The use of autologous stem cell transplantation, proteasome inhibitors, and immunomodulatory drugs has transformed the treatment landscape of patients with multiple myeloma (Jemal et al. 2010, National Comprehensive Cancer Network. 2010, Kumar et al. 2008). Despite these advances, the vast majority of patients will eventually relapse and succumb to their disease. In patients with particular high-risk features, such as those with abnormalities of chromosome 17p, circulating plasma cells, extra medullary disease, and short remission duration following aggressive induction/stem cell transplantation the outcome is especially poor with progression-free survival of less than 2 years (Richardson et al. 2011, Drake et al. 2010, Kapoor et al. 2009, Neben et al. 2012, Jimenez-Zepeda et al. 2012). Allogeneic (using donor stem cells) stem cell transplantation is an appropriate treatment option in these high-risk patients.

Allogeneic stem cell transplant can achieve better control of multiple myeloma, but carries a higher mortality as a consequence of complications related to graft-versus-host disease (GVHD) (Kumar et al. 2011). In GVHD, donor cells recognize the recipient as a foreign object and mount an immune reaction. Haploidentical blood or marrow stem cell transplantation has historically been limited by unacceptable rates of GVHD, graft failure, and nonrelapse mortality. As a result, patients with this type of transplantation were previously excluded from this protocol. However, modern transplant techniques have remarkably reduced GVHD and have led to the increasing utilization of haploidentical donors. The feasibility of haploidentical transplantation has dramatically expanded the donor pool, making allogeneic transplantation available for the vast majority of patients (McCurdy and Fuchs 2015, Kanate et al 2015). With the introduction of Protocol Amendment 3, haploidentical allogeneic transplantion is allowed.

Proteasome inhibitors have an anti-myeloma effect and are often used as either initial treatment or at relapse in patients with multiple myeloma. Proteasome inhibitors have also been shown in pre-clinical and clinical models to stimulate allogeneic immune cells to eliminate myeloma cells

and at the same time reduce the incidence and severity of GVHD (Koreth et al. 2009, El Cheik et al. 2008, Kroger et al. 2006). The use of proteasome inhibitors after stem cell transplant can therefore prolong remissions after transplant and reduce the incidence of GVHD.

This study investigates the role of MLN 9708 as maintenance in patients that undergo allogeneic stem cell transplant for high-risk multiple myeloma and in patients with multiple myeloma that undergo allogeneic stem cell transplant due to relapsing after an autologous stem cell transplant.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to assess the:

- Maximum-tolerated dose (MTD) of MLN9708 in this patient population
- Safety of MLN9708 when used as maintenance after allogeneic stem cell transplant for multiple myeloma.

2.2 Secondary Objectives

The secondary objectives of this study are to determine the:

- Progression-free survival (PFS) at 2 years after initiation of maintenance therapy
- Overall survival (OS) at 2 years after allogeneic stem cell transplant
- Incidence of graft-versus-host disease (GVHD) in patients receiving allogeneic stem cell transplant and maintenance with MLN9708
- Effect of MLN9708 on immune effector cells after allogeneic stem cell transplant.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

1. Symptomatic multiple myeloma or asymptomatic myeloma with myeloma-related organ damage diagnosed according to standard criteria in patients who received allogeneic transplant due to high-risk prognostic features, such as, but not limited to:
    - Chromosome 17p, partial deletion (del(17p), t(4;14), t(14;16), t(14;20)
    - Plasma cell leukemia
    - Progression-free survival of less than 2 years after autologous stem cell transplant

2. Evidence of engraftment of neutrophils (absolute neutrophil count [ANC] >1000 cells/mm^3) and platelets (platelets >60,000 cells/mm^3 [dose escalation phase] and >50,000 cells/mm^3 [dose expansion phase])
3. Achievement of at least a PR prior to allogeneic stem cell transplant.
4. Adequate liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 x the upper limit of normal (ULN)
   - Total bilirubin ≤2.0 x ULN
5. Adequate renal function defined as creatinine clearance ≥30 mL/min, estimated or calculated.
6. Aged ≥18 and ≤70 years, at time of enrollment
7. Ability to swallow oral medication
8. Absence of gastrointestinal symptoms that precludes oral intake and absorption of MLN9708 (nausea, vomiting, diarrhea, malabsorption)
9. Off antibiotics and amphotericin B formulations, voriconazole or other anti-fungal therapy for the treatment of proven, probable or possible infections (defined in accordance with the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [EORTC/MSG] criteria)
10. Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤ 2 (Appendix A)
11. Life expectancy ≥3 months
12. Male patients with female partners of childbearing potential and female patients of childbearing potential are required to use two forms of **acceptable** contraception, including one barrier method, during their participation in the study and for 90 days following last dose of study drug. Male patients must also refrain from donating sperm during their participation in the study (Appendix C).
13. Ability to understand the nature of this study, comply with the study procedures, and willingly give written informed consent before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

3. Patients who have progressive disease when compared to pre-transplant staging as defined by IMWG Uniform Response criteria for Multiple Myeloma (see Appendix E).
4. Umbilical cord blood transplant

5. Patients with > Grade 2 peripheral neuropathy with pain, or ≥ Grade 3 peripheral neuropathy per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0
6. Patients with uncontrolled bacterial, viral, or fungal infections
7. New York Heart Association (NYHA) Class III or IV heart failure uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities (see Appendix B). Prior to study entry, any electrocardiogram (ECG) abnormality at Screening has to be documented by the Investigator as not medically relevant.
8. Patients who are pregnant (positive beta-human chorionic gonadotropin [β-HCG]) or breastfeeding
9. Most recent chemotherapy ≤21 days and ≤ Grade 1 chemotherapy-related side effects, with the exception of alopecia
10. Use of a study drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of MLN9708. For study drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the study drug and administration of MLN9708 is required.
11. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤14 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy
12. Major surgical procedures ≤14 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement.
13. Ongoing or active systemic infection. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C
14. Central nervous system involvement
15. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
16. Systemic treatment with strong inhibitors of cytochrome P450 (CYP) 1A2 (CYP1A2) (fluvoxamine, enoxacin, ciprofloxacin), moderate inhibitors of CYP1A2 (mexiletine, propafenone, and zileuton), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, posaconazole, and nefazodone), moderate CYP3A inhibitors (amprenavir, aprepitant, diltiazem, erythromycin, fosamprenavir, grapefruit-containing products including grapefruit juice, and verapamil), or clinically significant CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, oxcarbazepine, primidone, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before study drug administration in the study.
17. Presence of other active cancers or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ

carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

18. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
19. Graft versus host disease > Grade 2; or GVHD Grade 1 or Grade 2 which requires > 0.5 mg/kg methylprednisolone, or equivalent

3.3 Discontinuation from Study Treatment

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Inability of the patient to comply with study requirements or lost to follow-up
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Pregnancy
- Protocol violation

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and eCRF. After discontinuation from protocol treatment, patients must be followed for AEs for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve, because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patients' medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the eCRF.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts. Human protection committee (Institutional Review Board [IRB]) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the SCRI Innovations Central Enrollment Desk. The enrollment desk may be reached by calling (877) MY-1-SCRI. Registration may be done via fax 1-866-346-1062 Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time. Patient registration will be confirmed via email within 24 hours, or by the next business day.

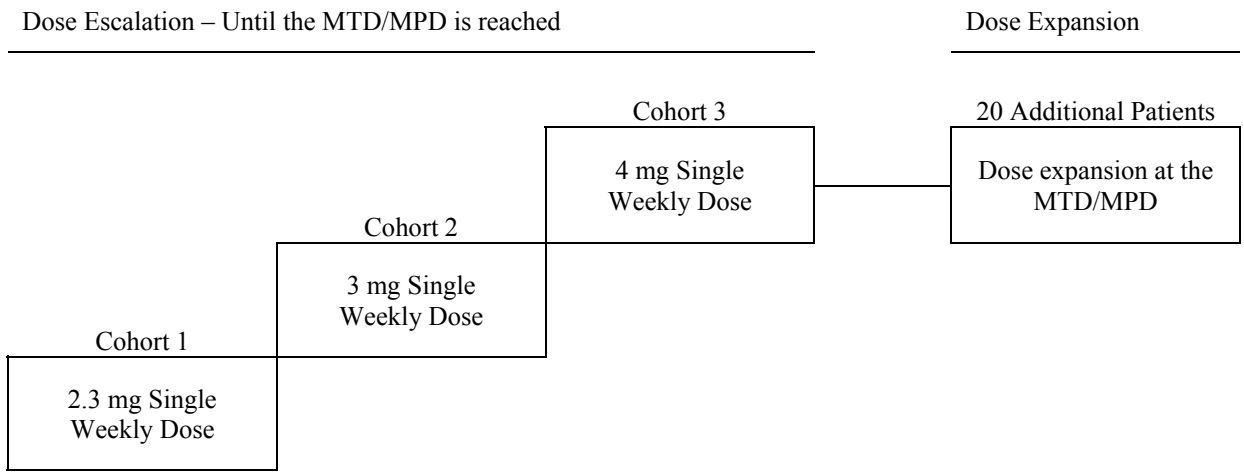
5. STUDY DESIGN

This is a Phase II, open-label, multicenter, non-randomized study to determine the feasibility of MLN9708 as maintenance after allogeneic stem cell transplant for multiple myeloma. Patients will be enrolled between Days 45 and 120 after allogeneic transplant and will receive MLN9708 on Days 1, 8, and 15 of each 28-day cycle for 6 cycles. Up to 18 patients will be enrolled in the dose-escalation phase to define the MTD of MLN9708. An additional 20 patients will be enrolled in the expansion phase at the MTD.

Up to 5 study sites are planned in the United States.

Dosing will start at 2.3 mg. If acceptable tolerability is demonstrated, escalations will be made to 3 mg and to the maximum-planned dose (MPD) of 4 mg. Once the MTD/MPD is determined, enrollment into the expansion phase will proceed at that dose. The study schema is presented in Figure 1.

Figure 1 Study Schema



MTD = Maximum-tolerated dose
MPD = Maximum-planned dose

5.1 Treatment Plan

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

MLN9708 will be administered orally as monotherapy. Dosing will start at 2.3 mg. If acceptable tolerability is demonstrated, escalations will be made to 3 mg and to the MPD of 4 mg. Once the MTD is determined, enrollment of an additional 20 patients into the expansion phase will proceed at that dose.

MLN9708 will be given on an empty stomach, with no food and fluids except for water and prescribed medications for 2 hours before and 1 hour after each dose. Each dose of MLN9708 will be given orally with approximately 8 oz (240 mL) of water. Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is at least 72 hours from that point in time. 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 be given a repeat dose, rather dosing should resume at the time of the next scheduled dose.

The capsules should not be chewed, broken, or opened for administration. Patients should be monitored for toxicity as necessary, and doses of MLN9708 should be modified on the basis of the patient's tolerability. This may include symptomatic treatment, dose interruptions, and/or adjustments of the MLN9708 dose. More conservative dose escalation, evaluation of alternative dosing, and expansion of an existing dose level are all permissible following discussions between

the Study Chair, Millennium, and the Investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity or exposure of MLN9708.

No routine prophylactic antiemetics will be given. However, antiemetics may be administered prior to treatment based on the patient's susceptibility to nausea and vomiting at the investigator's discretion, and may be given prophylactically afterwards.

5.1.1 Dose Escalation Procedure

The actual number of dose cohorts to be explored in this study will depend upon the MTD and the observed safety profile of MLN9708.

The 3 + 3 Dose-Escalation Design

Using a 3 + 3 dose escalation design, each cohort will enroll up to 6 evaluable patients. Evaluation of a cohort of at least 3 patients completing 1 cycle of treatment (28 days) is required prior to proceeding to the next dose level. Dose escalation decisions will take into account the safety profile of prior dose groups. Intrapatient dose escalation will not be allowed.

The 3 + 3 dose escalation procedure is presented in Table 3.

Table 3 Dose Escalation (3 + 3) Design

Number of Patients with a DLT	Action
0 of 3 patients	Escalate to next dose level as shown in Figure 1
1 of 3 patients	Accrue 3 additional evaluable patients at the current dose level (for a total of up to 6 evaluable patients)[a]
1 of 6 patients	Escalate to the next dose level as shown in Figure 1
2 or more patients in a dose level group of up to 6 patients	The MTD has been exceeded.

DLT = Dose-limiting toxicity

[a] For a patient to be considered "evaluable," he or she must have met the minimum safety evaluation requirements of the study, and/or experienced a DLT.

5.1.2 Dose-Limiting Toxicity

Toxicity will be assessed utilizing the NCI CTCAE v4.0, unless otherwise specified.

A toxicity will be considered dose-limiting if it occurs during the first cycle (28 days) of treatment with MLN9708 and deemed at least possibly related to therapy per treating physician's discretion. Patients who experience a dose-limiting toxicity (DLT) in the first cycle of therapy will discontinue treatment with MLN9708. Dose-limiting toxicities will be defined as the following:

- Grade 4 neutropenia for >7 days, or febrile neutropenia
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding

- Grade 3 or 4 non-hematologic toxicity with the following exceptions:
  - alopecia
  - Grade 3 rash, nausea, diarrhea, and vomiting, if controlled to ≤ Grade 2 with standard supportive care within 72 hours
- Treatment delay of ≥14 days due to unresolved toxicity
- For patients with ALT, ALP and bilirubin below ULN at enrollment: Hy's law: Hepatocellular injury (defined as ALT >2 x ULN and (ALT/ULN)/(alkaline phosphatase [ALP]/ULN) >5) and bilirubin >2 x ULN or jaundice ± ALK <2 x ULN
- For patients with ALT, ALP and/or bilirubin above ULN at enrolment: Increase of 3x above baseline level.

Determination of Dose-Limiting Toxicities

The patient population used for determination of DLTs will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT. Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives all (3 of 3) scheduled doses of MLN9708, completes all required safety evaluations, and is observed for at least 28 days following the first dose of MLN9708. An isolated laboratory abnormality could also be considered criteria for seriousness (e.g., results in hospitalization or considered medically significant).

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all end-of-treatment safety evaluations performed as described in the protocol (see Section 7.5). If a patient withdraws from treatment during Cycle 1 due to any reason other than a DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described above, that patient will be replaced.

5.1.3 Maximum-Tolerated Dose

The MTD is the highest dose at which ≤1 of 6 patients experience a DLT during 1 cycle (28 days) of therapy. If 2 or more patients in a dosing group of ≤6 patients experience a DLT, the MTD has been exceeded. If 2 or more patients in a doses group of up to 6 patients experience a DLT and only 3 patients were evaluated at the previous (i.e., next lower) dose, then an additional 3 patients will be evaluated at this next lower dose and if zero or one have DLTs then this previous dose level is declared the MTD.

5.1.4 Expansion after Determination of the Maximum-Tolerated Dose

Once the MTD is determined, the MTD cohort of patients will be expanded with an additional 20 patients to further characterize the safety and clinical benefits of maintenance with MLN9708 after allogeneic stem cell transplant. If the MTD is not reached, the expansion will proceed at the MPD.

5.2 Treatment Duration

The total duration of the study from first patient enrolled to last patient out is planned to be approximately 3 years.

Based on tolerability, patients will receive 6 cycles of MLN9708 as maintenance therapy following an allogeneic stem cell transplant.

5.3 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used prior to treatment based on the patient's susceptibility to nausea and vomiting 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.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted in Cycle 1 of the dose escalation phase if the patient has a neutrophil value that meets DLT criteria and after Cycle 1 of the dose escalation phase. Their use should follow published guidelines and/or institutional practice.
- Erythropoietin will be allowed in this study according to standard clinical practice. Their use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets in Cycle 1 of the dose escalation phase if the patient has a platelet value that meets DLT criteria and as clinically indicated and according to institutional guidelines.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator with the exception of those listed in Section 5.3.2.

5.3.2 Prohibited Concomitant Medications and Procedures

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients.
- Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted in this study. A DDI with a strong inhibitor would increase MLN2238 exposure:
    - Strong inhibitors of CYP1A2: fluvoxamine, ciprofloxacin, and enoxacin
    - Moderate inhibitors of CYP1A2: mexiletine, propafenone, and zileuton
    - Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, posaconazole and nefazodone
    - Moderate inhibitors of CYP3A: amprenavir, aprepitant, diltiazem, erythromycin, fosamprenavir, grapefruit-containing products (including grapefruit juice), and verapamil
- Systemic treatment with any of the following metabolizing enzyme inducers is not permitted in this study:
    - Clinically significant CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, oxcarbazepine, primidone, phenytoin, and phenobarbital

  For the most updated information, visit the following website: http://medicine.iupui.edu/clinpharm/ddis/.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

The following procedures are prohibited during the study:

- No anticancer agents should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study. Adjuvant hormone therapy for breast or prostate cancer
- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).
- Platelet transfusions to help patients meet eligibility criteria or pre-dose for dosing decisions on treatment are not allowed within 3 days before study drug dosing.

5.4 Precautions and Restrictions

Fluid deficits should be corrected before and throughout treatment.

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.

5.5 Correlative Studies

For patients who participate in the exploratory biomarker research component of this study, peripheral blood samples will be collected on Days 1 (pre-dose), 4, 8, and 15 of Cycle 1 and Day 1 (pre-dose) of Cycle 2. Participating patients will include 3 patients at each dose level and 5 additional patients at the MTD.

Immune analysis from the peripheral blood will include:

- CD3+, CD4+, CD8+, CD45+, CD19+ and CD56+/CD16+ cells by fluorescence-activated cell sorting
- Regulatory T cells by intracellular staining of FoxP3 and surface staining of CD4+ and CD25+ cells
- Inflammatory cytokines including IL-1β, IL-6, IL-8, IL-10 and TNF-α

Participating sites will process the samples, analyse them, and report data for the flow cytometric analysis. Samples for cytokine analysis will be shipped to a central laboratory for analysis. For shipment, handling, etc. of the correlative testing blood samples blood, see the Study Manual.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v4.0, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Study drug will be delayed if patients develop > Grade 2 GVHD and until GVHD is ≤ Grade 2. If GVHD severity returns to ≤ Grade 2, study drug can be restarted at the initial dose. If GVHD recurs, hold dose until GVHD is ≤ Grade 2 and restart at next lower dose level. GVHD stopping criteria during administration of study drug includes the development of Grade 3 or 4 GVHD in more 80%, 70%, or 60% of the first 10, 20, or 30 patients enrolled, respectively. Patients that do not complete one cycle of maintenance because of GVHD will be replaced. Criteria for GVHD are presented in Appendix F.

6.1 Dose Modifications Due to Hematologic Toxicity

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. Patients whose treatment is delayed due to toxicity will discontinue study drug or will proceed with the next cycle of treatment when toxicity has improved (as long as the toxicity resolves within 3 weeks) according to the dose modifications below. Treatment with MLN9708 will be held in any patient experiencing a DLT as described in Section 5.1.2 at any time during the study. Patients who experience a DLT in the first cycle of therapy will be discontinued from treatment with MLN9708. Dose modifications following treatment-related toxicity in subsequent cycleswill be according to the dose modifications below.

Dose reductions for toxicity will be allowed. For patients in the first cohort, MLN9708 may be delayed, but not reduced. For patients in Cohorts 2 and 3, doses will first be delayed and then

reductions will be allowed based on clinical judgment of the treatment physician (see Figure 1). If persistent toxicity occurs despite dose delays and/or reductions, the patient will be removed from the study.

Any patients who require a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment, unless the treating physician and the Study Chair agree that continued treatment at lower doses is in the best interest of the patient.

6.1.1 Recommended MLN9708 Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity on Day 1 of a New Cycle

Treatment with MLN9708 will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be $\geq 1{,}000/mm^3$.
- Platelet count must be $\geq 40{,}000/mm^3$.
- 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 initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to reevaluate. The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the Principal Investigator.

Table 4 Dose Modifications Due to Hematologic Toxicities within a Treatment Cycle (Day 8 and Day 15 of a Treatment Cycle)

Event	Action[d]
Neutropenia (ANC)	
ANC <0.5 x 10^9/L (Grade 4) or febrile neutropenia	Hold dose until recovery to ≤ Grade 2 [ANC ≥1.0 x 10^9/L], then resume MLN9708 at one lower dose level[a] (if applicable[b]). Note: If resolved in ≤5 days, then resume without a dose reduction.
Recurrence of ANC <0.5 x 10^9/L (Grade 4) or febrile neutropenia	Hold[a] dose until ANC recovery to ≤ Grade 2 [ANC ≥1.0 x 10^9/L], then resume MLN9708 at one lower dose level[a] (if applicable[b]).
Thrombocytopenia	
Platelets <30 x 10^9/L	Hold dose until improvement to platelets ≥30 x 10^9/L • If resolved in ≤5 days, then resume without a dose reduction[c]. • If resolved in >5 days but <3 weeks, then resume dose at one lower dose level[c] (if applicable[b]).

[a] Hold MLN9708 treatment; do at least weekly CBC with differential until toxicity resolves (ANC recovery ≥1.0 x 10^9/L and platelets ≥30 x 10^9/L).
[b] Patients on 2.3 mg of MLN9708 will not undergo a dose reduction.
[c] Re-treatment criteria = ANC recovery ≥1.0 x 10^9/L and platelets ≥30 x 10^9/L.
[d] Any patient who requires a treatment delay of more than 3 weeks due to treatment-related toxicity will be discontinued from study treatment, unless the treating Investigator and Study Chair agree that continued treatment at lower doses is in the best interest of the patient.ANC = absolute neutrophil count, CBC = complete blood count.

6.2 Dose Modifications due to Non-Hematologic Toxicity

The dose reduction guidelines for non-hematologic toxicities are presented in Table 5.

Table 5 Dose Reductions for Grade 3 or 4 Non-Hematologic Toxicities

Criteria	Action
Peripheral Neuropathy:	
Newly developed Grade 1 peripheral neuropathy with pain, ≥ Grade 2 peripheral neuropathy	Hold MLN9708 until resolution to ≤ Grade ≤ 1 without pain or baseline
Grade 2 neuropathy with pain or Grade 3 peripheral neuropathy	Hold MLN9708 until resolution to Grade ≤ 1 without pain or baseline. Reduce MLN9708 to next lower dose (if applicable*) upon recovery.

Criteria	Action
Grade 4 peripheral neuropathy	Discontinue MLN9708.
Grade 2 rash and/or pruritis	Follow at least weekly. See Section 6.3.4 Specific Recommendations for Management of Clinical Events
Grade 3 Non-Hematologic Toxicities or recurrent Grade 3 Non-Hematologic Toxicities that do not recover to Grade < 1 or baseline within 4 weeks	MLN9708 therapy should be withheld until symptoms have resolved to ≤ Grade 1 or baseline. Reduce MLN9708 to next lower dose (if applicable*) upon recovery. Note: a dose level reduction will be made either on the basis of within-cycle or for a subsequent cycle criteria, but not for both from the same cycle.
Grade 4 Non-Hematologic Toxicities	Discontinue MLN9708. Upon toxicity recovery, if the patient has received clinical benefit from therapy with MLN9708, the Investigator and the Study Chair may consider restarting therapy.

*Patients on 2.3 mg of MLN9708 will not undergo a dose reduction.

6.3 Specific Recommendations for 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.

6.3.1 Prophylaxis against Risk of Infection

Antiviral therapy such as acyclovir or valacyclovir may be initiated as clinically indicated and per institutional standards. Other antivirals are also acceptable. Patients who do not receive antiviral therapy should be made aware of risks, such as reactivation of herpes zoster and herpes simplex viruses.

6.3.2 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 based on the patient's susceptibility to nausea and vomiting; prophylactic anti-emetics may also be considered at the discretion of the investigator. Fluid deficit should be corrected before initiation of study drug and during treatment.

6.3.3 Diarrhea

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

6.3.4 Erythematous Rash With or Without Pruritus

Rash has been reported with MLN9708. As with bortezomib, rash with or without pruritus has been reported with MLN9708, primarily at the higher doses tested. The rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is 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 (10mg of prednisone/day) 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). . In the event of rash, a skin biopsy is suggested to assess etiology.

A rare risk is Stevens-Johnson syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. In the case of rash, punch biopsies for histopathological analysis are encouraged at the discretion of the Investigator.

6.3.5 Thrombocytopenia

Thrombocytopenia has been reported with MLN9708. 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 Table 4). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura, a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. Thrombotic thrombocytopenic purpura should be managed symptomatically according to standard medical practice.

6.3.6 Neutropenia

Neutropenia has been reported with MLN9708. 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 with G‑CSF according to standard clinical practice. MLN9708 administration should be modified as noted as per dose modification

recommendations in the protocol when neutropenia occurs (see Table 4). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

6.3.7 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 during treatment.

6.3.8 Hypotension

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

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

6.3.10 Transverse Myelitis

Transverse myelitis has also been reported with MLN9708. It is not known if MLN9708 causes transverse myelitis; however, because it happened to a patient receiving MLN9708, the possibility that MLN9708 may have contributed to transverse myelitis cannot be excluded.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix D.

Informed consent must be obtained ≤28 days prior to initiation of treatment and before any protocol-specific procedures are performed. The Baseline visit physical examination including vital signs, medical history, ECOG performance status, complete blood counts (CBC), differential and platelets, comprehensive metabolic profile (CMP), urinalysis, and PT/aPTT/INR should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of first study drug administration they do not have to be repeated on

Day 1 of Cycle 1. A pregnancy test must be performed within 72 hours of first study drug administration.

7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at Baseline ≤7 days prior to initiation of treatment unless otherwise noted:

- Written informed consent prior to any other study-related procedures (≤28 days of first study drug treatment)
- Medical history including:
  - Review of systems
  - Prior treatments for all significant conditions, including neuropathy
  - ECOG performance status prior to conditioning for allogeneic transplant
  - Pre allogeneic transplant overall comorbidity index
  - Transplant history including
    - Conditioning regimens including total dose and start and end dates
    - Type of transplant (syngeneic, autologous or allogeneic; bone marrow versus peripheral blood stem cells; match related versus matched unrelated)
    - Date of transplant
    - Date of engraftment of white cells and platelets
    - Number of allogeneic CD34+ cells received (record for allogeneic transplant only)
    - Graft versus host disease prophylaxis
    - Post-transplant infections
  - Prior systemic therapy for multiple myeloma with start and end dates and best overall response to therapy
  - Prior radiation therapy for multiple myeloma with total dose, start and end dates
  - Prior surgeries for multiple myeloma and date
- Physical examination, including a neurological evaluation, measurements of height (first visit), weight, and vital signs (resting heart rate, blood pressure [BP], respiratory rate, and oral temperature)
- ECOG performance status (see Appendix A)
- Acute GVHD assessment with overall grade (see Appendix F)
- Chronic GVHD assessment with overall grade (see Appendix F)
- 12-lead ECGs in triplicate approximately 5 minutes apart

- Chest X-ray
- Concomitant medication review of all medications taken within 21 days of first planned study drug administration for conditions other than GVHD
- Concomitant medication review specifically for GVHD prophylaxis since receiving the allogeneic transplant
- CBC, including 3-part differential (total neutrophil count including bands, lymphocytes, monocytes) hemoglobin, hematocrit, and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine (creatinine clearance calculated by Cockcroft-Gault), sodium, potassium, chloride, calcium, phosphorus, magnesium, carbon dioxide (CO_2), ALT, AST, ALP, lactate dehydrogenase (LDH), uric acid, total bilirubin, total protein, and albumin
- Urinalysis (dipstick)
- Coagulation tests: prothrombin time (PT), activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR)
- Serum or urine pregnancy test for women of childbearing status (must be performed within 72 hours prior to the initiation of treatment)
- Disease assessments:
    - Bone marrow aspirate and biopsy including:
        - Quantify percent myeloma cell involvement
        - Obtain bone marrow aspirate for cytogenetics [i.e., diploidy, del(13)] and include number of metaphases analyzed
        - Mutations detected in fluorescent in situ hybridization (FISH) studies [i.e., t(4:14); t(11:14); del(17p)]
        - If available, provide MRD by flow cytometry
    - Skeletal survey (lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri) ≤28 days of first study drug treatment.
    - Serum free light chains (SFLC)
    - Serum protein electrophoresis (SPEP) and serum protein immunofixation to determine M-protein
    - Urine protein electrophoresis (UPEP), urine protein immunofixation (requires a 24-hour urine collection), and total protein in urine
    - Serum quantitative immunoglobulins
    - Serum β2 microglobulin

- Known plasmacytomas, utilize same modality used to assess original disease (i.e., PET, MRI, CT, etc)

- Gene expression profile analysis, if available (prior to bone marrow transplant and prior to enrolment)

7.3 Study Treatment Assessments

7.3.1 All Cycles Day 1 (± 2 days)

- Medical history update
- Physical examination including a neurological evaluation, measurement of weight, and vital signs
- ECOG performance status
- Acute GVHD assessment with overall score
- Chronic GVHD assessment with overall score
- AE assessment
- Concomitant medication review of all medications taken for conditions other than GVHD
- Concomitant medication review specifically for GVHD prophylaxis since receiving the allogeneic transplant
- Percentage chimerism conducted per institutional guidelines
- CBC including 3-part differential (total neutrophil count including bands, lymphocytes, monocytes) hemoglobin, hematocrit, and platelets
- CMP to include: glucose, BUN, creatinine (creatinine clearance calculated by Cockcroft-Gault), sodium, potassium, chloride, calcium, phosphorus, magnesium, CO_2, ALT, AST, ALP, LDH, uric acid, total bilirubin, total protein, and albumin
- Urinalysis (dipstick; if abnormal microscopic performed as clinically indicated)
- PT/aPTT/INR
- Biomarker blood sample collection for flow cytometry (conducted and reported by participating sites) and cytokine analysis (conducted by a central laboratory) (**Cycles 1 and 2 only for patients participating in the exploratory biomarker research**)

7.3.2 Cycle 1 Days 4, 8, and 15

- Physical examination (symptom directed) (**Days 8 and 15 only**)
- AE assessment (**Days 4, 8, and 15**)
- Concomitant medication review of all medications taken for conditions other than GVHD (**Days 4, 8 and 15**)
- Concomitant medication review specifically for GVHD prophylaxis since receiving the allogeneic transplant (**Days 4, 8 and 15**)

- Acute GVHD assessment with overall score, only for patients who have onset of GVHD post allogeneic transplant **(Days 8 and 15 only)**
- Chronic GVHD assessment with overall score, only for patients who have onset of GVHD post allogeneic transplant **(Days 8 and 15 only)**
- CBC, including 3-part differential (total neutrophil count including bands, lymphocytes, monocytes) hemoglobin, hematocrit, and platelets (**Days 8 and 15 only**)
- CMP to include: glucose, BUN, creatinine (creatinine clearance calculated by Cockcroft-Gault), sodium, potassium, chloride, calcium, phosphorus, magnesium, CO_2, ALT, AST, ALP, LDH, uric acid, total bilirubin, total protein, and albumin (**Days 8 and 15 only**)
- Urinalysis (dipstick; if abnormal microscopic performed as clinically indicated) (**Days 8 and 15 only**)
- Biomarker blood sample collection for flow cytometry (conducted and reported by participating sites) and cytokine analysis (conducted by a central laboratory) (**Days 4, 8 and 15 for patients participating in the exploratory research**)

7.3.3 Cycles 2 through 6 Days 8 and 15

- AE assessment
- Concomitant medication review of all medications taken for conditions other than GVHD
- Concomitant medication review specifically for GVHD prophylaxis since receiving the allogeneic transplant
- Acute GVHD assessment with overall score, only for patients who have onset of GVHD post allogeneic transplant
- Chronic GVHD assessment with overall score, only for patients who have onset of GVHD post allogeneic transplant
- CBC, including 3-part differential (total neutrophil count including bands, lymphocytes, monocytes) hemoglobin, hematocrit, and platelets

7.4 Response Assessments

Patients will be re-evaluated for response to treatment after 2 cycles of treatment. Response will be assessed at 8-week intervals (±1 week) during study treatment. Patients with progressive disease (PD) or unacceptable toxicity should be discontinued from the study; patients with stable disease (SD) or response to therapy will continue treatment through 6 cycles.

The following assessments will be performed as clinically indicated:

- Bone marrow aspirate and biopsy (to confirm CR only) including:
  - Quantify percent myeloma cell involvement
  - Obtain bone marrow aspirate for cytogenetics [i.e., diploidy, del 13] and include number of metaphases analyzed

  - Mutations detected in FISH studies [i.e., t(4:14); t(11:14); del 17p]
  - If available, provide MRD by flow cytometry
- SFLC
- SPEP and serum protein immunofixation to determine M-protein
- UPEP, urine protein immunofixation (requires a 24-hour urine collection), and total protein in urine
- Serum quantitative immunoglobulins
- Known plasmacytomas, utilize same modality used to assess original disease (i.e., PET, MRI, CT, etc)

Above response assessment will be performed every 3 months for 2 years after completion of maintenance therapy until disease progression.

7.5 End-of-Treatment Visit

Patients are permitted to continue maintenance treatment with MLN9708 through 6 cycles. Patients may be discontinued before the end of 6 cycles due to disease progression, unacceptable toxicity, or the decision to discontinue treatment by the patient or the study physician. After withdrawal from or completion of protocol treatment, patients must be followed for any new AEs for 30 calendar days after the last dose of study drug.

Thirty days (±3 days) days after completion of the planned study treatment period or early discontinuation, the following tests and observations will be conducted:

- Update of medical history
- Physical examination including a neurological evaluation, measurement of weight, and vital signs
- ECOG performance status
- Acute GVHD assessment with overall score
- Chronic GVHD assessment with overall score
- AE assessment
- Concomitant medication review of all medications taken for conditions other than GVHD
- Concomitant medication review specifically for GVHD prophylaxis since receiving the allogeneic transplant
- CBC, including 3-part differential (total neutrophil count including bands, lymphocytes, monocytes) hemoglobin, hematocrit, and platelets
- CMP to include: glucose, BUN, creatinine (creatinine clearance calculated by Cockcroft-Gault), sodium, potassium, chloride, calcium, phosphorus, magnesium, CO_2, ALT, AST, ALP, LDH, uric acid, total bilirubin, total protein, and albumin

- Urinalysis (dipstick; if abnormal microscopic performed as clinically indicated)
- Disease assessment:
  - Bone marrow aspirate and biopsy (to confirm CR only) including:
    - Quantify percent myeloma cell involvement
    - Obtain bone marrow aspirate for cytogenetics [i.e., diploidy, del 13] and include number of metaphases analyzed
    - Mutations detected in FISH studies [i.e., t(4:14); t(11:14); del 17p] to confirm CR
    - If available, provide MRD by flow cytometry
  - SFLC
  - SPEP and serum protein immunofixation to determine M-protein
  - UPEP, urine protein immunofixation (requires a 24-hour urine collection), and total protein in urine
  - Serum quantitative immunoglobulins
  - Known plasmacytomas, utilize same modality used to assess original disease (i.e., PET, MRI, CT, etc)

7.6 Follow-up

Please see Appendix D.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 MLN9708

Investigational Product	Dosage Form and Strength	Manufacturer
MLN9708	2.3, 3.0, and 4.0mg	Millennium Pharmaceuticals, Inc

8.1.1 Labeling, Packaging, and Supply

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

MLN9708 will be supplied for oral administration by Millennium Pharmaceuticals, Inc. Capsules will be supplied color-coded by strength and will be individually packaged in blisters with a paper backing for child resistance.

The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations. The immediate packaging will contain a statement to conform with US Food and Drug Administration (FDA) Investigational New Drug (IND) requirements as follows: Caution: New Drug - Limited by Federal (or United States) law to investigational use.

All study drugs must be kept in a secure place under appropriate storage conditions. MLN9708 capsules should be stored unopened at 2 to 8ºC (36 to 46ºF). The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. The 2.3-, 3.0-, and 4.0 mg capsules are supplied as a 1 x 3 blister card in a child-resistant cardboard wallet.

The SCRI Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Storage and Handling

Upon receipt at the investigative site, MLN9708 should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). 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.

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 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 cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (e.g., 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.

8.1.3 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

8.1.4 Preparation and Administration of MLN9708

Patients will receive their study medication at the study site. The batch number of the study drug dispensed to the patient should be entered on the eCRF, if applicable.

MLN9708 will be given on an empty stomach, with no food and fluids except for water and prescribed medications for 2 hours before and 1 hour after each dose. Each dose of MLN9708 will be given with approximately 8 oz (240 mL) of water. If the patient vomits after taking a dose, another dose should not be given that day, but dosing should resume at the time of the next scheduled dose.

8.1.5 Precautions and Risks Associated with Handling MLN9708

MLN9708 drug product is a cytotoxic anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling MLN9708. Please refer to published guidelines regarding the proper handling and disposal of cytotoxic agents.

MLN9708 capsules must be administered as intact capsules and are not intended to be opened or manipulated in any way.

8.1.6 Potential Risks and Benefits

Please refer to the current MLN9708 Investigator's Brochure (IB) and its Safety Management Attachment (SMA) provided by Millennium.

MLN9708 is a modified dipeptide boronic acid proteasome inhibitor similar to b, which has a known safety profile [VELCADE PI]. The most frequent AEs reported to date in the ongoing MLN9708 phase 1 studies were anticipated based on preclinical data and previous experience with VELCADE, and are noted in the IB, the Safety Management Attachment, and the informed consent documents. However, it is possible that MLN9708 will have toxicities that were not previously observed in or predicted from such sources. Patients will be monitored closely for anticipated toxicities.

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 (Chow et al. 2012, Assouline et al. 2012, Lonial et al. 2012, Kumar et al. 2012 (a), Kumar et al. 2012 (b), Richardson et al. 2012 (c), San Miguel et al. 2012).

8.2 Accountability for All Study drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the Sponsor or its representatives and regulatory agency inspectors upon request.

At the end of the study, all SCRI Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the SCRI Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact SCRI Innovations regarding disposal of any study drug.

8.3 MLN9708 Destruction

Investigational MLN9708 (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the International Myeloma Working Group Uniform Response Criteria (see Appendix E).

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

All response categories (CR, sCR, VGPR, PR, PD) require two consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments are not required to be confirmed by repeat testing.

Complete response should be confirmed with a bone marrow biopsy for morphology and a bone marrow aspiration for flow cytometry, FISH, and cytogenetics performed locally. Additional confirmatory studies include SPEP, UPEP, immunofixation of blood and urine, and SFLC (see Appendix D).

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is an open-label, multicenter, non-randomized study to determine the feasibility of MLN9708 as maintenance after allogeneic stem cell transplant for multiple myeloma. Patients will be enrolled between Days 45 and 120 after allogeneic transplant and will receive MLN9708 on Days 1, 8, and 15 of each 28-day cycle for 6 cycles.

10.2 Sample Size Considerations

For the dose-escalation phase of the study, a minimum of 2 and a maximum of 6 patients will be enrolled in each of 3 cohorts. Therefore, the maximum number of patients to determine the MTD will be 18. When the MTD is determined, an additional 20 patients will be enrolled in the expansion phase at either the MTD or the MPD.

10.3 Analysis Population

The following analysis populations will be used:

- The Safety population will consist of all patients who received at least one dose of MLN9708. This population will be used in all safety summaries.
- The Efficacy Evaluable population will consist of all patients with measurable or evaluable disease at baseline who receive at least 1 dose of MLN9708 and undergo at least one post-baseline disease assessment. In addition, patients who discontinued the study prior to their first post-baseline disease assessment due to death or progressive disease will also be included in the Efficacy Evaluable population.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented.

10.4.1 Demographics and Baseline Characteristics

Demographic data and baseline disease characteristics will be summarized using descriptive statistics.

10.4.2 Efficacy Analysis

- PFS, defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by the International Myeloma Working Group Uniform Response Criteria (see Appendix E), or death on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.
- OS, defined as the time from the first day of study drug administration (Day 1) or death on study. Patients who are alive will be censored at the date of last known date alive.

Progression-free survival and OS (efficacy secondary endpoints) estimates will be generated using Kaplan-Meier methods, both for all patients enrolled and those patients receiving the MTD. Two-year PFS and OS estimates with 95% confidence intervals (CIs), and median PFS and OS with 95% CIs, will be generated and reported accordingly.

The effect of MLN9708 on immune effector cells after allogeneic stem cell transplant will be analyzed by examining the difference in the actual change from baseline at Cycle 1 Day 4, Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 2 Day 1, and the percentage change from baseline at Cycle 1 Day 4, Cycle 1 Day 8, Cycle 1 Day 15, and Cycle 2 Day 1, among those patients participating in the biomarker research component. Each analysis will be performed within dose level and total patients.

The following parameters will be examined:

- CD3+, CD4+, CD8+, CD45+, CD19+ and CD56+/CD16+ cell counts, by fluorescence-activated cell sorting
- Regulatory T cell counts by intracellular staining of FoxP3, and surface staining of CD4+ and CD25+ cells
- Inflammatory cytokine concentrations of IL-1β, IL-6, IL-8, IL-10 and TNF-α.

For each parameter, the actual change from baseline and the percentage change from baseline, at each time point, will be analyzed using the two-sided Wilcoxon signed-rank procedure to test whether either the change is statistically different from zero.

The significance level will be set at 10%, and there will be no adjustment to the alpha level for multiple comparisons. The rationale for the reporting of p-values in these analyses is for hypothesis-generating purposes only.

10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE v4.0.

The AEs will be coded using Medical Dictionary for Regulatory Activities, and summarized using system organ class and preferred term by dose level for all patients in the Safety Population. In addition, summaries of serious AEs (SAEs), AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented by dose level.

Safety of MLN9708 when used in this indication (primary endpoint) will be evaluated as follows: Toxicity profile data will include AEs, laboratory parameters, vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation. Safety data will be tabulated for all patients who receive any amount of study medication. Adverse events will be tabulated by system organ class, preferred term, severity, and relation to treatment. The tabulation of laboratory parameters will indicate the normal range of each parameter. Each analyte value will be classified as falling above, below, or within the normal range.

Incidence of GVHD (safety secondary endpoint) will reported in a manner consistent with the AE reporting previously described.

10.4.4 Planned Interim Analysis

Data will be reviewed by the Investigator and Study Chair before advancing to the next cohort, but formal interim analyses will not be performed.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting AEs to the SCRI Innovations Safety Department (see Section 11.1.7). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of that IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 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.

11.1.2 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

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.

11.1.3 Serious Adverse Event

An AE or a suspected adverse reaction is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE (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)**
- **Inpatient hospitalization of at least 24-hours or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 hospitalization, or 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.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.4 Adverse Event of Special Interest Definition

Adverse Events of Special Interest (AESIs) are a subset of AEs that are to be reported to Millennium on a quarterly basis by the sponsor-investigator. Millennium will provide the current list of AESIs and updates to the list will be distributed to the sponsor-investigator as appropriate.

11.1.5 Adverse Reaction

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

11.1.6 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.7 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the Investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the Investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.0, and changes will be documented.

If the AE is serious, it should be reported immediately to SCRI Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs

(i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the Investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to MLN9708 treatment (called study treatment), spanning from the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment related are to be reported.

11.1.8 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.

NO: Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating Investigator as serious require expeditious handling and reporting to SCRI Innovations Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through 30 days after the last dose of study drug. **The SCRI Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to SCRI Innovations Safety Department via fax or e-mail using the using the following contact information (during both business and non-business hours):

SCRI Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@ scri-innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Innovations Safety Department as soon as it is available; these reports should be submitted using the SCRI Innovations SAE Report Form.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the Investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the SCRI Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as a SAE to the SCRI Innovations Safety Department.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.3). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form should be completed and faxed to the SCRI Innovations Safety Department. SCRI Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to SCRI Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the SCRI Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A

Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 MLN9708 Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the SCRI Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

Five cases of overdose are described in the IB. No significant information was identified concerning MLN9708 overdose. The AEs reported with these cases were the same type as seen in the population receiving the appropriately prescribed dose.

11.4 Sponsor Serious Adverse Event Reporting Requirements

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the date the participant signs Informed Consent through 30 days after administration of the last dose of MLN9708. Any SAE that occurs at any time after completion of MLN9708 treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, SCRI Innovations Safety Department on behalf of the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Follow-up information on the SAE may be requested by Millennium. The SAE report must include event term(s), serious criteria, and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

SCRI Innovations Safety Department will forward SAE information to Millennium Pharmaceuticals, Inc., within 1 business day of SCRI Innovations Safety Department personnel becoming aware of the SAE.

SAE and Pregnancy Reporting Contact Information

Millennium Pharmacovigilance or Designee

SAE and Pregnancy Reporting Contact Information

FAX Number 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

SCRI Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Conference on Harmonisation guidelines and FDA regulations.

11.4.1 Procedures for Reporting AESIs

AEs may be 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. 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 one comprehensive event. For nonserious AEs (including AESIs), the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

11.4.2 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-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 11.4). 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-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 11.4). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (a sample is provided in Appendix G)

11.4.3 Sponsor Assessment of Unexpected

The Sponsor is responsible for assessing an AE or suspected AE as "unexpected".

An AE or suspected adverse reaction is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current US Package Insert)
- Event(s) is not listed at the specificity or severity that has been observed

- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or Suspected Adverse Reactions that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation

When applicable, an unexpected AE may also apply to an event that is not listed in the current IB or an event that may be mentioned in the IB, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the IB), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the current IB.

11.4.4 Sponsor Reporting for Clinical Studies Under an Investigational New Drug Application

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s) as soon as possible but no later than 4 calendar days of such communication.

Millennium Pharmacovigilance or Designee

SAE and Pregnancy Reporting Contact Information

FAX Number 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

12. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice (GCP) outlined in the International Congress on Harmonisation (ICH) E6 Tripartite Guideline and the Code of Federal Regulations (CFR) Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.1 Institutional Review Board Approval

The clinical study protocol, informed consent form (ICF), IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements),

information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for MLN9708, will be prepared by the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

12.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

12.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB/IEC submission.

12.3.1 Confidentiality

12.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of Sponsor, the regulatory authorities, Millennium, and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

12.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub Investigator, SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

12.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the SCRI Innovations and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

12.5 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

13. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

13.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and/or FDA or other regulatory authorities approval which include but are not limited to the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug

- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Principal Investigator.

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

13.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

SCRI Development Innovations
3322 West End Avenue, Suite 900
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the Principal Investigator and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of SCRI-Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

13.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are

obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed CRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRF records, and medical records), all original, signed ICFs, and copies of all eCRF records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the

Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor throughout the study, and will be transferred to the Sponsor at the conclusion of the study.

13.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI and replaced instead with the patient number and patient's initials. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF system must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

13.5 Study Monitoring, Auditing, and Inspecting

The Investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for inspections of applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification may be performed on all data items or a percentage thereof.

Participation as an Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB and the Sponsor or its representative(s).

13.6 Quality Assurance and Quality Control

Each study site shall be required to have Standard Operating Procedures to define and ensure quality assurance/control processes for study conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

13.7 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication strategy.

13.8 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. 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 applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

13.9 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact 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.

For Product Complaints
call MedComm Solutions at
877-674-3784 (877 MPI DRUG)
(US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 11.4).

13.10 Closure of the Study

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

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

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

13.11 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s).

14. 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 trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

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16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >> 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

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.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Guidelines for Women of Childbearing Potential and Fertile Male Patients

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 in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (i.e., 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 in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Appendix D: MM 42 Schedule of Assessments

Procedures	Pre-TX	Cycle 1 Cycle = 28 days				Cycles 2 to 6 Cycle = 28 days			Reassess Every 2 Cycles (8 weeks)	End of Study Treatment[r]	Follow-up	
	Baseline	Day				Day					Off Study Prior to Progression[s]	After Disease Progression[t]
		1	4	8	15	1 (± 2 days)	8	15				
TESTS & OBSERVATIONS												
Written informed consent[a]	X											
Medical history[b]	X	X				X				X	X	
Physical examination[b,c]	X	X	X[c]	X[c]	X[c]	X				X	X	
ECOG performance status[b]	X	X				X				X	X	
GVHD assessment[d]	X	X		X[d]	X[d]	X	X[d]	X[d]		X	X	
12-lead ECG[e]	X											
Chest X-ray	X											
Adverse event evaluation		X	X	X	X	X	X	X		X	X	
Concomitant medications (GVHD and non-GVHD)	X	X	X	X	X	X	X	X		X	X	
Response assessment[f]									X[e]	X[e]	X[e]	
Survival status												X
LABORATORY TESTS												
CBC, 3-part diff &platelets[b,g]	X	X		X	X	X	X	X		X	X	
CMP[b,h]	X	X		X	X	X				X	X	
Urinalysis[b,i]	X	X		X	X	X				X		
PT/aPTT/INR[b]	X	X				X						
Serum or Urine β-HCG[j]	X											
Biomarker blood sample[k]		X	X	X	X	X						
Percentage chimerism[l]		X[l]				X[l]					X[l]	
DISEASE ASSESSMENTS												
Bone Marrow Aspira/Biopsy[m]	X								X[m]	X[m]		
Skeletal Survey[n]	X											
Serum free light chain	X								X[q]	X[q]	X[q]	
SPEP & immunofixation	X								X	X	X	
UPEP & immunofixation[o]	X								X	X	X	
Serum immunoglobulins	X								X	X	X	
Serum β-2 microglobulin	X											
Known plasmacytomas[p]	X								X	X	X	

[a] Written informed consent must be obtained before any study-related procedure is performed and ≤28 days prior to the initiation of study treatment.

[b] The Baseline visit physical examination, medical history (see Section 7.2), ECOG performance status, CBC, CMP, PT/aPTT/INR, and urinalysis should be done <7 days prior to initiation of treatment. However, if these initial examinations are obtained ≤72 hours before first study treatment they do not have to be repeated on Day 1 of Cycle 1.

[c] Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature). At the Baseline visit only, height will also be recorded. Physical examinations will be done on Day 1 of each cycle. In addition during Cycle 1 only, patients will have a symptom directed physical examination done on Days 4, 8, and 15.

[d] Acute and chronic GVHD assessment is to be conducted at baseline and Day 1 of every cycle. Patients that develop GVHD will have the assessment conducted every visit on Days 1, 8, and 15 of every cycle.

[e] Three 12-lead ECGs will be collected approximately 5 minutes apart at the Baseline visit. Additional ECGs will be done as clinically indicated.

[f] Patients will be re-evaluated for response to treatment after 2 cycles of treatment. Response will be assessed at 8-week intervals (±1 week) during study treatment. Patients with progressive disease (PD) or unacceptable toxicity should be discontinued from the study; patients with stable disease (SD) or response to therapy will continue treatment.

[g] Hematology parameters include the following laboratory tests: CBC with 3-part differential (total neutrophil count including bands, lymphocytes, monocytes) hemoglobin, hematocrit and platelets.

[h] CMP to include: glucose, BUN, creatinine (creatinine clearance calculated by Cockcroft-Gault), sodium, potassium, chloride, calcium, phosphorus, magnesium, CO_2, ALT, AST, ALP, LDH, uric acid, total bilirubin, total protein, and albumin.

[i] A urine dipstick will be done weekly during Cycle 1. Thereafter, urine dipstick will be done on Day 1 of each 4-week cycle. If abnormalities are present on urine dipstick, additional testing (e.g., microscopic examination, urine protein:creatinine ratio [UPC], etc.) should be done as clinically indicated.

[j] A serum pregnancy test will be performed only for women of childbearing potential within 72 hours of study drug administration (see Appendix C).

[k] Biomarker blood samples: peripheral blood samples will be collected on Days 1 (pre-dose), 4, 8, and 15 of Cycle 1 and on Day 1 (pre-dose) of Cycle 2 only. Participating patients will include 3 patients at each dose level and 5 additional patients at the MTD/MPD.

[l] Report percentage chimerism conducted by institutional guidelines. Above provided schedule is preferred, but not required.

[m] Bone marrow aspirate and biopsy – quantify percent myeloma cell involvement, and obtain bone marrow aspirate for cytogenetics [i.e., diploidy, del(13)] and FISH studies [i.e., t(4:14); t(11:14);del(17p)], and at the response assessments to confirm CR only. If available, provide MRD by flow cytometry at baseline.

[n] Skeletal survey (lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri) ≤28 days of first study drug treatment. Only repeat if clinically indicated (i.e., bone pain).

[o] UPEP requires the collection of a 24-hour urine sample.

[p] Repeat if abnormal at baseline.

[q] All patients will undergo the end of treatment visit assessments listed within 30 days after treatment ends due to completion of the planned study treatment period, or once a patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End of Treatment Visit. After withdrawal from or completion of protocol treatment, patients must be followed for AEs for 30 calendar days after the last dose of study drug.

[r] Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months during years 1 and 2.

[s] After disease progression is documented, patients will be followed every 3 months during years 1and 2 for survival assessment.

[t] For known plasmacytomas, utilize the same modality used to assess original disease (i.e., PET, MRI, CT, etc).

Appendix E: International Myeloma Working Group Uniform Response Criteria

Response Category	Definition
sCR **Stringent Complete Response**	CR criteria as defined below AND • Normal free light chain (FLC) ratio AND • Absence of phenotypically aberrant PCs in bone marrow[b] analyzed by multiparametric flow cytometry
CR **Complete Response**	• Negative immunofixation on the serum and urine AND • Disappearance of any soft tissue plasmacytoma(s) AND • ≤ 5% plasma cells in bone marrow[b]. • In case the only measurable disease in a patient with CR at baseline is the serum FLC level, a normal FLC ratio of 0.26 to 1.65 is required additionally to qualify for CR.
VGPR **Very Good Partial Response**	• Serum and urine M-protein detectable by immunofixation but not by electrophoresis (PEP) or ≥90% reduction from baseline serum) AND urine M-protein level <100 mg/ 24h AND • In case of presence of soft tissue plasmacytoma(s) at baseline, disappearance of any soft tissue plasmacytomas In case the only measurable disease in a patient with VGPR at baseline is the serum FLC level (i.e. no measurable disease in serum and urine PEP), a decrease of > 90% in the difference between involved and uninvolved FLC levels from baseline is required.
PR **Partial Response**	≥50% reduction from baseline in serum M-protein AND ≥ 90% reduction from baseline in 24h urinary M-protein OR urine M-protein <200 mg/24h If serum and urine M-protein are non-measureable at baseline, a ≥ 50% reduction form baseline in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are non-measurable, and serum free light assay is also non-measurable, ≥50% reduction from baseline in percent plasma cells in bone marrow is required instead of M-protein measurement, provided baseline plasma cells in bone marrow was ≥ 30%. AND In case of presence of soft tissue plasmacytoma(s) at baseline, a reduction in the SPD by ≥50% is required.

Appendix E: International Myeloma Working Group Uniform Response Criteria: Complete Response and Other Response Categories (continuation)

SD	Not meeting criteria for sCR, CR, VGPR, PR or PD
PD **Progressive Disease**	Increase of ≥ 25% from the nadir in at least one of the following criteria: • serum M-protein (absolute increase must be ≥0.5 g/dL and absolute value must be ≥1 g/dL) • urine M-protein (absolute increase must be ≥200 mg/24h) • only in patients with non-measurable serum and urine M-protein levels: difference in involved and uninvolved FLC levels (absolute increase must be >10 mg/L) • Bone marrow plasma cell percentage (absolute % must be ≥10%) OR • development of new lytic bone lesions or increase from baseline in size of lytic bone lesion(s) OR • development of new soft tissue plasmacytoma(s) or definite increase from nadir in existing soft tissue plasmacytomas OR • development of hypercalcemia (corrected serum calcium >11.5 mg/dL) for patients without hypercalcemia at baseline. In case of preexisting hypercalcemia at baseline, PD will only be assessed due to the hypercalcemia criterion in case the corrected serum calcium level was ≤11.5 mg/dL post-baseline and increased thereafter beyond 11.5 mg/dL.

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

Source: Kyle RA and Rajkumar SV Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009. 23:3-9

Appendix F: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Acute and Chronic Graft-Versus-Host Disease

Organ Staging of Acute GVHD

Stage	Skin	Liver	GI tract
Organ staging 0	No rash due to GvHD	Bilirubin < 2 mg/dl or 35 µmol/l	None
I	Maculopapular rash < 25% of body surface area without associated symptoms	Bilirubin from 2 mg/dl to < 3 mg/dl or 35-50 µmol/l	Diarrhea > 500-1000 ml/day; nausea and emesis
II	Maculopapular rash or erythema with puritis or other associated symptoms ≥ 25% of body surface area or localized desquamation	Bilirubin from 3 mg/dl to < 6 mg/dl or 51-102 µmol/l	Diarrhea> 1000 to 1500 ml/day; nausea and emesis
III	Generalized erythroderma or symptomatic macular, papular, or vesicular eruption with bullous formation or desquamation covering ≥ 50% of body surface area	Bilirubin 6 mg/dl to < 15 mg/dl or 103-225 µmol/l	Diarrhea > 1500 ml/day; nausea and emesis
IV	Generalized exfoliative dermatitis or bullous eruption	Bilirubin > 15 mg/dl or > 225 µmol/l	Diarrhea > 1500 ml/day; nausea and emesis. Abdominal pain or ileus

Overall Clinical Grading of Acute GVHD

Grade	Skin	Liver	GI tract	Performance status
0	0	0	0	0
I	1-2	0	0	0
II	1-3	1	1	1
III	2-3	2-3	2-3	2
IV	2-4	2-4	2-4	2-4

Reference for both tables for acute GVHD: Przepiorka et al. 1995

Organ Staging of Chronic GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS[†] FEV1 ☐ DLCO ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl ___	Progressive onset___	

OTHERS: Specify:_____

Reference for chronic GVHD tables: Filipovich et al. 2005

Appendix G: Pregnancy Reporting Form

Pregnancy Form

Report Type: ❒ Initial ❒ Follow-up | Date of Report: ___/___/_____ (DD MM Yr)

REPORTER INFORMATION: (Please forward if an alternative physician is more appropriate)

Reporter name: _____ Title: _____

Address: _____ Telephone No.: _____ Fax No. _____

City, State/Province: _____ Postal Code: _____ Country: _____

FATHER'S INFORMATION ❒ Father Unknown

Initials: _____ Date of Birth: ___/___/_____ (DD MM Yr) or Age: _____ years

Participating in an MPI clinical study? ❒ No ❒ Yes

If no, what company product was taken: _____

If yes, please provide: Study drug: _____ Protocol No: _____

Center No: _____ Patient No: _____

Medical / Familial / Social History

(i.e. include chronic illnesses: specify, familial birth defects/genetic/chromosomal disorders; habitual exposure: specify, alcohol/tobacco; drug exposure: specify, substance abuse and medication use. Please include drug treatment prior to or around the time of conception and/or during pregnancy)

_____

_____

Race: _____

Occupation: _____

Number of children: _____

MOTHER'S INFORMATION:

Initials: _____ Date of Birth: ___/___/_____ (DD MM Yr) or Age: _____ years

Participating in an MPI clinical study? ❒ No ❒ Yes

If no, what company product was taken: _____

If yes, please provide: Study drug: _____ Protocol No: _____

Center No: _____ Patient No: _____

Race: _____

Occupation: _____

Medical / Familial / Social History

(i.e. include alcohol/tobacco and substance abuse; complications of past pregnancy, labor/delivery, fetus/baby; illnesses during this pregnancy; assisted conception: specify; other disorders including familial birth defects/genetic/chromosomal disorders; method of diagnosis consanguinity, etc.)

_____

_____

_____

Number of previous pregnancies: Full term ____ Pre-term ____

Outcomes of previous pregnancies:

(Please indicate number of occurrences)

- Spontaneous abortion: _____
- Therapeutic abortion: _____
- Elective abortion: _____
- Other: _____
- Normal live birth: _____
- Children born with defects: _____
- Stillbirth: _____
- Outcome unknown: _____

MOTHER'S DRUG EXPOSURE INFORMATION

Please include medical prescriptions, vaccinations, medical devices, OTC products, pregnancy supplements (such as folic acid, multivitamins)

Product Name	Dosage	Route administered to patient	Date of first use (DD/MM/Yr)	Date of end treatment (DD/MM/Yr)	Indication	Contraindicated to pregnancy
			(__/__/____)	(__/__/____)		❒Yes ❒No ❒Unk
			(__/__/____)	(__/__/____)		❒Yes ❒No ❒Unk
			(__/__/____)	(__/__/____)		❒Yes ❒No ❒Unk
			(__/__/____)	(__/__/____)		❒Yes ❒No ❒Unk

e-Pregnancy Form (27 November 2013)

Appendix G: Pregnancy Reporting

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form

CURRENT PREGNANCY INFORMATION

Period at exposure: _____ weeks Trimester (1) (2) (3)
Date of last menstrual period: ___/___/_____ (DD MM Yr) ❒ Unknown

Pregnancy Status
- ◯ Pregnancy Ongoing
  Estimated date of delivery: ___/___/_____ (DD MM Yr)
- ◯ Live Birth
- ◯ Stillbirth
- ◯ Early Termination
  - ◯ Spontaneous abortion*
  - ◯ Therapeutic abortion*
  - ◯ Elective abortion*
  - ◯ Other*:_____

**If box is checked, please note reason in "Additional Details" section below*

Fetal/Neonatal Status
- ❒ Normal
- ❒ Birth defect (structural/chromosomal disorder)*
- ❒ Other (non-structural, premature birth, intrauterine death/stillbirth)*

**If box is checked, please note details in "Additional details" section below*

Additional Details:

Is there evidence of a defect from a prenatal test? ❒Yes ❒No

If yes, indicate which test(s) showed evidence of birth defect:

❒Ultrasound ❒Amniocentesis ❒Maternal Serum-Alpha-Fetoprotein

❒Chorionic Villi Sampling ❒Human Chorionic Gonadotropin ❒Other:_____

Please specify details of defect(s), disorder(s), and/or other anomaly(ies): _____

What are the defect(s) attributed to:_____

Infant Information:

Gestational weeks at birth or at termination: _____weeks

Date of birth or termination: ___/___/_____ (DD MM Yr)

If multiple births (e.g. twins), indicate number: ____

(Please complete separate form for each child)

Birth Order (1, 2, 3, etc.) _____

Breast-fed: ❒Yes ❒ No ❒ Unk

Method of delivery: ❒ Normal vaginal ❒ Caesarean section ❒ Other: _____

Sex: ❒ Male ❒ Female ❒ Unk

Length: _____ ❒ cm ❒ in

Weight: _____ ❒ g ❒ lbs

Head circumference: _____ ❒ cm ❒ in

Apgar score (0-10) at 1 minute: ____ ❒ Unk

Apgar score (0-10) at 5 minute: ____ ❒ Unk

Resuscitation required: ❒ Yes ❒ No ❒ Unk

Admission to intensive care required: ❒ Yes ❒ No ❒ Unk

Additional Notes:

_____

_____

_____

Please attach RELEVANT LABORATORY TESTS AND PROCEDURES (e.g. results of ultrasounds, amniocentesis, chorionic villi sampling, or miscellaneous testing as applicable). In the case of an abnormal evolution or outcome, please send copies of results of all relevant laboratory testing and procedures, including pathology results of products of conception and or autopsy reports if applicable. Please submit any additional relevant information on a separate sheet.

Investigator signature: _____ Date: ___/___/_____ (DD MM Yr)

Investigator Name: _____

e-Pregnancy Form (27 November 2013)

Form