Protocol title: The MLN9708 for the prophylaxis of chronic graft-versus-host disease in patient undergoing allogeneic transplantation.

Document date: 03-13-18

NCT number: NCT02250300

The MLN9708 for the prophylaxis of chronic graft-versus-host disease in patient undergoing allogeneic transplantation.

Principal Investigator: Mehdi Hamadani, MD
Associate Professor of Medicine,
Division of Hematology and Oncology
Froedtert Hospital and the Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226

Protocol Team: Parameswaran Hari, MD, MRCP, MS
William R Drobyski, MD
Timothy S. Fenske, MD
Douglas Rizzo, MD
Marcelo Pasquini, MD
Mary Eapen, MD
Wael Saber, MD
Anita D'Souza, MD
Bronwen Shaw, MD
Nirav Shah, MD
Sameem Abedin, MD
Lyndsey Runaas, MD
James Jerkins, MD

Statistician: Alexis Visotcky, MS
Biostatistician II
Division of Biostatistics
Institute for Health and Society
avisotcky@mcw.edu

Study Coordinator:
For Medical College of Wisconsin:
Kassandra Cantrall
Froedtert Hospital and the Medical College of Wisconsin
Cancer Center Clinical Trials Office
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Phone: 414-805-8755
Fax: 414-805-0596
Email: kcantrall@mcw.edu

Pharmacist
For Medical College of Wisconsin:
Angela Urmanski, Pharm D.
Froedtert Hospital
Inpatient Pharmacy
Attn: Senad Novic
9200 W Wisconsin Ave
Milwaukee, WI 53226

CLINICAL STUDY PROTOCOL

Protocol Number = IISR-2013-M100104; Grant Number: X16034
MLN9708 for the prophylaxis of chronic graft-versus-host disease in patient undergoing allogeneic transplantation.

Indication: Chronic graft-versus-host disease prophylaxis
Phase: Phase I/II

Protocol History

Original	23 August 2013
Amendment 1	04 November 2014
Amendment 2	25 June 2015
Amendment 3	15 March 2017
Amendment 4	14 September 2017
Amendment 5	13 March 2018

This is an investigator-initiated study. The principal investigator Mehdi Hamadani, MD (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

Study Title: MLN9708 for the prophylaxis of chronic graft-versus-host disease.

Phase: Phase I/II

Number of Patients: 6 patients were enrolled in phase I portion. No DLTs were seen. In the phase II portion a total of 52 patients (25 sibling and 27 unrelated donor transplantation) will be enrolled. Total accrual = 58 patients.

Study Objectives

Primary Objectives:

Phase I Primary Objectives:

1. To determine the maximum tolerated dose (MTD), dose limiting toxicity (DLT) and recommended phase II dose (RDP) of MLN9708 for the prophylaxis of chronic GVHD in patients undergoing allogeneic hematopoietic cell transplantation (HCT).

Phase II Primary Objectives:

2. Determine the 1-year (from the date of HCT) cumulative incidence of chronic GVHD following MLN9708 administration as prophylaxis, in patients undergoing matched sibling allogeneic HCT.
3. Determine the 1-year (from the date of HCT) cumulative incidence of chronic GVHD following MLN9708 administration as prophylaxis, in patients undergoing unrelated donor allogeneic HCT.

Phase I/II Primary Objectives:

4. Assess the safety of chronic GVHD prophylaxis with MLN9708 in patients undergoing allogeneic HCT.

Secondary Objectives:

1. To assess the 1-year and 2-year (from the date of HCT) cumulative incidence of corticosteroid requiring chronic GVHD, in the matched sibling and unrelated donor cohorts separately.
2. Determine the 2-year (from the date of HCT) cumulative incidence of chronic GVHD following MLN9708 administration as prophylaxis, in the matched sibling and unrelated donor cohorts separately.
3. To assess the 1-year and 2-year (from the date of HCT) cumulative incidence of mild, moderate and severe chronic GVHD (by NIH criteria) and limited or extensive chronic GVHD (by conventional criteria), in the matched sibling and unrelated donor cohorts separately.
4. To assess cumulative incidence of grade II-IV acute GVHD at days +100, +180 and +365, in

the matched sibling and unrelated donor cohorts separately.

5. To assess cumulative incidence of grade III-IV acute GVHD at days +100, +180 and +365, in the matched sibling and unrelated donor cohorts separately.
6. To assess non-relapse mortality rate at 100 days, 1-year post-HCT.
7. To assess the incidence of motor and sensory neuropathy associated with MLN9708
8. To assess incidence of secondary graft failure.
9. To assess incidence of secondary immunologic graft rejection.
10. To assess relapse rate of the primary hematological malignancy.
11. To assess lineage specific chimerism kinetics in patients at baseline (approximately day +30), day +100, day +180 and day +365.
12. To assess immune reconstitution following transplantation at baseline (approximately day +30), day +100, day +180, day +365 and day +730.
13. To assess absolute neutrophil count on day +100, day +180 and day +365.
14. Response of acute GVHD to MLN9708 at day +100, in those patients with controlled grade I-II acute GVHD at the time of enrollment.
15. To assess 1-year and 2-years progression free survival (PFS) and overall survival (OS) following transplantation.
16. To evaluate biologic markers potentially associated with GVHD and/or MLN9708.

Overview of Study Design:

This is a phase I/II study of MLN9708 for the prophylaxis of chronic GVHD in patients undergoing allogeneic HSCT. During the phase I portion patients undergoing both sibling and unrelated donor transplantation will be enrolled on the same arm to determine the DLT and MTD. During the phase II portion of the trial, patients will be enrolled into two separate and independent cohorts: a) Matched sibling transplants and b) Unrelated donors transplants. Both cohorts will be enrolled and analyzed separately.

Study Population:

Inclusion criteria:

1. Patients with a history of a hematological malignancy or bone marrow failure syndrome undergoing (or status post) a peripheral blood allogeneic HCT.
2. Patients aged ≥18 are eligible.
3. All patients must have received or plan to receive an allograft from a suitable HLA-matched sibling or unrelated donor according to transplant center's guidelines (for selection of appropriate donor).
4. Voluntary written consent must be given before patient registration and 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.
5. Bilirubin ≤ 2 x the ULN. For patients with Gilbert's syndrome or suspected mild veno-occlusive disease, bilirubin ≤ 3 x ULN is permitted.
6. Creatinine clearance of ≥ 30 mL/min calculated by Cockcroft-Gault equation.
7. Karnofsky performance status > 60.
8. A negative pregnancy test will be required for all women of child bearing potential. Females of child bearing potential should 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 [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.). Breast feeding is not permitted.
9. Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following: practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or 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 (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
10. No evidence of uncontrolled bacterial, viral or fungal infections at the time of enrollment.
11. No known active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

Exclusion Criteria:

1. Patients with active ≥ grade 3 peripheral neuropathy or grade 2 with pain on clinical examination during the screening period will be excluded.
2. Patients with history of allergy and/or intolerance to MLN9708 are not eligible.
3. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 including difficulty swallowing is not permitted.
4. Patients receiving (or status post) a cord blood or a haplo-identical allograft will not be eligible.
5. Patients undergoing (or status post) a T-cell depleted allogeneic transplantation will not be eligible.
6. Patients receiving (or status post) conditioning regimens containing antithymocyte globulin, and/or campath, one receiving post-HCT planned cyclophosphamide will not be eligible.
7. Method of stem-cell collection from the donor will be at the discretion of the treating physician. Although it is anticipated that majority of patients will receive allograft mobilized with G-CSF alone; however donors receiving allografts mobilized with experimental agents (e.g. plerixafor) will remain eligible for the study.
8. Patients experiencing disease relapse (for those in complete remission at the time of HCT) or progression (for those in partial remission, stable or refractory disease at the time of HCT) will be excluded.
9. Donor lymphocyte infusions between day zero of HCT and first dose of MLN9708 are not permitted.
10. Rituximab (or other B-cell depleting monoclonal antibodies) or bortezomib administration between day zero of HCT and before the first day of MLN9708 is not permitted.
11. Patients with steroid refractory (defined as no improvement of symptoms after 7 days of systemic corticosteroids at a dose of ≥1mg/kg/day) grade II-IV acute GVHD, that is active at the time of enrollment will be excluded.
12. Patients with grade III-IV acute GVHD (even if it is not meeting criteria for steroid refractory acute GVHD), that is active at the time of enrollment will be excluded. Patients with controlled grade I-II acute GVHD can be enrolled after discussing with study PI. Topical or systemic corticosteroids therapy, as per standard of care for such grade I-II acute GVHD patients is permitted.
13. Patients with active chronic GVHD (although unlikely before day +100) will be excluded.
14. No major surgery within 14 days before enrollment.
15. No radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the MLN9708.
16. No evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months. Cardiac enzyme elevations for reasons other than document myocardial infarction is not an exclusion.
17. No systemic treatment, within 14 days before the first dose of MLN9708, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone,

posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

18. No serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
19. No participation in clinical trials with other investigational agents, within 21days of the start of this trial and for two weeks after the last dose of MLN9708 or resolution of MLN9708 related adverse events to grade 1 or less (whichever occurs later). However, co-enrollment on trials evaluating conditioning regimens, institutional protocols evaluating atorvastatin for acute GVHD prophylaxis, and stem cell collection protocols in transplant donors will be permitted. In addition, patients randomized to standard-of-care (non-experimental) arms of available phase II/III trials will be eligible for this study.

Duration of Study: Accrual period: Approximately 24-30 months.

ABBREVIATIONS USED:

AE: ADVERSE EVENT

AESIS: ADVERSE EVENTS OF SPECIAL INTEREST

APC: ANTIGEN PRESENTING CELLS

BAFF: B CELL ACTIVATING FACTOR

BCRP: BREAST CANCER RESISTANCE PROTEIN

CL: CLEARANCE

CYP: CYTOCHROME P450

DLT: DOSE LIMITING TOXICITY

FDA: FOOD AND DRUG ADMINISTRATION

FOXP3: FORKHEAD BOX P3

GVHD: GRAFT-VERSUS-HOST DISEASE

GVL: GRAFT-VERSUS-LEUKEMIA

HSCT: ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

IL-1: INTERLEUKIN 1

IFN: INTERFERON

MHC: MAJOR HISTOCOMPATIBILITY COMPLEX CLASS

MRP2: MULTIDRUG RESISTANCE ASSOCIATED PROTEIN

MTD: MAXIMUM TOLERATED DOSE NDMM: NEWLY DIAGNOSED MULTIPLE MYELOMA

P-GP: P GLYCOPROTEIN

PK: PHARMACOKINETIC

RDP: RECOMMENDED PHASE II DOSE

SAE: SERIOUS ADVERSE EVENT

STATINS: HMG-COA REDUCTASE INHIBITORS

TH-1: T HELPER TYPE 1

TH-2: T HELPER TYPE 2

TMAX: MAXIMUM PLASMA CONCENTRATION

TNF: TUMOR NECROSIS FACTOR

TREG: REGULATORY T

TW: TWICE WEEKLY

W: WEEKLY

Table of Contents

1. Introduction:

Graft-versus-host disease (GVHD) is one of the most frequent complications after allogeneic hematopoietic stem cell transplantation (HSCT) [1]. Acute and chronic forms of GVHD develops in 30-75% of recipients of allogeneic HSCT depending on the degree of histocompatibility between the donor and the recipient, number of T-cells in the graft, recipient's age and GVHD prophylactic regimen used [2-4]. Novel strategies designed to effectively prevent the development of this life threatening complication of allogeneic transplantation are urgently needed. Immune modulation with atorvastatin in matched sibling transplantation, in our experience has shown promise in preventing acute GVHD; however rates of chronic GVHD remain high. No pharmacological agents are currently approved or considered standard treatment for preventing chronic GVHD, following allogeneic HSCT. Extensive preclinical and clinical data (discussed in subsequent sections) suggest efficacy of proteasome inhibitors as novel agents, with potential to prevent chronic GVHD. MLN9708 is an oral proteasome inhibitor, associated with reduced risk of peripheral neuropathy. The current phase I/II study aims to investigate the role of MLN9708, as a novel, oral pharmacological prophylaxis for chronic GVHD in patients receiving standard acute GVHD prophylaxis post allogeneic HSCT.

Pathophysiology of Acute GVHD:

Acute GVHD is initiated when donor T cells encounter host APCs in lymphoid tissues and become activated [5]. This T-cell activation process requires co-stimulation via CD80 and CD86, which are up-regulated on APCs during the early phase of acute GVHD. Activation is enhanced by local tissue damage due to the conditioning regimen. Local proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin 1 (IL-1), and interferon (IFN)-gamma, promote Th-1 differentiation of donor-derived T cells and enhance their proliferation and reactivity against host tissues [6]. Massive cytokine release related to the Th-1 phenotype predicts the incidence and severity of acute GVHD in both murine models and humans, whereas patients with high IL-10 production are less at risk for GVHD development [7-9].

Statins as Potential Modulators of GVHD:

HMG-CoA reductase inhibitors (statins), the cholesterol-lowering drugs that are prescribed worldwide to prevent and treat atherosclerosis, are increasingly being recognized to exhibit a variety of immunomodulatory properties [10]. Reduced mevalonate production by statins, not only inhibits the synthesis of cholesterol but also that of key isoprenoid intermediate molecules required for the isoprenylation of GTP-binding cell signaling proteins such as Ras, Rho and Rac [11]. By inhibiting this posttranslational modification, statins affect intracellular signaling pathways and cellular functions such as differentiation, motility, secretion and proliferation [12, 13]. Inhibiting Ras leads to a bias towards T helper type 2 (Th-2) cell development, and inhibition of pro-inflammatory Th-1 driven responses [12, 14]. This change in intracellular signaling can also affect the development of regulatory T (Treg) cells, as exposure of human CD4+ T cells to atorvastatin *in vitro* increases expression of forkhead box P3 (FOXP3) [15]. In fact. increased numbers of circulating FOXP3+ Treg cells are present in dyslipidemic patients taking statins for 4-6 weeks [15]. In addition to direct effects on T cells, statins can also indirectly decrease T-cell activation by inhibiting interferon-γ–induced expression of major histocompatibility complex class (MHC) II and by blocking up-regulation of a variety of co-stimulatory molecules and cytokines in antigen presenting cells (APCs) [12]. Hence statins appear to suppress T cell–dependent immune responses at many levels and hold promise as a new class of immunomodulatory drugs, with potential role in preventing acute GVHD.

Statins and Murine Acute GVHD:

Zeiser and colleagues [16] reported protective effects of atorvastatin against acute GVHD in a MHC mismatched mouse model. In a series of elegant experiments, the authors demonstrated reduced risk of lethal acute GVHD by pre-treating the donor mice with atorvastatin. T-cells derived from these atorvastatin pre-treated mice not only showed reduced proliferation potential, but also displayed (both in-vivo and in-vitro) reduced Th-1 cytokine (TNF, IFN-gamma) and increased Th-2 cytokine (IL-10, IL-4) production. Zeiser and colleagues also investigated the impact of atorvastatin administration to recipient mice. Atorvastatin when given to recipient mice only translated into acute GVHD protection with a long-term survival of 50%, compared with 0% survival in control animals. Recipient APCs derived from liver, spleen, and lymph nodes of recipient mice getting atorvastatin or PBS

were analyzed at different time points after transplantation. Surface expression of CD80, CD86, CD40, and MHC class II was decreased in animals treated with the atorvastatin as compared with PBS-treated recipients. Interestingly pre-treating both donor and recipient mice with atorvastatin produced synergistic protective effects, when compare with survival of only donor or recipient pre-treated groups. Perhaps the most significant finding was that atorvastatin pretreatment did not interfere with perforin-mediated cytolysis or Fas–Fas-ligand interaction–mediated killing. In summary, these key experiments highlight the potential of atorvastatin in protecting against acute GVHD, while preserving the graft-versus-leukemia (GVL) effects.

Clinical Trial Data for Statin use for Preventing GVHD:

A number of retrospective studies suggest projective role of statins against acute and chronic GVHD [17-19]. Based on this data, our group conducted a single-arm phase-II study evaluating the safety and efficacy of atorvastatin for the prophylaxis of acute graft-versus-host disease in patients with hematological malignancies undergoing HLA-matched sibling donor hematopoietic SCT (www.clinicaltrials.gov NCT01175148). Atorvastatin administration in healthy donors and recipients was not associated with any grade 3-4 adverse events. The cumulative incidence rates of grade II-IV acute GVHD at days +100 and +180 were 3.3% (95%CI=0.2 - 14.8%) and 11.1% (95%CI=2.7-26.4%), respectively. The 1-year cumulative incidence of chronic GVHD was 52.3% (95%CI=27.6-72.1%). One-year cumulative incidences of non-relapse mortality and relapse were 9.8% (95%CI=1.4-28%) and 25.4% (95%CI=10.9-42.9%), respectively. The 1-year overall survival and progression-free survival were 74% (95%CI=58-96%) and 65% (95%CI=48-87%), respectively. Compared to baseline, atorvastatin administration in sibling donors was associated with a trend towards increased mean plasma interleukin-10 concentrations (5.6pg/ml vs. 7.1 pg/ml; p=0.06). This study showed that a novel two-pronged strategy of atorvastatin administration to both donors and recipients of matched sibling allogeneic HCT appears to be a feasible, safe and potentially effective strategy to prevent acute GVHD (*manuscript submitted for publication*). In an ongoing protocol, we are evaluating the role of atorvastatin for the prophylaxis of acute GVHD when administered to recipients of matched sibling and unrelated donor transplants alone, to assess if routine administration of atorvastatin to healthy sibling donors is warranted (www.clinicaltrials.gov NCT01665677). *The results of*

NCT01175148 and the preliminary observations from NCT01665677 suggest that while an atorvastatin-based GVHD prophylaxis provides protection against acute GVHD; compared to historical controls [3, 4] the incidence of chronic GVHD remains high and represents a significant clinical challenge. This preliminary data underscores the need to develop prophylactic strategies for chronic GVHD in allogeneic transplant patients getting atorvastatin based acute GVHD prophylaxis in particular, and for patients undergoing allografting in general.

Role of B-cells in Pathogenesis of Chronic GVHD:

Although the exact causes of chronic GVHD remain unknown, higher antibody levels have been associated with autoimmunity and implicated in chronic GVHD [20]. Newly diagnosed patients with extensive chronic GVHD have elevated soluble B cell activating factor (BAFF) levels and anti-double-strand DNA antibodies [21, 22], suggesting that B-cells play a role in chronic GVHD pathogenesis. Peripheral B cells in post allogeneic transplant patients with chronic GVHD have significantly higher BAFF/B-cell ratios compared with patients without chronic GVHD [23]. In chronic GVHD, increasing BAFF concentrations correlate with increased numbers of circulating pre-germinal center (GC) B-cells and post-GC "plasmablast-like" cells, suggesting in vivo BAFF dependence of these two CD27+ B-cell subsets [23]. The patients who develop chronic GVHD have delayed reconstitution of naive B-cells despite persistent BAFF elevation as well as proportional increase in CD27+ B cells in the first year after transplantation [23]. B cells from chronic GVHD patients are hyperresponsive to Toll-like receptor-9 signaling and have up-regulated CD86 levels [24], suggesting an important participatory role for B cells in establishing chronic GVHD. Recent studies also reveal that B-cells from patients with active chronic GVHD are in a heightened metabolic state and are resistant to apoptosis [25]. These B-cells have significantly increased signaling through ERK and AKT that is associated with decreased levels of proapoptotic Bim, suggesting a mechanistic link between elevated BAFF levels and aberrant B-cell survival [25]. Altered B cell homeostasis in chronic GVHD is associated with persistence of circulating, potentially autoreactive, B-cells [23]. A murine study demonstrated that allogeneic antibody deposit in chronic GVHD-affected tissues, and chronic GVHD was prevented when the donor graft was genetically prevented from secreting IgG [26]. Moreover, during GVHD onset, donor B-cells are activated by donor CD4+ T cells to upregulate MHC II and

costimulatory molecules. Acting as efficient APCs, donor B-cells augment donor CD4+ clonal T-cell expansion, autoreactivity, IL-7Rα expression, and survival. These qualitative changes markedly augment donor CD4+ T cells' capacity in mediating autoimmune-like chronic GVHD [27]. Collectively these data support an integral role of B-cell in the pathogenesis of chronic GVHD.

Rituximab for Chronic GVHD Prophylaxis:

Treatment of steroid refractory chronic GVHD patients with rituximab, a B cell–depleting anti-CD20 monoclonal antibody, has shown encouraging activity [28, 29], with overall response rates of 29% to 36% for oral, hepatic, gastrointestinal, and lung chronic GVHD, and 60% for cutaneous chronic GVHD [30] in aggregate data from multiple trials. Based on rituximab's activity in the steroid refractory setting, recent studies have evaluated its role as chronic GVHD prophylactic agent. Rituximab added to fludarabine and cyclophosphamide conditioning resulted in a low rate of chronic GVHD in 10 chronic lymphocytic leukemia patients [31]. Arai S et al. used prophylactic rituximab 2 months after transplantation to decrease the incidence of chronic GVHD [32]. The study included 35 patients undergoing total lymphoid irradiation/antithymocyte globulin conditioning. Rituximab (375 mg/m^2) was infused weekly on days 56, 63, 70, and 77 after transplantation. The incidence of acute GVHD was 6%. The cumulative incidence of chronic GVHD was 20%. Non-relapse mortality was 3%. Rituximab treatment after allogeneic transplantation significantly reduced B-cell allogeneic immunity, with complete prevention of alloreactive H-Y Ab development in male patients with female donors (P = .01) [32]. Similarly Cutler and colleagues using an alternative rituximab prophylaxis schedule reported chronic GVHD and systemic corticosteroid-requiring chronic GVHD cumulative incidence at 2 years from transplantation of 48% and 31% respectively, both lower than the corresponding rates in a concurrent control cohort (60%, p=0.1 and 48.5%, p=0.015) [28].

In addition to infusion reactions, cost and requirements for parenteral administration, rituximab used post AHCT can also potentially lead to life threatening neutropenia and infections. McIver et al reported the rituximab administration within six months of an allogeneic transplant was associated with prolonged, profound and life-threatening cytopenias [33]. In experience by Arai et al neutropenia after rituximab infusion was observed in 40% of the patients and should be a caution when using rituximab after transplantation [32].

Proteasome Inhibitors and GVHD:

Bortezomib is the prototype proteasome inhibitor. Bortezomib is effective against multiple myeloma via inhibition of nuclear factor–κB, attenuation of interleukin (IL)-6 mediated cell growth, a direct apoptotic effect, and possibly antiangiogenic and other mechanisms. Nuclear factor–κB plays an important role in cytokine signaling and T-cell activation, proliferation, and apoptosis [34, 35]. Bortezomib inhibits APCs by attenuating Toll-like-receptor 4–mediated activation, with reduced cytokine production and immunostimulatory activity [36]. In addition, treatment of CD4+ T cells with bortezomib was found to preserve natural regulatory T-cells while allowing the emergence of a distinct suppressor T cell population that inhibited the proliferation, IFN-γ production, and CD40L expression in stimulated effector T cells [37]. In the preclinical setting, bortezomib preferentially and specifically depletes alloreactive T lymphocytes [38]. In mouse models of HLA-mismatched allografting, administration of bortezomib protects against GVHD without impairing engraftment [39, 40]. In summary proteasome inhibition eliminates alloreactive plasma cells and alloreactive T cells. Furthermore, it interferes with APC function and reduces inflammatory cytokine production either by eliminating the cytokine-secreting cell or by inhibiting its production through the downmodulation of NF-κB-dependent transcription, supporting the role of proteasome inhibitors as GVHD prophylactic agents.

Mateos-Mazon et al. [41]found that bortezomib may be useful in the management of chronic GVHD. The investigators administered bortezomib to 8 patients who relapsed after reduced-intensity conditioning allogeneic transplantation. At the time of bortezomib administration, 4 patients had chronic GVHD, including severe punctate keratopathy in 3 patients. Interestingly, in all 4 patients, chronic GVHD significantly improved; especially in the 3 patients with ocular involvement, in whom both symptoms and conjunctival ulcerations responded. As previously shown and noted by the investigators, NF-κB activation plays a crucial function in inflammatory eye disease; therefore, NF-κB blockade may have an important role in the management of ocular GVHD [42]. In another study by El-Cheikh et al. [43], bortezomib was administered as salvage treatment after multiple myeloma relapse or progression after allogeneic stem cell transplantation in 37 patients. Before the start of treatment, 8 patients were suffering limited chronic GVHD, whereas 3 patients had extensive signs. Two of the 3 patients with extensive chronic GVHD signs before the start of treatment

showed a significant improvement in GVHD. Koreth et al [44] used bortezomib for acute GVHD prophylaxis in a phase I/ trial. They found that 180-day cumulative incidence of grades II to IV acute GVHD was 22%. One-year cumulative incidence of chronic GVHD was only 29%. Disease relapse were comparable to historical controls, underscoring the fact that proteasome inhibitors do not interfere with GVL effects. *Taken together, the above results demonstrate the potential of proteasome inhibitors in the prevention of chronic GVHD due to marked immunomodulatory activity*. However, administration of bortezomib requires parenteral or subcutaneous administration and is often complicated by severe painful peripheral neuropathy. To circumvent these limitations, MLN9708, a novel oral proteasome inhibitor with reduced risk of peripheral neuropathy warrants investigation for chronic GVHD prophylaxis, in patients undergoing allogeneic transplantation.

MLN9708:

Preclinical Experience

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

Clinical Experience

As of 30 April 2012, 382 patients have been treated with MLN9708 across 9 enrolling, sponsor-led phase 1 or phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. MLN9708 is available as an intravenous and oral formulation. Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral MLN9708 has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and systemic light chain amyloidosis. A clinical pharmacology study looking at drug-drug interactions, the effect of food, and bioavailability also uses the oral formulation. Details of these trials can be found in Pharmacokinetics and Drug Metabolism ClinicalTrials.gov and the MLN9708 IB.

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over in 4 hours. Oral MLN9708 is rapidly absorbed with a median time to first maximum plasma concentration (Tmax) of approximately 0.5 to 2.0 hours and terminal t1/2 after multiple dosing of approximately 5 to 7 days [45]. Results of a population PK analysis (N = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[2] Based on this data, a recommendation was made for *fixed dosing* (4mg on days 1, 8, and 15 of a 28-day cycle) in the clinical trial. Hence, the 4mg dose will be the highest dose level tested, in the phase 1 portion of current clinical trial. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5-major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

Clinical Trial Experience Using the Oral Formulation of MLN9708

In the 7 studies actively enrolling patients to investigate oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and

lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708, either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-1.

Table 1-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 58	PO, twice weekly (TW), single agent	0.24-2.23 mg/m^2, TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia
C16004 RRMM N = 52	PO, weekly (W), single agent	0.24-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea
C16005 NDMM N = 65	PO, W, combination with LenDex 28 day cycle	1.68-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D*: 4.0 mg fixed (switched to fixed dosing in phase 2, relevant to 2.23 mg/m^2)
C16006 NDMM N = 28	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with melphalan and prednisone	Arm A*: 3-3.7 mg, fixed dose, TW DLT: rash, thrombocytopenia, subileus Arm B*: 5.5 mg, fixed dose, W DLT: Esophageal ulcer
C16007 RR-AL N = 6	PO, W, single agent	4-5.5 mg, fixed dose*, W MTD: 4 mg DLT: thrombocytopenia, dirrhea, dyspnea, acute rise in creatinine, cardiac arrest
C16008 NDMM N=11	PO, TW, combination with LenDex 21 day cycle	3.0-3.7 mg fixed dose* W MTD: 4 mg DLT:
C16009 Solid tumors, Lymphomas N = 22	PO, W, single agent	5.5 mg fixed dose* W
C16010 RRMM N = 1	PO, W, combination with LenDex	4.0 mg fixed dose* W
TB-MC010034 RRMM N = 5	PO, W, single agent in 1s part of study then in combination with LenDex in 2nd part	3.0 mg fixed dose* W DLT: thrombocytopenia, nausea, hypertension, diarrhea

Abbreviations: RRAL = Relapsed or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area ; DLT = dose-limiting toxicity; IV = intravenuously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RRMM = relapsed and/or refractory multiple myeloma; RPh2D = recommended phase 2 dose

* Approximate body surface area (BSA) and fixed dosing equivalence: 3 mg ~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg ~ equivalent to 2.97 mg/m^2 BSA dosing.

Overview of the Oral Formulation of MLN9708

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

In 4 clinical studies (C16003, C16004, C16007, and C16009) investigating single-agent oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 146 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral MLN9708 Studies is shown in Table 1.

Table 1 Summary of Most Common (At Least 10% of Total) All Grade Treatment-Emergent Adverse Events (Oral MLN9708 Single-Agent [C16003/4/7/9] Safety Population)

Primary System Organ Class	Preferred Term and Incidence N=146n (%)
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 102 (70)	Nausea 68 (47); Diarrhea 55 (38); Vomiting 51 (35); Abdominal pain 21 (14); Constipation 21 (14)
General disorders and administration site conditions 98 (67)	Fatigue 71 (49); Pyrexia 31 (21); Oedema peripheral 15 (10)
Blood and lymphatic system disorders 77 (53)	Thrombocytopenia 60 (41); Anemia 30 (21); Neutropenia 23 (16); Leukopenia 15 (10)
Nervous system disorders 63 (43)	Headache 20 (14); Dizziness 18 (12)
Metabolism and nutrition disorders 60 (41)	Decreased appetite 39 (27) Dehydration 21 (14)
Respiratory, thoracic and mediastinal disorders 60 (41)	Cough 22 (15); Dyspnoea 21 (14)
Skin and subcutaneous tissue disorders 60 (41)	Rash macular 17 (12)
Musculoskeletal and connective tissue disorders 56 (38)	Arthralgia 20 (14); Back pain 17 (12)
Infections and infestations 54 (37)	Upper respiratory tract infection 21 (14)

Source: MLN9708 Investigator's Brochure Edition 6

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, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator

In the 3 studies actively enrolling patients to investigate oral MLN9708 in combination with standard combination regimens in patients with newly diagnosed multiple myeloma, a total of 96 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 in combination with lenalidomide and dexamethasone in 2 trials (C16005 and C16008) and with melphalan and prednisone in 1 trial (C16006). The most frequent (at least 10%) adverse events occurring in the pooled safety population from Studies C16005, C16006, and C16008 is shown in Table 1-3. In combinations trials, related is defined as possibly related to any drug in the combination regimen, not just specifically related to MLN9708.

Table 1-3 Summary of Most Common (At Least 10% of Total) Treatment- Emergent Adverse Events (Oral MLN9708 Combination Agent [C16005/6/8] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N= 96 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 70 (73)	Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26) Diarrhea 22 (23)
General disorders and administration site conditions 64 (67)	Fatigue 37 (39); Oedema peripheral 20 (21); Pyrexia 19 (20)
Skin and subcutaneous tissue disorders 57 (59)	Rash 13 (14)
Nervous system disorders 46 (48)	Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11)
Musculoskeletal and connective tissue disorders 45 (47)	Back pain 18 (19); Muscle spasms 10 (10)
Blood and lymphatic system disorders 42 (44)	Thrombocytopenia 28 (29); Anemia 22 (23); Neutropenia 19 (20)
Infections and infestations 40 (42)	Upper respiratory tract infection 17 (18);
Metabolism and nutrition disorders 38 (40)	Decreased appetite 11 (11)
Respiratory, thoracic and mediastinal disorders 34 (35)	Dyspnoea 13 (14); Cough 11 (11)
Psychiatric disorders 23 (24)	Insomnia 15 (16)

The clinical experience with MLN9708 also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent MLN9708, when combined with established therapies, and across the malignancies studied (advanced solid tumors [46], non-Hodgkin's disease, Hodgkin's disease [47], relapsed and/or

refractory multiple myeloma [RRMM; [48, 49]], relapsed or refractory systemic light chain amyloidosis [RRAL; [50]], and newly diagnosed multiple myeloma [NDMM; [51-53]]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of MLN9708.

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agent MLN9708 is administered weekly in patients with RRMM or RRAL, respectively.

Relapsed and/or Refractory Multiple Myeloma

Study C16004 is an open-label, dose-escalation, phase 1 study of MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. The dose-escalation phase of the trial has completed. In this study, 2 of 3 patients experienced protocol-defined DLTs (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m2. As per protocol, subsequent patients were treated at 1 dose level below (2.97mg/m2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral MLN9708 was determined to be 2.97 mg/m2.

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

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];

2. Carfilzomib expansion cohort

3. Proteasome Inhibitor-Naïve expansion cohort

4. VELCADE-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest MLN9708 has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated.[54, 55]

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

A summary of the safety profile of patients treated in Study C16004 is outlined in Table 1-4. Overall, 92% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/ 2 in 6 patients, with 3 patients reporting baseline Grade 1 PN at study entry.

Table 1-4 Study C16004, Oral MLN9708, Single Agent, Given Weekly: Most Common TEAEs as of 30 April 12 (N= 52)

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

Source: MLN9708 Investigator's Brochure Edition 6
* Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic, pruritus, rash erythematous, exfoliative rash, and rash popular

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

Study C16007 is evaluating single agent weekly, Day 1, 8, and 15 of a 28-day cycle, oral dosing in patients with RRAL after at least 1 prior therapy. The objectives of this study are to determine the safety, tolerability, and MTD, as well as to determine hematologic and organ response rates in this patient population. The starting dose level was selected from Study C16004 as previously described. In Study C16007 the dose was switched from the BSA-based dosing to the fixed dose, thereby the 4.0 mg fixed starting dose in Study C16007 corresponds to the 2.23 mg/m2 dose (one dose level below MTD) from Study C16004. This study is currently enrolling patients in the dose-expansion portion of the trial.

As of 30 April 2012, 14 patients have been treated in this study. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which met the definition of a DLT due to the delay in starting Cycle 2). As per protocol, the dose was escalated to 5.5 mg for the next cohort of patients where 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram on study entry, but did have substantial renal involvement. After the occurrence of this DLT, diagnoses included cardiac involvement and CHF. The MTD of weekly oral MLN9708 was determined to be 4.0 mg. Following the establishment of the MTD, patients are currently being enrolled in to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed.[56]

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

A summary of the safety profile of patients treated in Study C16007 is outlined in Table 1-5. Overall, 86% of patients experienced a TEAE of any grade and of any cause.

Table 1-5 Study C16007, Oral MLN9708, Single Agent Given Weekly Most Common TEAEs as of 30April 12 (N = 14)

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

Source: MLN9708 Investigator's Brochure Edition 6

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

The potential risks reported with MLN9708 use, pooled from all studies using the oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the MLN9708 IB, SMA, and ICF documents. Regardless of whether MLN9708 is administered on the once weekly or twice weekly dosing schedule, there is consistency among the type of TEAEs reported, despite some differences in the frequency and severity of the reported events. While the predominant potential toxicities may be severe in some cases, they are largely reversible, and can be managed by routine clinical monitoring and standard medical interventions, which may include dose reductions and supportive care. Please refer to the MLN9708 IB and SMA for further information.

Newly Diagnosed Multiple Myeloma (NDMM)

In Study C16005, MLN9708 is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle. Enrollment to this study is closed.

Clinical data as of 30 April 2012 is available. The MTD in Study C16005 was determined to be 2.97 mg/m^2 given weekly in a 28-day cycle with LenDex. The DLTs were urticarial rash, dizziness, nausea, orthostatic hypotension, vomiting, diarrhea, and syncope. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to, analyses of efficacy results

and adverse events (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Given that the dose of MLN9708 at 2.97 mg/m^2 compromised the maximal dosing of lenalidomide and that the dose of 2.23 mg/m^2 is very tolerable and clinically active, Millennium designated 2.23 mg/m^2 as the RP2D after evaluation of the data and discussion with investigators. The RP2D of 2.23 mg/m^2 has been translated into a fixed dose of 4.0 mg based on the results from the population PK analysis. Enrollment in this study has been completed; final study results are not available, but preliminary data suggests oral MLN9708 given weekly plus lenalidomide and dexamethasone in a 28-day cycle appears well tolerated with manageable toxicity and encouraging antitumor activity.

In Study C16005, 15 of 15 (100%) patients in the dose escalation portion of the study experienced at least 1 TEAE irrespective of grade or causality. At the MTD across all dose expansion cohorts 49 of 53 patients (including 3 patients from the dose escalation cohort [92%]) reported at least 1 TEAE irrespective of grade or causality. In the MTD cohorts, fatigue was the most common AE reported (38%). Other common AEs reported include nausea (32%), constipation (30%), upper respiratory infection (23%), and peripheral oedema (21%). Skin toxicity, primarily erythematous rash, occurred in 62% of patients (of note, rash is an overlapping toxicity with MLN9708 and lenalidomide). Peripheral neuropathy was reported in 13% of patients; Grade 3 in 1 patient.

A summary of the overall safety profile of patients treated in Study C16005 is outlined in Table 1-6. Overall, 100% of 65 patients experienced at least one TEAE of any grade and of any cause.

Table 1-6 Study C16005: Oral MLN9708 Given Weekly in Combination With Lenalidomide and Dexamethasone, Most Common TEAEs as of 30 April 2012

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (37%)
	Nausea (34%)
	Constipation (31%)
	Vomiting (28%)
	Diarrhea (26%)
	Thrombocytopenia (23%)
	Upper respiratory tract infection (22%)
	Anemia and oedema peripheral (20% each)
Drug-Related[a] Grade ≥ 3 in ≥ 2 Patients	Nausea, vomiting (n=3 each)
	Thrombocytopenia, lymphopenia, rash pruritic (n=2 each)

Source: MLN9708 Investigator's Brochure Edition 6.

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

The most common drug-related SAEs reported in Study C16005 as of 30 April 2012 include pneumonia, infection, diverticulitis, localized infection, gastrointestinal hemorrhage, respiratory

syncytial virus (RSV) pneumonia faecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral oedma, asthenia, hyponatraemia vomiting, diarrhea, nausea, chest pain, dehydration, anemia, dizziness, peripheral sensory neuropathy, orthostatic hypotension, embolism, muscular weakness, acute renal failure, blood creatinine increased, maculopapular rash, atrial fibrillation, syncope, hypotension, and deep vein thrombosis, and back pain.

As of the clinical data cutoff, 4 patients have discontinued treatment due to TEAEs including gastrointestinal hemorrhage, angioedema, syncope, and RSV pneumonia.

One death was reported for a patient with RSV pneumonia; the event was deemed by the investigator to be related to treatment with MLN9708.

Clinical Trial Experience Using the Intravenous Formulation of MLN9708

See the IB for descriptions of the 2 ongoing studies investigating IV MLN9708 in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

Study Rationale:

Proteasome inhibition eliminates alloreactive T cells, interferes with APC function and reduces inflammatory cytokine production either by eliminating the cytokine-secreting cell or by inhibiting its production through the downmodulation of NF-κB-dependent transcription, supporting the role of proteasome inhibitors as GVHD prophylactic agents. Based on the previously discussed preclinical and limited clinical data, we now propose a phase I/II study of chronic GVHD prophylaxis with oral proteasome inhibitor MLN9708 in patients undergoing matched related or unrelated donor allogeneic transplantation. Phase I will be conducted as a single site study and Phase II as a multi-site study. The additional site, the University of West Virginia, will be added when the Phase II portion of the study is opened. Building on our prior experience showing reduced rates of acute GVHD with an atorvastatin-containing acute GVHD prophylaxis, the *preferred acute GVHD prophylactic regimen* on the current study will be atorvastatin, mini-dose methotrexate and tacrolimus; however the acute GVHD prophylaxis used will remain at the discretion of the treating physician since rate of acute GVHD is not the primary outcome of the current protocol. Furthermore flexibility in type of acute GVHD prophylaxis permitted, will support robust accrual on the current protocol.

Potential Risks and Benefits:

Please refer to the current MLN9708 Investigator's Brochure (IB). MLN9708 is a modified dipeptide boronic acid proteasome inhibitor similar to VELCADE, 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.[46, 47, 49-56]

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

2. Objectives:

Primary Objectives:

Phase I Primary Objectives:

- To determine the maximum tolerated dose (MTD), dose limiting toxicity (DLT) and recommended phase II dose (RDP) of MLN9708 for the prophylaxis of chronic GVHD in patients undergoing allogeneic hematopoietic cell transplantation (HCT).

Phase II Primary Objectives:

- Determine the 1-year (from the date of HCT) cumulative incidence of chronic GVHD following MLN9708 administration as prophylaxis, in patients undergoing matched sibling allogeneic HCT.
- Determine the 1-year (from the date of HCT) cumulative incidence of chronic GVHD following MLN9708 administration as prophylaxis, in patients undergoing unrelated donor allogeneic HCT.

Phase I/II Primary Objectives:

- Assess the safety of chronic GVHD prophylaxis with MLN9708 in patients undergoing allogeneic HCT.

Secondary Objectives:

- To assess the 1-year and 2-year (from the date of HCT) cumulative incidence of corticosteroid requiring chronic GVHD, in the matched sibling and unrelated donor cohorts separately.
- Determine the 2-year (from the date of HCT) cumulative incidence of chronic GVHD following MLN9708 administration as prophylaxis, in the matched sibling and unrelated donor cohorts separately.
- To assess the 1-year and 2-year (from the date of HCT) cumulative incidence of mild, moderate and severe chronic GVHD (by NIH criteria) and limited or extensive chronic GVHD (by conventional criteria), in the matched sibling and unrelated donor cohorts separately.
- To assess cumulative incidence of grade II-IV acute GVHD at days +100, +180 and +365, in the matched sibling and unrelated donor cohorts separately.
- To assess cumulative incidence of grade III-IV acute GVHD at days +100, +180 and +365, in the matched sibling and unrelated donor cohorts separately.
- To assess non-relapse mortality rate at 100 days, 1-year post-HCT.
- To assess the incidence of motor and sensory neuropathy associated with MLN9708
- To assess incidence of secondary graft failure.
- To assess incidence of secondary immunologic graft rejection.
- To assess relapse rate of the primary hematological malignancy.
- To assess lineage specific chimerism kinetics in patients at baseline (approximately day +30), day +100, day +180 and day +365.
- To assess immune reconstitution following transplantation at baseline (approximately day +30), day +100, day +180, day +365 and day +730.
- To assess absolute neutrophil count on day +100, day +180 and day +365.

- Response of acute GVHD to MLN9708 at day +100, in those patients with controlled grade I-II acute GVHD at the time of enrollment.
- To assess 1-year and 2-years progression free survival (PFS) and overall survival (OS) following transplantation.
- To evaluate biologic [BRAF levels] markers potentially associated with GVHD and/or MLN9708.

3. Eligibility Criteria:

Inclusion criteria:

- Patients with a history of a hematological malignancy or bone marrow failure syndrome undergoing (or status post) a peripheral blood allogeneic HCT.
- Patients aged ≥18 are eligible.
- All patients must have received or plan to receive an allograft from a suitable HLA-matched sibling or unrelated donor according to transplant center's guidelines (for selection of appropriate donor).
- Voluntary written consent must be given before patient registration and 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.
    - Bilirubin ≤ 2 x the ULN. For patients with Gilbert's syndrome or suspected mild veno-occlusive disease, bilirubin ≤ 3 x ULN is permitted.
    - Creatinine clearance of ≥ 30 mL/min calculated by Cockcroft-Gault equation.
- Karnofsky performance status ≥ 60.
- A negative pregnancy test will be required for all women of child bearing potential. Females of child bearing potential should 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 [eg, calendar, ovulation, symptothermal, post-ovulation

methods] and withdrawal are not acceptable methods of contraception.). Breast feeding is not permitted.

- Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following: practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or 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 (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
- No evidence of uncontrolled bacterial, viral or fungal infections at the time of enrollment.
- No known active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

Exclusion Criteria:

- Patients with active ≥ grade 3 peripheral neuropathy or grade 2 with pain on clinical examination during the screening period will be excluded.
- Patients with history of allergy and/or intolerance to MLN9708 are not eligible.
- Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 including difficulty swallowing is not permitted.
- Patients receiving (or status post) a cord blood or a haplo-identical allograft will not be eligible.
- Patients undergoing (or status post) a T-cell depleted allogeneic transplantation will not be eligible.
- Patients receiving (or status post) conditioning regimens containing antithymocyte globulin, and/or campath, one receiving post-HCT planned cyclophosphamide will not be eligible.
- Method of stem-cell collection from the donor will be at the discretion of the treating physician. Although it is anticipated that majority of patients will receive allograft

mobilized with G-CSF alone; however donors receiving allografts mobilized with experimental agents (e.g. plerixafor) will remain eligible for the study.

- Patients experiencing disease relapse (for those in complete remission at the time of HCT) or progression (for those in partial remission, stable or refractory disease at the time of HCT) will be excluded.
- Donor lymphocyte infusions between day zero of HCT and first dose of MLN9708 are not permitted.
- Rituximab (or other B-cell depleting monoclonal antibodies) or bortezomib administration between day zero of HCT and before the first day of MLN9708 is not permitted.
- Patients with steroid refractory (defined as no improvement of symptoms after 7 days of systemic corticosteroids at a dose of ≥1mg/kg/day) grade II-IV acute GVHD, that is active at the time of enrollment will be excluded.
- Patients with grade III-IV acute GVHD (even if it is not meeting criteria for steroid refractory acute GVHD), that is active at the time of enrollment will be excluded. Patients with controlled grade I-II acute GVHD can be enrolled after discussing with study PI. Topical or systemic corticosteroids therapy, as per standard of care for such grade I-II acute GVHD patients is permitted.
- Patients with active chronic GVHD (although unlikely before day +100) will be excluded.

- No major surgery within 14 days before enrollment.

- No radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the MLN9708.

- No evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months. Cardiac enzyme elevations for reasons other than document myocardial infarction is not an exclusion.

- No systemic treatment, within 14 days before the first dose of MLN9708, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of

CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

- No serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

- No participation in clinical trials with other investigational agents, within 21days of the start of this trial and for two weeks after the last dose of MLN9708 or resolution of MLN9708 related adverse events to grade 1 or less (whichever occurs later). However, co-enrollment on trials evaluating conditioning regimens, institutional protocols evaluating atorvastatin for acute GVHD prophylaxis, and stem cell collection protocols in transplant donors will be permitted. In addition, patients randomized to standard-of-care (non-experimental) arms of available phase II/III trials will be eligible for this study.

4. Registration Procedure:

Registration

- All source documents that support eligibility include a signed informed consent/HIPAA and signed eligibility checklist. These must be available for review and verification.
- At the point of registration, the study staff will register the patient in the electronic database (where applicable), including demographic, consent and on-study information. The patient will be assigned a unique sequence number for the study.
- Patients will be enrolled on this trial after day zero of HCT (ideally between days +60 - 90).

5. Treatment Plan:

This is a phase I/II study of MLN9708 for the prophylaxis of chronic GVHD in patients undergoing allogeneic HSCT. During the phase I portion patients undergoing both sibling and unrelated donor transplantation will be enrolled on the same arm to determine the DLT and MTD. During the phase II portion of the trial, patients will be enrolled into two separate and

independent cohorts: a) Matched sibling transplants and b) Unrelated donors transplants. Both cohorts will be enrolled and analyzed separately.

Administration schedule to Transplant recipients

- For potential candidates for this trial, the *recommended* acute GVHD prophylaxis is tacrolimus, methotrexate and atorvastatin combination. However, any acute GVHD prophylaxis regimen at the discretion of treating physician (not involving *in-vivo* or *ex-vivo* T-cell depletion, CD34+ cell selection, or post-HCT cyclophosphamide) will be permitted.
- During the phase I portion, for chronic GVHD prophylaxis, four doses of MLN9708 will be administered orally (to patients undergoing either matched sibling or unrelated donor transplantation) on days 1, 8, 15 and 22, starting on day +60 to +74 post allogeneic HCT. Dose escalation will be conducted as shown in Table 2 to determine the MTD and DLT.

Table 2. Phase I dose escalation schema.

MLN 9708 Phase I dose Levels	Oral Dose (given on days 1, 8, 15 and 22)
-1	2.3 mg
1	3.0 mg
2	4.0 mg

- Dose escalation will start at dose level 1 and will be carried out according to standard 3+3 design. If 0 of 3 patients experiences DLT, dose escalation will proceed to the next higher dose level, at which 3 patients will be enrolled. On observing a DLT, the cohort will be expanded to 6 patients. Dose escalation will continue if no greater than 1 of 6 patients experience DLT, up to a maximum dose of 4mg. If 0 of 3 patients experiences DLT at dose level 2, then it will be considered MTD. If 2 or more patients experience a DLT, dose escalation will halt and the dose level below will be expanded to 6 patients to determine the MTD. If the dose level below already has 6 patients, enrolled, then it will be considered the MTD. If 2 or more patients experience DLT on first dose level (i.e.

dose level 1), then patients will be enrolled on dose level -1. No intrapatient dose escalation will be permitted.

- MTD is defined at maximum dose level with fewer than 2 of 6 patients experiencing DLT.
- Toxicity will be evaluated according to *CTCAE v4.0*. DLT will be defined as shown in Table 3. DLT observation period will be from first dose of MLN9708 to 28 days after the last dose. Dose escalation to higher dose level will require the last patient on the previous dose level to be out of DLT observation period.

Table 3. Definition of DLT for patients receiving MLN9708
Non-hematologic toxicities
• Grade 2 peripheral neuropathy with pain or Grade 3 or greater peripheral neuropathy, (definitely or probably) related to MLN9708 • Any grade 3-4 non-hematologic toxicity (definitely or probably) related to MLN9708, with the exception of alopecia, transient electrolyte or LFT abnormalities which resolve to ≤ grade 1 within 72hours, Grade 3 arthralgia/myalgia, and brief (<1 week) Grade 3 fatigue • Grade 3 or greater nausea and/or emesis (not due to GVHD) despite the use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-HT3 antagonist given in standard doses and according to standard schedules. • Grade 3 or greater diarrhea (definitely or probably) related to MLN9708 that occurs despite maximal supportive therapy.
Hematologic and infectious toxicity
• Drop in donor myeloid-cell chimerism by more than 50% at day +90 (±7days) (in the absence of relapsed disease) • Unexplained immunologic graft rejection at day +90 (±7days) (define as donor myeloid-cell chimerism of <5%) • Grade 4 neutropenia (ANC <500/mm^3) lasting ≥14 consecutive days, (definitely or probably) related to MLN9708 • Grade 3 neutropenia with fever and/or infection, where fever is defined as a temperature ≥ 38.5°C, (definitely or probably) related to MLN9708 • Grade 4 thrombocytopenia (platelets <25,000/mm^3) lasting at least 7 consecutive days, (definitely or probably) related to MLN9708

- The phase II portion will utilize the MTD for MLN9708, determined from phase I portion of the study. In phase II, patients will be enrolled in two independent cohorts of matched sibling and matched unrelated donor transplants.

- During the phase II portion, for chronic GVHD prophylaxis, four doses of MLN9708 will be administered orally on days 1, 8, 15 and 22, starting on day +60 to +90 post allogeneic HCT.
- 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 sub-investigator(s). Patients should be monitored for toxicity, as necessary.
- Capsules of MLN9708 will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 2.3, 3.0 and 4.0 mg MLN9708.
- Patients should be instructed to swallow MLN9708 capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.
- All MLN9708 doses will be administered by authorized study personnel during patients' inpatient or outpatient visits, to ensure compliance. If the patient vomits after taking the study drug, the dose should not be repeated but should resume dosing at the time of the next scheduled dose. Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose.
- Acute GVHD medications expected to be ongoing at the time of MLN9708 administration include calineurine inhibitors (e.g. tacrolimus or cyclosporine) OR mycophenolate mofetil OR sirolimus OR atorvastatin.
- Tapering of any concomitant acute GVHD prophylaxis will be per institutional guidelines, however in absence of acute GVHD, renal insufficiency and disease relapse/progression it is recommended that taper **SHOULD NOT** commence before day +100. The recommended goal of tapering is the complete discontinuation of immunosuppressive medications by day +180.

Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. A DDI with a strong inhibitor would increase MLN2238 exposure.

- Concomitant administration of strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin) and strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole).

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use. A DDI with a strong inducer would decrease MLN2238 exposure.

- Strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin and phenobarbital).
- The dietary supplements St. John's wort and Ginkgo biloba are not permitted.

- Antibiotic prophylaxis will be given according to institutional guidelines. Herpes zoster prophylaxis per institutional guidelines will be required during prophylaxis with MLN9708.
- Patients missing a single dose of MLN9708 (due to decreased oral intake secondary to severe nausea, vomiting, mucositis etc.) should be discussed with study PI. Patients missing >1 dose will need to be replaced. In case MLN9708 therapy is interrupted, the time interval should be recorded.
- Toxicity will be evaluated according to CTCAE v4.0.
- Progression free survival (PFS) and overall survival (OS) following transplantation will be recorded.

Dose modification

- Patients experiencing a grade 3-4 hematological or non-hematological toxicity (as specified in CTCAE v4.0) thought to be related to MLN9708 will be removed from the study permanently (except the exceptions allowed in Table 3). No dose modifications are permitted.
- If a patient experiences a Grade 3 or 4 non-drug-related renal function impairment or hepatic function impairment, MLN9708, can be held until recovery to Grade 1 or baseline (up to a maximum of 14 days). Upon recovery of the toxicity to a level allowing continuation of therapy, a dose reduction is not necessary.

Duration of therapy

MLN9708 will be continued until any one of the following criteria is met:

- Patient finishes four doses of MLN9708.
- Patient develops grade III-IV acute GVHD.
- Patient develops severe chronic GVHD.
- Patient develops any grade 3-4 toxicity related to MLN9708 use.

Data Safety Monitoring Plan

The Medical College of Wisconsin (MCW) Cancer Center (CC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all cancer center investigator initiated clinical trials. A six to eight member Data and Safety Monitoring Committee will complete a review of protocol-specific data safety monitoring reports, to provide recommendations on trial continuation, suspension or termination.

A summary of the MCW CC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.)
- Review all DSMC reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

A copy of the MCW CC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will

review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

6. Measurement of Effect:

Follow up schedule:

The schedule for follow up on the study is shown in the table below.

Study Visit	Approximate target Day Post-Transplant
1	60 days
2	67 days
3	74 days
4	81 days
5	90-100 days
6	180 days
7	365 days
8	2 years

Patients will be followed for survival, relapse and cause of death for 5 years post transplantation.

Phase I patients will be seen weekly for toxicity assessment during the DLT period.

GVHD Assessment:

At the time of enrollment and/or first dose of MLN9708 patients will be graded for acute and chronic GVHD. Subsequently patients will be monitored for development of acute and chronic GVHD approximately once a week until day +100. After Day 100, patients will be assessed at each study visit for the presence of GVHD. Diagnosis of acute GVHD will ideally require biopsy confirmation in at least one involved organ. When more than one organ is involved, biopsy confirmation of all involved organs is recommended but not necessary. Liver-only GVHD must be confirmed by biopsy. Acute GVHD will be assessed by consensus criteria (Appendix A) [57] and graded on BMT CTN MOP suggested grading sheets (Appendix A). Acute GVHD assessment and grading will be performed by **treating physicians.** Chronic GVHD diagnosis and grading will be according to NIH Criteria. Please see Appendix B [58, 59].

Clinical Grading of Chronic GVHD (According to Appendix B)

None

Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung: see below ‡), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites)

Moderate chronic GVHD involves: (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). ‡A lung score of 1 will also be considered moderate chronic GVHD.

Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). ‡A lung score of 2 or greater will also be considered severe chronic GVHD.

Presence of limited or extensive chronic GVHD will be also be recorded.

Chimerism Assessment and Immune Reconstitution:

Chimerism will be evaluated using sorted whole blood in CD3 and CD33 fractions. For the purpose of this protocol, mixed chimerism is defined as the presence of donor cells, as a proportion of total cells to be < 95% but > 5% in the bone marrow or peripheral blood. Full donor chimerism is defined as ≥ 95% of donor cells. Mixed and full chimerism will be evidence of donor cell engraftment. Donor cells of ≤ 5% will be considered as graft rejection. Similarly, platelet recovery is defined as first day of platelet count ≥ 20,000 x 10^9/L, without transfusion for 7 consecutive days. Lineage specific chimerism analysis (myeloid, T-cell [B-cell if available] subsets), quantitative immunoglobulins and immune reconstitution will be performed at baseline (if not performed as standard of care at or around day +30) and then on approximately days +90, +180 and +365.

Secondary graft failure is defined as, ANC <500 x 10^9/L after post-transplant neutrophil recovery in the absence of disease relapse/progression. Immunological graft rejection is defined as detecting <5% donor myeloid cells on chimerism analysis.

7. Study Parameters (Study Calendar):

Patient Study Calendar:

The table below summarizes the patient clinical assessments over the course of the study.

Study Assessment	Screening[1]	MLN Dosing days (starting on day +60 to +90 post HCT)				Days Post Transplant (~ ±10 days up to day 365 and then ±28 days)						
		1	8±1	15±1	22±1	90-100	180	365	730	3 year	4 year	5 year
Informed consent	X											
H & PE[2]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky performance status	X	X	X	X	X	X	X	X	X	X	X	X
CBC/differential & platelet count	X	X	X	X	X	X	X	X	X			
Serum chemistries panel[4]	X	X	X	X	X	X	X	X	X			
CMV quantitative PCR[12]	X	X	X	X	X	X						
B-HCG serum pregnancy test [5]	X											
Quantitative immunoglobulins[6]	X					X	X	X	X			
Peripheral blood for chimerism	X[7]					X	X	X				
Immune reconstitution panel[8]	X					X	X	X	X			
CD34/CD3 cell dose infused	X											
Acute GVHD assessment	X	X	X	X	X	X	X	X	X			
Chronic GVHD assessment	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity assessment[9]	X	X	X	X	X	X	X	X	X			
Research specimens (optional)[10]	X					X	X	X	X			
ANC and platelet recovery[11]	X											
Specify (if any) co-enrollment	X											

with other clinical trials												

Notes

H & PE= history and physical examination

[1]Baseline refers to the period prior to enrolling on trial. Assessments should be made within 6 weeks prior to first planned dose of MLN9708, unless a longer window is allowed.

[2]History is only required at baseline.

[3]Vital signs: blood pressure, pulse rate, respiratory rate and temperature.

[4]Serum chemistries panel: electrolytes, BUN, ALT, AST, creatinine, bilirubin. Electrolytes to include sodium, potassium.

[5]Females of reproductive potential only.

[6]IgG, IgM and IgA.

[7]Baseline assessment of chimerism can be done any day between day 28 posttransplant and first dose of MLN9708. Chimerism testing should be sorted (lineage specific) to assess myeloid and lymphoid cell chimerism.

[8]Peripheral blood flow cytometry to assess recipient immune reconstitution. The Immune reconstitution panel at the minimum should include determination of CD4+ T-cells, CD8+ T-cell, natural killer -cells (defined as CD3-CD56+CD16+) and CD19+ B cells. It is recommended (but not required) that this panel should include the following:

a. CD4+ Memory T-cells defined as CD3+CD27+CD45RO+CD4+

b. CD8+ Memory T-cells defined as CD3+CD27+CD45RO+CD8+

c. CD4+ naïve T-cells defined as CD3+CD45RA+CD45RO-CD4+

d. CD8+ naïve T-cells defined as CD3+CD45RA+CD45RO-CD8+

e. Regulatory T-cells defined as either CD3+CD4+CD25$^{med\text{-}high}$CD127^{low} OR CD4+CD25+FOXP3+

[9]Phase I patients will be seen weekly for toxicity assessment (along with CBC/differential & platelet count and serum chemistries panel[4]), during the DLT period.

[10]Peripheral whole blood specimens: draw in two 15 mL purple top (EDTA containing) tubes. Plasma will be separated from one whole blood tube by centrifugation at 600 × g. Plasma will be stored in aliquots at −80°C. The second whole blood tube will be used for separation and cryopreservation of mononuclear cells.

[11]Record time to neutrophil engraftment defined as first of three consecutive days with ANC ≥ 500 x 10^9/L, and platelet engraftment defined as first day of platelet count ≥ 20,000 x 10^9/L, without transfusion for 7 consecutive days

[12] CMV quantitative PCR may be drawn within the window of plus/minus 7 days

.

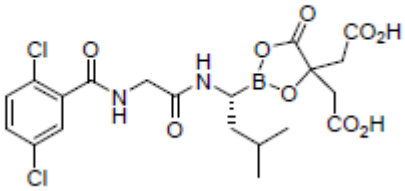
8. Drug Formulation and Procurement

MLN9708 (Ixazomib® Millennium Pharmaceuticals, Inc.)

Drug description

MLN9708 is Millennium's next generation small molecule inhibitor of the 20S proteasome that is under development for the treatment of nonhematologic malignancies, lymphoma, multiple myeloma (MM), and plasma cell dyscrasias. Inhibition of the 20S proteasome has been validated as a therapeutic target for the treatment of malignancies using VELCADE (bortezomib) for Injection, Millennium Pharmaceuticals, Inc.'s first-in-class proteasome inhibitor. MLN2238 refers to the biologically active, boronic acid form of the drug substance, MLN9708. (Conversely, MLN9708 refers to the citrate ester of MLN2238.) In water or aqueous systems, the equilibrium shifts from MLN9708 to the biologically active boronic acid form MLN2238.

Structure of MLN9708



Pharmacodynamics

The pharmacodynamic effect being evaluated in the development of MLN9708 is proteasome inhibition as measured by whole blood 20S proteasome activity, as well as elevation of the transcription factor ATF-3 in solid tumors (Study C16001) to explore target engagement. Following a single dose of MLN9708, maximal 20S proteasome inhibition occurs at the first sampling time postdose (0.08 hr) with substantial return towards baseline by 4 hours for all dose groups except 2.34 mg/m^2. Maximal 20S proteasome inhibition also occurs at the first sampling time postdose (0.08 hr) following the Day 11 dose of MLN9708. There is substantial return

towards baseline by 2 hours for doses of 0.125 to 1.0 mg/m^2 and by 96 hours for doses 1.33 to 2.34 mg/m^2.

Pharmacokinetics

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

Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5-major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

Contraindications

Hypersensitivity to any Component of this Medication

Pregnancy

Nursing Mothers

Concomitant Medications

Systemic treatment with any of the following metabolizing enzyme inhibitors is discouraged during this study. A drug-drug interaction (DDI) with a strong inhibitor would increase MLN2238 exposure.

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

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use. A DDI with a strong inducer would decrease MLN2238 exposure.

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- The dietary supplements St John's wort and Ginkgo biloba are not permitted.

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice. Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.

- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Supportive measures consistent with optimal patient care may be given throughout the study.

Safety:

As of the clinical data cutoff of 30 April 2012, a total of 382 patients have received at least 1 dose of MLN9708 in Studies C16001 (advanced solid tumors), C16002 (advanced lymphoma), C16003 (relapsed and/or refractory multiple myeloma [RRMM]), C16004 (RRMM), C16005 (newly diagnosed multiple myeloma [NDMM]), C16006 (NDMM), C16007 (AL amyloidosis), C16008 (NDMM), and C16009 (clinical pharmacology stud in nonhematologic malignancy or lymphoma).

The most frequent (at least 10% of the total safety population) AEs occurring in the pooled safety population from all ongoing studies irrespective of MLN9708 causality, are shown below:

Pooled Data From All Ongoing Studies for Treatment-Emergent Adverse Events in At Least 10% of Patients as Reported by Preferred Term

MedRA Preferred Term	IV Studies N = 140 n (%)	Oral Studies N = 242 n (%)	Total N = 382 n (%)
Subjects with at Least 1 AE	**139 (99)**	**228 (94)**	**367 (96)**
Fatigue	85 (61)	108 (45)	193 (51)
Nausea	54 (39)	100 (41)	154 (40)
Thrombocytopenia	62 (44)	88 (36)	150 (39)
Vomiting	57 (41)	76 (31)	133 (35)
Diarrhoea	46 (33)	77 (32)	123 (32)
Decreased appetite	52 (37)	50 (21)	102 (27)
Pyrexia	45 (32)	50 (21)	95 (25)
Constipation	33 (24)	50 (21)	83 (22)
Anaemia	29 (21)	52 (21)	81 (21)
Oedema peripheral	29 (21)	35 (14)	64 (17)
Cough	30 (21)	33 (14)	63 (16)
Dyspnoea	29 (21)	34 (14)	63 (16)
Back pain	26 (19)	35 (14)	61 (16)
Headache	29 (21)	29 (12)	58 (15)
Neutropenia	13 (9)	42 (17)	55 (14)
Dizziness	23 (16)	29 (12)	52 (14)
Abdominal pain	24 (17)	25 (10)	49 (13)
Upper respiratory tract infection	11 (8)	38 (16)	49 (13)
Dehydration	24 (17)	24 (10)	48 (13)
Neuropathy peripheral	16 (11)	26 (11)	42 (11)
Arthralgia	14 (10)	27 (11)	41 (11)
Chills	25 (18)	15 (6)	40 (10)

Source: \biostatistics\MLNM9708\IB\2012\Tables\T14.1.3-TEAE_Pct10_Pooled.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities Version 12.0 (C16001, C16002, C16003, and C16004), Version 13.1 (C16005), and Version 15.0 (C16006, C16007, C16008, and C16009).

Side effects not listed above but mentioned in informed consent form include: skin rash, distortion of the sense of taste, trouble falling asleep, staying asleep, or both, electrolyte imbalance, elevated blood creatinine (including renal failure and possible need for dialysis), headache, flu-like symptoms and other upper respiratory tract infections, hypotension, light headedness, or dizziness on standing, lymphopenia, and pain (muscular) in extremities.

Preparation, Reconstitution, and Dispensing

MLN9708 is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling MLN9708 capsules. 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. The appropriate study personnel will maintain records of study drug receipt and dispensing.

Packaging and Labeling

The study drug MLN9708 capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

MLN9708 capsules should be stored unopened at 2°C to 8°C (36°F-46°F). The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. The 0.2-, 0.5-, and 2.0 mg capsules are in 1 × 4 blister strips that are individually perforated. The strips (1 × 4) are placed in cartons containing 6 strips (24 total capsules) of the same strength. 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.

Storage, Handling, and Accountability

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.

9. Statistical Considerations:

The study is a multicenter phase I/II trial evaluating the safety and efficacy of MLN9708 for the prophylaxis of chronic GVHD in patients with hematological malignancies and bone marrow failure syndromes undergoing allogeneic HCT. The primary objectives of this study is to determine the MTD, DLT, RDP, and safety of MLN9708 as chronic GVHD prophylaxis in allogeneic HCT, as well as to evaluate the 1 year cumulative incidence of chronic GVHD patients prophylaxis with MLN9708. During the phase I portion, dose escalation will be carried out according to standard 3+3 design. MTD will be the dose level with ≤1 out of six patients developing DLTs. No intrapatient dose escalation will be permitted. Patients undergoing either matched sibling or unrelated donor allogeneic HCT will be eligible for phase I study.

Due to the differences in the incidence rates of chronic GVHD after sibling and unrelated donor transplantation, this study will be designed to accrue these 2 cohorts separately but in parallel, with the null hypothesis of a rate of chronic GVHD at 1-year of 55% after sibling transplantation and 65% after unrelated transplantation. The alternative hypothesis will be a 25% reduction with the use of new treatment in both cohorts. With this hypothesis, using an exact binomial distribution, the probability of

concluding the new treatment is promising, will be 0.80 (statistical power) when the true but unknown rate of developing chronic GVHD is 30% or 0.04 (type I error) when the true rate is 55% in related donor transplantation (Cohort A [matched sibling donor transplantation] with a sample size of 25). Similarly, the probability of concluding the new treatment is promising, will be 0.81 (statistical power) when the true but unknown rate of developing chronic GVHD is 40% or 0.05 (type I error) when the true rate is 65% in unrelated transplantation (Cohort B [unrelated donor transplantation] with a sample size of 26). The efficacy endpoint is chronic GVHD-free at 1 year and there will be no interim analysis on efficacy for this multi-center study. In the final analysis in Cohort A, if 10 or more of 25 patients have chronic GVHD, we will conclude the new treatment is ineffective in Cohort A; for Cohort B, if 13 or more of 26 patients have chronic GVHD, we will conclude the new treatment is ineffective in Cohort B.

Demographic and baseline laboratory results will be summarized using descriptive statistics, including means with standard deviations, or medians with ranges, histograms and box-plot. The chronic GVHD rate at 1-year and its 95% CI will be calculated by cumulative incidence method, while accounting for competing events. Progression-free survival and overall survival will be estimated using the Kaplan-Meier method. Cumulative incidence of acute and chronic GVHD, disease relapse and non-relapse mortality will be calculated by accounting for competing events. Competing events for acute GVHD disease are relapse or death without acute GVHD, while those for chronic GVHD are relapse or death without chronic GVHD. Disease relapse and non-relapse mortality are competing events for each other. Toxicity will be reported by type, frequency and severity. Worst toxicity grades per patient will be tabulated for selected adverse events and laboratory measurements. Patients replaced on the protocol (as specified in the Dose Modification Section) will remain evaluable for safety and toxicity assessment.

Safety/Stopping Rules:

For the phase II portion of the study we propose to accrue 51 patients over 24–30 months, which will enroll about 12 patients every 6 month time period. We plan to

monitor and evaluate short term adverse events at each additional 12 patients who have been enrolled in the study. The expected 100 day post-transplant immunologic graft rejection (defined as less than 5% donor myeloid cells) rate is approximately 2.5% (in absence of relapsed disease) and the enrollment will be put on hold if more than 5% graft rejection rate is seen. For the development of grade 3-4 adverse events deemed to be related to MLN9708, the true rate is 5% and enrollment will be on hold if more than 10% adverse events are observed. The stopping boundaries for graft rejection and development of grade 3-4 adverse events are shown in Table below. In the case of a safety event suspending study, a prompt cumulative examination of all data and circumstances of these events will be conducted by the Medical College of Wisconsin DSMC to determine whether study should be resumed, whether the protocol will be revised or whether the study will be discontinued permanently.

Table. Stopping boundary for adverse events.

Number of patients enrolled	Stopping boundary for immunologic graft-rejection	Stopping boundary for developing grade 3-4 adverse events related to MLN9708
12	≥ 3	≥ 3
24	≥ 3	≥ 4
36	≥ 4	≥ 6
48	≥ 4	≥ 6
51	≥ 5	≥ 7

Accrual Estimate: 6-12 patients will be enrolled in the phase I part of the protocol. In the phase II portion a total of 52 patients (25 sibling and 27 unrelated donor transplantation) will be enrolled, with 1-3 per month. Total estimated accrual = 58 patients.

Accrual Period : Approximately 24-30 months

Follow-Up Period : Two years to evaluate incidence of acute and chronic GVHD and relapse pattern, and five years for survival outcomes.

10. Adverse Event Reporting Requirements

11. Definitions

The following are definitions of adverse events as defined by 21CFR312.32.

Types of Adverse Events

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

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

Life-threatening adverse event or life-threatening suspected adverse reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator or sponsor, it results in any of the following outcomes:

- Death,
- Is life-threatening (as defined above),
- Requires inpatient hospitalization or prolongation of an existing hospitalization,

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- 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 of the outcomes listed above.

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

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, it is not consistent with the risk information currently described.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

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.

Adverse Event Grading

Grade	Description
0	**No AE** (or within normal limits).
1	**Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	**Moderate**; minimal, local or noninvasive intervention (e.g., packing cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
3	**Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	**Life-threatening** consequences; urgent intervention indicated.
5	**Death** related to AE

Adverse Event Attribution

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly **NOT** related* to the intervention
	Unlikely	The AE *is **doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

Reporting of Adverse Events

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 serious AEs, the

investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

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, the principal investigator Dr. Mehdi Hamadani, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to Millennium Pharmacovigilance:

Fatal and Life Threatening SAEs within 24 hours but no later than 4 calendar days of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non-life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The sponsor-investigator must fax the SAE Form per the timelines above. A sample of an SAE Form is provided (See Appendix C).

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

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

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

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

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**

Suggested Reporting Form:

- SAE Report Form (a sample is provided in Appendix C)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

Because all of the study transplant recipients will be receiving potentially toxic preparative therapy, significant regimen related toxicity is expected. These risks are listed in the transplant consent form. A study specific toxicity CRF will be designed to capture information regarding these expected events. Transplant is also related to a degree of mortality and this will also be captured by a study designed CRF. Unexpected adverse events will be reported throughout the study.

Unexpected Adverse Events

All unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol, will be reported to the MCW Cancer Center DSMC. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge). If the Grade 3-5 event is determined to be an unanticipated problem, the event will be forwarded to the MCW IRB for review as required by their policy. Unexpected adverse events, regardless of severity, will be reported to the MCW Cancer Center DSMC and reviewed on a quarterly basis.

Expected Adverse Events

Expected adverse events that are being captured on the study toxicity form will be reported at the time of the form's scheduled due date.

All MCW Cancer Center DSMC reports and recommendations will be submitted to the IRB for their review.

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 non-serious AEs (including AESIs), the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

AESIs must be reported to Millennium on a quarterly basis.

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 Reporting of Adverse Events). 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 Reporting of Adverse Events). 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 D)

Adverse Events Occurring after the End of the Study

Follow-up of AEs

Any unexpected AEs ongoing at the time of study discontinuation will be followed until resolution or stable for at least 2 months.

FDA Reporting Procedures

Commercial Agents: Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. The following procedures should be followed to determine if an adverse is reportable to the FDA:

Refer to the pharmaceutical section of the protocol to determine if an agent is investigational or commercial.

- **WHAT TO REPORT:** An unexpected, life-threatening (Grade 4) or unexpected, fatal (Grade 5) adverse event with an attribution of possible, probable or definite.

- **WHEN TO REPORT:** These events should be reported within (7) working days.

- **WHERE TO REPORT:** These adverse events with commercial agents must be reported to the FDA using the MedWatch form. A copy of the MedWatch form can be obtained from theFDA's MedWatch web site at www.fda.gov/medwatch. You can mail the reports to the address below or fax it 1-800-332-0178.

  MedWatch
  5600 Fishers Lane
  Rockville, MD 20852-9787

12. Administrative Requirements

Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and 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.

Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB/IEC submission.

Subject Information and Informed Consent

Written informed consent must be obtained from the subject prior to study participation.

The informed consent document must be signed and dated by the subject and properly witnessed (if applicable) before initiation of any study procedures including any change in medication or initiation of study drug dosing.

Subjects must be consented in accordance with all local regulatory and legal requirements. This process must include a verbal explanation of the nature, scope, and possible consequences of the study provided in plain language. The information should be presented by the investigator unless a designee is permitted by local regulations. The potential study subject should be encouraged to ask questions about the study.

The informed consent document must be prepared in accordance with GCP guidelines and with local regulatory and legal requirements. A copy of the signed consent form will be given to the subject and the original document must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes.

The informed consent will be updated as appropriate (e.g., due to protocol amendment or if significant new safety information that may be relevant to consent of the subjects becomes available). If the informed consent is revised, it is the investigator's responsibility to ensure that an amended consent form is reviewed and signed by all subjects subsequently entered into the study and those currently in the study.

Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. If requested, the investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

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.

On-site Audits

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

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.

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.

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
- Plans to modify, suspend or discontinue the development of the drug.

Record Retention

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

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.

Peer Review Statement

This study was reviewed and approved by the Medical College of Wisconsin Scientific Review Committee on 04/29/2014.

13. References

1. Deeg HJ. How I treat refractory acute GVHD. Blood. 2007;109(10):4119-4126.

2. Antin JH, Kim HT, Cutler C, et al. Sirolimus, tacrolimus, and low-dose methotrexate for graft-versus-host disease prophylaxis in mismatched related donor or unrelated donor transplantation. Blood. 2003;102(5):1601-1605.

3. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. Blood. 1998;92(7):2303-2314.

4. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. Blood. 2000;96(6):2062-2068.

5. Shlomchik WD, Couzens MS, Tang CB, et al. Prevention of graft versus host disease by inactivation of host antigen-presenting cells. Science. 1999;285(5426):412-415.

6. Ferrara JL and Deeg HJ. Graft-versus-host disease. N Engl J Med. 1991;324(10):667-674.

7. Blazar BR, Korngold R, Vallera DA. Recent advances in graft-versus-host disease (GVHD) prevention. Immunol Rev. 1997;157:79-109.

8. Lin MT, Storer B, Martin PJ, et al. Relation of an interleukin-10 promoter polymorphism to graft-versus-host disease and survival after hematopoietic-cell transplantation. N Engl J Med. 2003;349(23):2201-2210.

9. Nikolic B, Lee S, Bronson RT, Grusby MJ, Sykes M. Th1 and Th2 mediate acute graft-versus-host disease, each with distinct end-organ targets. J Clin Invest. 2000;105(9):1289-1298.

10. Broady R and Levings MK. Graft-versus-host disease: suppression by statins. Nat Med. 2008;14(11):1155-1156.

11. Liao JK and Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005;45:89-118.

12. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nat Rev Immunol. 2006;6(5):358-370.

13. Greenwood J, Walters CE, Pryce G, et al. Lovastatin inhibits brain endothelial cell Rho-mediated lymphocyte migration and attenuates experimental autoimmune encephalomyelitis. FASEB J. 2003;17(8):905-907.

14. Dunn SE, Youssef S, Goldstein MJ, et al. Isoprenoids determine Th1/Th2 fate in pathogenic T cells, providing a mechanism of modulation of autoimmunity by atorvastatin. J Exp Med. 2006;203(2):401-412.

15. Mausner-Fainberg K, Luboshits G, Mor A, et al. The effect of HMG-CoA reductase inhibitors on naturally occurring CD4+CD25+ T cells. Atherosclerosis. 2008;197(2):829-839.

16. Zeiser R, Youssef S, Baker J, Kambham N, Steinman L, Negrin RS. Preemptive HMG-CoA reductase inhibition provides graft-versus-host disease protection by Th-2 polarization while sparing graft-versus-leukemia activity. Blood. 2007;110(13):4588-4598.

17. Hamadani M, Awan FT, Devine SM. The impact of HMG-CoA reductase inhibition on the incidence and severity of graft-versus-host disease in patients with acute leukemia undergoing allogeneic transplantation. Blood. 2008;111(7):3901-3902.

18. Rotta M, Storer BE, Storb R, et al. Impact of recipient statin treatment on graft-versus-host disease after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2010;16(10):1463-1466.

19. Rotta M, Storer BE, Storb RF, et al. Donor statin treatment protects against severe acute graft-versus-host disease after related allogeneic hematopoietic cell transplantation. Blood. 2010;115(6):1288-1295.

20. Kapur R, Ebeling S, Hagenbeek A. B-cell involvement in chronic graft-versus-host disease. Haematologica. 2008;93(11):1702-1711.

21. Fujii H, Cuvelier G, She K, et al. Biomarkers in newly diagnosed pediatric-extensive chronic graft-versus-host disease: a report from the Children's Oncology Group. Blood. 2008;111(6):3276-3285.

22. Sarantopoulos S, Stevenson KE, Kim HT, et al. High levels of B-cell activating factor in patients with active chronic graft-versus-host disease. Clin Cancer Res. 2007;13(20):6107-6114.

23. Sarantopoulos S, Stevenson KE, Kim HT, et al. Altered B-cell homeostasis and excess BAFF in human chronic graft-versus-host disease. Blood. 2009;113(16):3865-3874.

24. She K, Gilman AL, Aslanian S, et al. Altered Toll-like receptor 9 responses in circulating B cells at the onset of extensive chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2007;13(4):386-397.

25. Allen JL, Fore MS, Wooten J, et al. B cells from patients with chronic GVHD are activated and primed for survival via BAFF-mediated pathways. Blood. 2012;120(12):2529-2536.

26. Srinivasan M, Flynn R, Price A, et al. Donor B-cell alloantibody deposition and germinal center formation are required for the development of murine chronic GVHD and bronchiolitis obliterans. Blood. 2012;119(6):1570-1580.

27. Young JS, Wu T, Chen Y, et al. Donor B cells in transplants augment clonal expansion and survival of pathogenic CD4+ T cells that mediate autoimmune-like chronic graft-versus-host disease. J Immunol. 2012;189(1):222-233.

28. Cutler C, Kim HT, Bindra B, et al. Rituximab prophylaxis prevents corticosteroid-requiring chronic GVHD after allogeneic peripheral blood stem cell transplantation: results of a phase II trial. Blood. 2013.

29. Miklos DB, Kim HT, Miller KH, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood. 2005;105(7):2973-2978.

30. Kharfan-Dabaja MA, Mhaskar AR, Djulbegovic B, Cutler C, Mohty M, Kumar A. Efficacy of rituximab in the setting of steroid-refractory chronic graft-versus-host disease: a systematic review and meta-analysis. Biol Blood Marrow Transplant. 2009;15(9):1005-1013.

31. Khouri IF, Lee MS, Saliba RM, et al. Nonablative allogeneic stem cell transplantation for chronic lymphocytic leukemia: impact of rituximab on immunomodulation and survival. Exp Hematol. 2004;32(1):28-35.

32. Arai S, Sahaf B, Narasimhan B, et al. Prophylactic rituximab after allogeneic transplantation decreases B-cell alloimmunity with low chronic GVHD incidence. Blood. 2012;119(25):6145-6154.

33. McIver Z, Stephens N, Grim A, Barrett AJ. Rituximab administration within 6 months of T cell-depleted allogeneic SCT is associated with prolonged life-threatening cytopenias. Biol Blood Marrow Transplant. 2010;16(11):1549-1556.

34. Ghosh S, May MJ, Kopp EB. NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. Annu Rev Immunol. 1998;16:225-260.

35. Finn PW, Stone JR, Boothby MR, Perkins DL. Inhibition of NF-kappaB-dependent T cell activation abrogates acute allograft rejection. J Immunol. 2001;167(10):5994-6001.

36. Nencioni A, Schwarzenberg K, Brauer KM, et al. Proteasome inhibitor bortezomib modulates TLR4-induced dendritic cell activation. Blood. 2006;108(2):551-558.

37. Blanco B, Perez-Simon JA, Sanchez-Abarca LI, et al. Treatment with bortezomib of human CD4+ T cells preserves natural regulatory T cells and allows the emergence of a distinct suppressor T-cell population. Haematologica. 2009;94(7):975-983.

38. Blanco B, Perez-Simon JA, Sanchez-Abarca LI, et al. Bortezomib induces selective depletion of alloreactive T lymphocytes and decreases the production of Th1 cytokines. Blood. 2006;107(9):3575-3583.

39. Vodanovic-Jankovic S, Hari P, Jacobs P, Komorowski R, Drobyski WR. NF-kappaB as a target for the prevention of graft-versus-host disease: comparative efficacy of bortezomib and PS-1145. Blood. 2006;107(2):827-834.

40. Sun K, Welniak LA, Panoskaltsis-Mortari A, et al. Inhibition of acute graft-versus-host disease with retention of graft-versus-tumor effects by the proteasome inhibitor bortezomib. Proc Natl Acad Sci U S A. 2004;101(21):8120-8125.

41. Mateos-Mazon J, Perez-Simon JA, Lopez O, Hernandez E, Etxebarria J, San Miguel JF. Use of bortezomib in the management of chronic graft-versus-host disease among multiple myeloma patients relapsing after allogeneic transplantation. Haematologica. 2007;92(9):1295-1296.

42. Wang XC, Jobin C, Allen JB, Roberts WL, Jaffe GJ. Suppression of NF-kappaB-dependent proinflammatory gene expression in human RPE cells by a proteasome inhibitor. Invest Ophthalmol Vis Sci. 1999;40(2):477-486.

43. El-Cheikh J, Michallet M, Nagler A, et al. High response rate and improved graft-versus-host disease following bortezomib as salvage therapy after reduced intensity conditioning allogeneic stem cell transplantation for multiple myeloma. Haematologica. 2008;93(3):455-458.

44. Koreth J, Stevenson KE, Kim HT, et al. Bortezomib-based graft-versus-host disease prophylaxis in HLA-mismatched unrelated donor transplantation. J Clin Oncol. 2012;30(26):3202-3208.

45. Chauhan D, Tian Z, Zhou B, et al. In vitro and in vivo selective antitumor activity of a novel orally bioavailable proteasome inhibitor MLN9708 against multiple myeloma cells. Clin Cancer Res. 2011;17(16):5311-5321.

46. Chow LQ. MLN9708, an investigational proteasome inhibitor, in patients with solid tumors; Updated phase 1 results in Head and Neck Symposium. 2012. Phoenix, AZ . In: Anonymous .

47. Assouline S. Once-weekly MLN9708, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma: results of a phase 1 dose-escalation study in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands. .

48. Lonial S. Phase I study of twice-weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed and/or refractory multiple myeloma (MM) in ASCO Annual Meeting. 2012. Chicago, Illinois. .

49. Kumar S. Oral weekly MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma (MM): A phase I/II study in ASCO Annual Meeting. 2012. Chicago, Illinois. .

50. Merlini G. MLN9708, a Novel, Investigational Oral Proteasome Inhibitor, in Patients with Relapsed or Refractory Light-Chain Amyloidosis (AL): Results of a Phase 1 Study in 54th ASH Annual Meeting and Exposition. 2012. Atlanta, Georgia. .

51. Kumar S. A Phase 1/2 Study of Weekly MLN9708, an Investigational Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM) in 54th ASH Annual Meeting and Exposition. 2012. Atlanta, Georgia. .

52. Richardson PG. MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in previously untreated multiple myeloma patients (pts): Evaluation of weekly and twice-weekly dosing in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands. .

53. San Miguel J. Oral MLN9708, an an investigational proteasome inhibitor, in combination with melphalan and prednisone in patients with previously untreated multiple myeloma: a phase 1 study in 17th EHA Annual Congress. 2012. Amsterdam, the Netherlands. .

54. Kumar S. Weekly Dosing of the Investigational Oral Proteasome Inhibitor MLN9708 in Patients with Relapsed and/or Refractory Multiple Myeloma: Results From a Phase 1 DoseEscalation Study in 53rd ASH Annual Meeting and Exposition. 2011. San Diego, CA.

55. Kumar S. Weekly dosing of the investigational oral proteasome inhibitor MLN9708 in patients (pts) with relapsed/refractory multiple myeloma (MM): A phase I study in ASCO Annual Meeting. 2012. Chicago, Illinois. .

56. Sanchorawala V. Poster Presentation: Phase 1 study of MLN9708, a novel, investigational oralproteasome inhibitor, in patients with relapsed or refractory light-chain amyloidosis.XIII International Symposium on Amyloidosis, Groningen, The Netherlands 2012. .

57. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-828.

58. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on

Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biol Blood Marrow Transplant. 2006;12(3):252-266.

59. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945-956.

14. Appendix A Assessment of Acute GVHD

Clinical Acute GVHD Assessment

Date _____ Patient ID _____ Karnofsky/Lansky _____

	Code							Differential Diagnosis						
	0	1	2	3	4	5		GVHD	Drug Rxn	Cond Reg	TPN	Infect	VOD	Other
Skin	☐	☐	☐	☐	☐		% body rash:____	☐	☐	☐		☐		_____
Lower GI	☐	☐	☐	☐	☐	☐	Vol: _____	☐	☐	☐	☐	☐		_____
Upper GI	☐	☐						☐	☐	☐	☐	☐		_____
Liver	☐	☐	☐	☐	☐		Max bili: _____	☐	☐	☐	☐	☐	☐	_____

Treatment: ☐ CSA ☐ Tacrolimus ☐ Pred ☐ Methylpred ☐ Ontak
☐ Pentostatin ☐ MMF ☐ Etanercept ☐ Other _____

Code Definitions:

Skin:
0 No rash
1 Maculopapular rash, <25% of body surface
2 Maculopapular rash, 25-50% of body surface
3 Generalized erythroderma
4 Generalized erythroderma with bullous formation and desquamation

Lower GI (Diarrhea):
0 None
1 ≤500 mL/day or <280 mL/m^2
2 501-1000 mL/day or 280- 555 mL/m^2
3 1001-1500 mL/day or 556- 833 mL/m^2
4 >1500 mL/day or >833 mL/m^2
5 Severe abdominal pain with or without ileus, or stool with frank blood or melena

Upper GI:
0 No protracted nausea and vomiting
1 Persistent nausea, vomiting or anorexia

Liver (Bilirubin):
0 <2.0 mg/dl
1 2.1-3.0 mg/dl
2 3.1-6.0 mg/dl
3 6.1-15.0 mg/dl
4 >15.1 mg/dl

Signature _____

TABLE 1.3.1 – GVHD STAGING

Stage	Skin	GI	Liver
1	< 25% rash	Diarrhea > 500ml/d or persistent nausea	Bilirubin 2-3mg/dl
2	25-50%	> 1000 ml/d	Bilirubin 3-6 mg/dl
3	> 50%	> 1500 ml/d	Bilirubin 6-15 mg/dl
4	Generalized erythroderma with bullae	Large volume diarrhea and severe abdominal pain ± ileus	Bilirubin > 15 mg/dl

TABLE 1.3.2 – CONSENSUS GVHD GRADING (PRZEPIORKA, ET. AL., 1995)

Grade	Skin	GI	Liver
I	Stage 1-2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III	---	Stage 2-4	Stage 2-3
IV	Stage 4	---	Stage 4

15. Appendix B Grading of Chronic GVHD (NIH Criteria)

Check all that apply	Score 0 - None	Score 1 - Mild	Score 2 - Moderate	Score 3 - Severe
Skin: *Clinical features:* ❑Maculopapular rash ❑Lichen planus-like features ❑Papulosquamous lesions or ichthyosis ❑Hyperpigmentation ❑Hypopigmentation ❑Keratosis pilaris ❑Erythema ❑Erythroderma ❑Sclerotic features ❑Poikiloderma ❑Pruritus ❑Hair Involvement ❑Nail Involvement % BSA involved __%	❑No symptoms	❑< 18% BSA with disease signs but NO sclerotic features	❑19-50% BSA, ❑Involvement with superficial sclerotic features "not hidebound" (able to pinch)	❑> 50% BSA ❑Deep sclerotic features "hidebound" (unable to pinch) ❑Impaired mobility, ulceration or severe pruritis
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 WITH major limitation of oral intake
Eyes: Mean tear test (mm): ❑> 10 ❑6-10 ❑≤ 5 ❑Not done	❑	❑Mild dry eyes symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) ❑Asymptomatic signs of keratoconjunctivitis sicca	❑Moderate dry eyes symptoms partially affecting ADL (requiring eyedrops > 3 x per day or punctual plugs) WITHOUT vision impairment	❑Severe dry eyes symptoms significantly affecting ADL (special eyewear to relieve pain) ❑Unable to work because of ocular symptoms ❑Loss of vision caused by keratoconjuctivitis sicca
Pulmonary **FEV1** ❑Not done **Pulmonary Fibrosis** **Bronchiolitis Obliterans** **Supplemental O2 required?** ❑Yes ❑No	❑No symptoms ❑FEV1> 80% ❑None ❑Not assessed ❑None ❑Yes, clinical ❑Yes, histologic ❑Not assessed	❑Mild symptoms (shortness of breath after climbing one flight of steps) ❑FEV1 60-78% ❑ Minimal radiographic findings	❑Moderate symptoms (shortness of breath after walking on flat ground) ❑FEV1 40-51% ❑Patchy or bi-basilar radiographic findings	❑Severe symptoms (shortness of breath at rest; requiring O_2) ❑FEV1 ≤ 39% ❑Extensive radiographic findings
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 caloric needs ❑Esophageal dilation
Liver:	❑Normal LFT	❑Elevated Bilirubin, AP, AST or ALT < 2 x ULN	❑Bilirubin 3 – 10 mg/dl; liver enzymes 2-5 x ULN	❑Bilirubin > 10 mg/dL; liver enzymes > 5 x ULN
Genital Tract:	❑No symptoms	❑Symptomatic with mild signs on exam AND no effect on coitus and minimal discomfort with gynecological exam	❑Symptomatic with moderate signs on exam AND with mild dyspareunia or discomfort with gynecological exam	❑Symptomatic WITH advanced signs (stricture, labial agglutination or severe ulceration) AND severe pain with coitus or inability to insert vaginal speculum

Check all that apply	Score 0 - None	Score 1 - Mild	Score 2 - Moderate	Score 3 - Severe
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 ❑ Joint contractures, erythema thought due to fascitis, moderate decreased ROM AND mild to moderate limitation of ADL	❑ Contractures WITH significant decrease of ROM AND significant limitation of ADLs (unable to tie shoes, button shirts, dress self etc.)

Other indicators, clinical manifestations or complications related to Chronic GvHD (check all that apply).
Assign a score to it's severity based on functional impact, where applicable (0= none, 1=mild, 2 = moderate, 3= severe)

❑ Ascites (serositis) ___	❑ Esophageal stricture or web___	❑ Nephrotic syndrome ___	❑ Pleural effusions ___
❑ Cardiac conduction defects ___	❑ Eosinophilia > 500 µl ___	❑ Pericardial effusion ___	❑ Polymyositis ___
❑ Cardiomyopathy ___	❑ Myasthenia Gravis ___	❑ Peripheral neuropathy ___	❑ Progressive onset___
❑ Coronary artery involvement ___		❑ Platelets < 100,000/µl ___	
❑ Other(s): Specify & score___			

Based on observations checked in the above table, select the severity of chronic GvHD for this assessment (Check only one)

☐ **None**

☐ **Mild chronic GVHD** involves only 1 or 2 organs or sites (except the lung: see below ‡), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites)

☐ **Moderate chronic GVHD** involves: (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). ‡*A lung score of 1 will also be considered moderate chronic GVHD.*

☐ **Severe chronic GVHD** indicates major disability caused by chronic GVHD (score of 3 in any organ or site). ‡*A lung score of 2 or greater will also be considered severe chronic GVHD.*

16. Appendix C. Sample SAE Form

(please see on the following page)

Serious Adverse Event Form

Protocol # ______________________________ Subject ID: ______________________________
Site # ______________________________ Subject Initials: ______________________________

Investigator Information		Patient Information	
Date of report: _____/_____/_____ (dd mmm yyyy)	Report type: ❑ Initial ❑ Follow-up	Date of birth ____/____/____ (dd mmm yyyy)	Race: ❑White ❑Black ❑Hispanic ❑American Indian or Alaskan Native ❑Asian or Pacific Islander ❑Other_________
Principal Investigator's Name:	Tel. # (____)______________	Gender: ❑ Male ❑ Female	
Principal Investigator's Address:	Fax # (____)______________	Height: _____ cm /**or** _____ in	
	Email: ____________________	Weight: _____ kg /**or** _____ lb	

Study Drug Information				
Indication for use:		Indication diagnosis date: _____/_____/_____ (dd mmm yyyy)		
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:

Medical history and laboratory/diagnostic tests

Please provide or attach *anonymized* relevant data regarding:

- Past medical and allergy history
- History of past therapy for indication for use
- Concomitant medication
- Relevant laboratory and diagnostic tests

Study contact completing form _________ (Initials) _________ (Date (dd/mmm/yyyy))   Principal Investigator _________ (Initials) _________ (Date (dd/mmm/yyyy))

Serious Adverse Event Form

Protocol # _____ Subject ID: _____
Site # _____ Subject Initials: _____

If more than one serious adverse event, please copy this page and complete all fields on page individually for each SAE

Serious Adverse Event: _____

SAE onset date: _____/_____/_____ (dd / mmm / yyyy)

Serious Criteria (check all that apply):
- ❑ Death
- ❑ Life threatening
- ❑ Hospitalization / prolonged hospitalization
- ❑ Persistent or significant disability / incapacity
- ❑ Congenital anomaly / birth defect
- ❑ Important medical event

Maximum Intensity:
- ❑ Grade 1 / Mild
- ❑ Grade 2 / Moderate
- ❑ Grade 3 / Severe
- ❑ Grade 4
- ❑ Grade 5

Did SAE(s) abate after stopping study drug? ❑ Yes ❑ No ❑ NA

Did SAE(s) reappear after reintroducing study drug? ❑ Yes ❑ No ❑ NA

Action taken with study drug (check all that apply):

Drug(s)

_____
- ❑ Dose continued unchanged
- ❑ Dose reduced. Date decreased: _____/_____/_____ (dd / mmm / yyyy)
- ❑ Dose increased. Date increased: _____/_____/_____ (dd / mmm / yyyy)
- ❑ Dose delayed. Date held: _____/_____/_____ (dd / mmm / yyyy)
- ❑ Discontinued permanently due to this SAE. _____/_____/_____ (dd / mmm / yyyy)
- ❑ Not applicable, patient no longer receiving study drug.

Status of SAE at time of this report:
- ❑ Fatal
- ❑ Completely resolved _____/_____/_____ (dd / mmm / yyyy)
- ❑ Resolved with sequelae _____/_____/_____ (dd / mmm / yyyy)
- ❑ Not completely resolved
  - ❍ ongoing and unchanged
  - ❍ ongoing with increased intensity
  - ❍ ongoing with decreased intensity

Study Drug	Is there a reasonable possibility that the event is associated with this study medication?	
1. _____	❑ Yes	❑ No
2. _____	❑ Yes	❑ No
3. _____	❑ Yes	❑ No
4. _____	❑ Yes	❑ No
5. _____	❑ Yes	❑ No
6. _____	❑ Yes	❑ No
7. _____	❑ Yes	❑ No
8. _____	❑ Yes	❑ No
9. _____	❑ Yes	❑ No

Is there a reasonable possibility that the event is associated with:
- ❑ Non-study drug, procedure, or therapy *Specify:* _____
- ❑ Another alternative etiology (e.g. indication for use, intercurrent illness) *Specify:* _____
- ❑ Protocol design or procedures (alone or in addition to study drug) *Specify:* _____

Study contact completing form _____ (Initials) _____ (Date (dd/mmm/yyyy))

Principal Investigator _____ (Initials) _____ (Date (dd/mmm/yyyy))

Description of Serious Adverse Event(s)

Please provide a brief narrative description of the SAE (presenting symptoms, clinical course, treatment, etc.). or attach extra pages, if available.

Death Information

Date of death: _____/_____/_____
dd mmm yyyy

Autopsy performed? ❑ Yes ❑ No

If yes, autopsy report attached? ❑ Yes ❑ No

Cause(s) of death (list primary cause of death first):

_____

_____

_____

Was the patient's death related to:

Study drug(s)? ❑ Yes ❑ No If yes, please specify all that apply _____

_____

Protocol design or procedures (alone or in addition to study drug)? ❑ Yes ❑ No If yes, please specify _____

_____

Study contact completing form printed name	Study contact completing form signature	Date (dd/mmm/yyyy)
Principal investigator printed name	Principal investigator signature	Date (dd/mmm/yyyy)

17. Appendix D. Millennium Pregnancy Reporting Form

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

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: ___/___/_____ or Age: _____years
DD MM Yr

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

CURRENT PREGNANCY INFORMATION

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

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: _____