Case CCC Study: CASE 4A13

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Title: A Phase I/II Study of MLN9708 (Ixazomib) in Combination with Panobinostat and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

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PROTOCOL SUMMARY

Title: A Phase I/II Study of MLN9708 (Ixazomib) in Combination with Panobinostat and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

Objectives

The primary objective of this study is to:

- Define the tolerability and safety of MLN9708 (ixazomib) administered on a day 1,8,15 every 28 day schedule up to 4mg in combination with fixed doses of panobinostat and dexamethasone in patients with relapsed or refractory myeloma

The secondary objectives of this study are to:

- Assess response and clinical benefit response rates according to international uniform response criteria and adapted EBMT criteria, respectively (see under 8.1)
- Assess progression-free survival (PFS) and overall survival (OS)

Patient Population

Specific inclusion and exclusion criteria are detailed in Section 6.1.2

Number of Patients

31 patients (11 in phase I, 20 in phase II)

Study Design and Methodology

Phase I: This study will use a modified 3 + 3 design to define the tolerability and safety of MLN9708 (ixazomib) administered to at least 6 patients with relapsed or refractory myeloma on a day 1,8,15 every 28 day schedule at up to 4mg in combination with fixed doses of panobinostat and dexamethasone.

Dose limiting toxicities (DLTs, see under 5.4) will be assessed at the end of the first cycle, on day 28. The trial will accrue up to three patients at any given DL who will need to be assessed for DLTs before the next three patients can be enrolled. Determination of the highest tolerated dose of two tested dose levels will require treatment of at least 6 patients at the respective dose level with no more than one patient developing a DLT.

The first three patients will be treated at DL1. If no patient develops any DLT, the next three patients will be enrolled at DL2. If 1 patient develops any DLT, three additional patients will be enrolled at DL1. If no more than 1 of 6 patients treated at DL1 develops a DLT, the next three patients will be enrolled at DL2. If 2 or more of 2-6 patients treated at DL1 develop DLTs further enrollment will be stopped and a change in the protocol will be discussed. If DL2 opens to enrollment, and 0-1 of the first three patients develop any DLT, additional three patients will be enrolled at DL2 and if no more than 1 of 6 patients treated at DL2 develop any DLT, DL2 will be considered a tolerated MLN9708 dose and further dose escalation will not be done. If 2 of three or up to 6 patients enrolled at DL2 develop any DLT, further enrollment at that dose level will be stopped and enrollment will continue at DL1 unless 6 patients have already been treated at that dose level. If no more than 1 patient treated at DL1 develops any DLT that dose level will be considered tolerated and an intermediate dose level may be discussed. If 2 or more

of up to 6 patients treated at DL1 develop a DLT, further enrollment will be stopped and a change in the protocol will be discussed.
Phase II: Twenty additional patients will be treated at target doses of DL2 which has been found to be well tolerated without any DLT in phase I.

Treatments Administered

Dose levels

Dose level	PO Panobinostat	PO MLN9708 (Ixazomib)	PO Dexamethasone
1	20mg d 1,3,5,15,17,19 q 28 d	3mg d1,8,15 q 28 d	20mg d 1,2,8,9,15,16 q 28 d
2	20mg d 1,3,5,15,17,19 q 28 d	4mg d1,8,15 q 28 d	20mg d 1,2,8,9,15,16 q 28 d

Phase I: Patients will remain on study for six 28-day cycles or until criteria for discontinuation (7.6.1) are met, whichever comes earlier. Decisions on subsequent maintenance therapy will at the discretion of the treating physician but if the patient's myeloma is controlled (at least in stable disease) panobinostat, dexamethasone, and ixazomib may be continued and will be provided free of charge to the patient. This protocol may be amended to include a formal maintenance phase and/or a phase II portion after review of safety and preliminary efficacy data and approval by Novartis, Millennium, and the sponsor institution (Cleveland Clinic).
Phase II: Patients will receive therapy according to DL2 and will remain on study until criteria for discontinuation (7.6.1) are met.

Efficacy Data Collected
The following evaluations will be conducted to assess the efficacy of this regimen:

Response will be assessed according to international uniform response criteria and clinical benefit response according to modified EBMT response criteria (8.1), using myeloma panels obtained at the beginning of each cycle that include SPEP, 24 h UPEP, serum and urine IFEs, and serum free light chains. In addition, a baseline bone marrow exam and skeletal survey will be obtained and repeated as clinically indicated, including repeat bone marrow exam for confirmation of complete remission (see also Section 8 schedule of assessments).

Pharmacokinetic/Pharmacodynamic/Pharmacogenomic/Correlative Studies Collected
None.

Safety Data Collected
The following evaluations will be conducted to assess the safety of this regimen:

- Dose limiting toxicity will be evaluated after the first cycle for patients in phase I
- Toxicity will be evaluated according to CTCAE version 4.0, weekly during the first cycle and whenever the dose of a drug is increased, then at the start of each subsequent

cycle

Statistical Procedures
Due to low patient numbers and short study duration results will only be described. Appropriate statistical analysis will be added if the study is extended into a phase II evaluation.

Phase II: Kaplan-Meier survival and progression-free survival estimates will be calculated.

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List of abbreviations

AE	**adverse event**
ALT	**alanine aminotransferase/glutamic pyruvic transaminase/GPT**
ANC	**absolute neutrophil count**
APL	**acute promyelocytic leukemia**
ASCO	**American Society of Clinical Oncologists**
AST	**aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT**
ATRA	**all trans-retinoic acid**
AUC	**area under the curve**
BCR-ABL	**a fusion gene of the BCR and ABL genes**
BUN	**blood urea nitrogen**
CIS	**carcinoma in-situ**
Cmax	**maximum concentration of drug**
CML	**chronic myelogenous leukemia**
CNS	**central nervous system**
CR	**complete response/remission**
CS&E	**clinical safety and epidemiology**
CTCAE	**NCI common terminology criteria for adverse events (version 3.0)**
CTCL	**cutaneous T-cell lymphoma**

CV	**coefficient of variation**
DLT	**dose-limiting toxicity**
DNA	**deoxyribose nucleic acid**
ECG	**12 lead electrocardiogram**
ECOG	**Eastern Cooperative Oncology Group**
eRT	**eResearchTechnology**
FACT	**functional assessment of cancer therapy**
FDA	**food and drug administration**
G-CSF	**granulocyte colony-stimulating factor (e.g. filgrastim)**
GM-CSF	**granulocyte-macrophage colony-stimulating factor (e.g. sargramostim)**
H3, H4	**histones H3, H4**
HAT	**histone acetyltransferase**
HDAC	**histone deacetylase**
HDACi	**histone deacetylase inhibitor**
hERG	**human ether-a-go-go related gene**
HIV	**human immunodeficiency virus**
i.v.	**intravenous(ly)**
ICH	**international conference on harmonization**
IEC	**independent ethics committee**
IRB	**institutional review board**
LLN	**lower limit of normal**
LVEF	**left ventricular ejection fraction**
mg/m2	**milligrams per square meter**
MM	**Multiple myeloma**
RRMM	**Relapsed or refractory multiple myeloma**
MTD	**maximum tolerated dose**
MUGA	**multiple uptake gated acquisition scan**
MWF	**monday, wednesday, friday**
NCI	**national cancer institute**
NDMM	**Newly diagnosed multiple myeloma**
NHL	**non-hodgkin's lymphoma**
NIH	**national institutes of health**
PD	**pharmacodynamic**
P-gp	**p-glycoprotein**
PK	**pharmacokinetic**
PLT	**platelet**
PR	**partial response**
REB	**research ethics board**

SAE	**serious adverse event**
SAHA	**suberoylanilide hydroxamic acid**
SD	**stable disease**
SOP	**standard operating procedure**
T4	**thyroxine**
TSH	**thyroid stimulating hormone**
ULN	**upper limit of normal**
WBC	**white blood cell**
WNL	**within normal limits**
WOCBP	**women of childbearing potential**

1 Introduction

1.1 Overview of targeted Multiple Myeloma

Multiple myeloma, a cancer of antibody producing plasma cells, is the second most common hematologic malignancy in the United States. Based on SEER data (http://seer.cancer.gov/statfacts/html/mulmy.html, accessed 1/31/2013) it is estimated that 21,700 individuals were diagnosed with multiple myeloma in 2012 and that 10,710 died of the disease. Treatment has improved life expectancy with major milestones marked by the introduction of oral melphalan therapy in the late 1950s, corticosteroids prednisone or dexamethasone shortly thereafter, high dose melphalan with autologous stem cell transplant in the 1990s, and discovery of profound antimyeloma effects with the use of "new drugs" thalidomide, bortezomib, and lenalidomide around the turn of the century [1]. With improved life expectancy myeloma prevalence increases and was 71,213 in 2009 (http://seer.cancer.gov/statfacts/html/mulmy.html, accessed 1/31/2013). Almost all patients still experience disease progression and ultimately their disease becomes refractory to available standard therapy which includes various combinations of "new drugs" corticosteroids, and conventional chemotherapeutic agents. More recent progress includes development of carfilzomib, a second generation proteasome inhibitor which in contrast to bortezomib does not cause significant neurotoxicity and produces at least minor responses as single agent in more than one third of patients with refractory myeloma [2] leading to FDA approval in 2012. Pomalidomide, an analogue of lenalidomide, in combination with dexamethasone yielded about similarly promising results in refractory myeloma [3-5] and obtained FDA approval in 2013. Despite these developments, the majority of patients with relapsed and refractory multiple myeloma do not respond to available therapy creating an unmet need for further drug development. One of the mechanisms of increasingly uncontrollable growth of cancer cells during clonal evolution as it occurs in most cancers including myeloma is epigenetic silencing of genes required for senescence, differentiation, cell death, and immune attack [6]. The pan-histone deactelyase inhibitor panobinostat may restore intrinsic and extrinsic growth control by reactivation of respective genes and pathways through its chromatin opening effects and enhance cell death induction through inhibition of deacetylation of non-histone proteins. In a clinical study that enrolled patients who were refractory to their last bortezomib containing regimen, panobinostat added to bortezomib and dexamethasone yielded a remarkable clinical benefit response (at least minor response) of about 50% [7]. The need for parenteral administration and neurotoxic adverse events with the use of bortezomib has led to the development of the oral proteasome inhibitor MLN9708 which has shown single agent activity in relapsed and refractory myeloma without clinically significant neuropathy [8-10]. The maximal tolerated dose for MLN9708 when given as a single agent in either a twice-a-week ($2mg/m^2$) [10] or weekly ($2.97mg/m^2$) [9] administration schedule has been determined. Dosing of MLN9708 became more

straightforward after analysis of pharmacokinetic data of patients on IV and PO clinical trials revealed that body size only affects distribution but not AUC of MLN9708, allowing formulation of fixed tablet strengths [11]. In combination with lenalidomide and dexamethasone, MLN9708 can safely be given at 4mg weekly for 3 out of 4 weeks [8] and a phase 3 study for upfront therapy in transplant-ineligible patients has already opened (NCT01564537). Panobinostat may synergize with MLN9708 and dexamethasone in relapsed and refractory myeloma in a similar way as with bortezomib. In this study we will investigate whether MLN9708 at up to 4mg day 1,8,15 every 28 days can be given safely in combination with a fixed dose schedule of panobinostat and dexamethasone, selected based on the experience with twice a week bortezomib combination at effective doses but adjusted to the 4 week MLN9708 schedule. The most refractory myeloma patient population often requires combination of more than three agents for disease control. MLN9708, panobinostat, and dexamethasone may serve as a platform for addition of agents. Lenalidomide has been shown to synergize with proteasome inhibitors and corticosteroids[12,13] and to be well tolerated in combination with MLN9708 and dexamethasone[8]. It appears to synergize with histone deacetylase inhibitors as well[14] and patients with relapsed and refractory Hodgkin's lymphoma appear to tolerate twice the amount of panobinostat proposed here in combination with standard lenalidomide 25mg day 1-21 every 28 days[15]. The three-drug oral regimen we propose to develop here may therefore lend itself for further intensification by addition of another active compound to treat the most refractory myelomas.without need for parenteral administration.

1.2 Overview of Panobinostat

1.2.1 Anticancer activity of DAC inhibitors

Alterations in chromosome structure play critical roles in the control of gene transcription. These epigenetic alterations include modification of histones and others proteins by acetylation and/or phosphorylation. Normally, these modifications are balanced finely and are highly reversible in normal tissues, but they may be imbalanced and heritable in tumor cells. DAC inhibitors increase histone acetylation, thereby modulating the expression of a subset of genes in a coordinated fashion. Several tumors suppressor genes associated with the malignant phenotype are repressed by epigenetic mechanisms in sporadic cancers. Thus therapy with DAC inhibitors may alter tumor phenotype and inhibit growth in such tumors.

Multiple hallmarks of cancer are regulated by acetylation/deacetylation:

- DAC inhibition targets both histone and nonhistone proteins. Targeting the acetylation status of nonhistone, tumor-associated proteins that mediate proliferation may be the underlying antitumor mechanism of DAC inhibitors [16].
- Nonhistone proteins regulated by acetylation include α-tubulin, p53, HIF-1α, and HSP90. These proteins are substrates of DACs [17].

- The ability of a single agent to target multiple molecular features of tumor cells may result in good efficacy against a range of different tumor types.
- HSP90 is involved in protein stability and degradation; the inhibition of HSP90 affects protein turnover in diseases such as multiple myeloma and B-cell malignancies [18]
- Acetylated HIF-1α is degraded and can no longer act as a tumor growth factor. Class II DAC inhibitors target histone deacetylase (HDAC or DAC) 6, resulting in increased acetylation of HIF-1α and decreased vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis [19].
- Both acetylation and ubiquitylation often occur on the same lysine residue, but these processes cannot occur simultaneously. Acetylation allows for increased stability, and ubiquitylation leads to protein degradation. Therefore, DACs decrease the half-life of a protein by exposing the lysine residue for ubiquitylation [20].

1.2.2 Panobinostat (LBH589)

Panobinostat (LBH589) is a deacetylase inhibitor (DACi) belonging to a structurally novel cinnamic hydroxamic acid class of compounds. It is a potent class I/II pan-DAC inhibitor (pan-DACi) that has shown anti-tumor activity in pre-clinical models and cancer patients. Deacetylases (DAC) target lysine groups on chromatin and transcription factors and various non-histone proteins such as p53, tubulin, HSP90 and Rb. Panobinostat is formulated as an oral capsule and a solution for intravenous (i.v.) injection. Both the oral and i.v. formulations are currently being investigated in ongoing Phase I and Phase II studies in advanced solid tumors and hematological malignancies.

Inhibition of DAC provides a novel approach for cancer treatment. Histones are part of the core proteins of nucleosomes, and acetylation and deacetylation of these proteins play a role in the regulation of gene expression. Highly charged deacetylated histones bind tightly to the phosphate backbone of DNA, inhibiting transcription, presumably, by limiting access of transcription factors and RNA polymerases to DNA. Acetylation neutralizes the charge of histones and generates a more open DNA conformation. This conformation allows transcription factors and associated transcription apparatus access to the DNA, promoting expression of the corresponding genes. The opposing activities of two groups of enzymes, histone acetyltransferase (HAT) and DAC control the amount of acetylation. In normal cells a balance exists between HAT and DAC activity that leads to cell specific patterns of gene expression. Perturbation of the balance produces changes in gene expression.

Several lines of evidence suggest that aberrant recruitment of DAC and the resulting modification of chromatin structure may play a role in changing the gene expression seen in transformed cells. For example, silencing of tumor suppressor genes at the level of chromatin is common in human tumors [21-28] and DAC complexes have been shown to be crucial to the activity of the AML-specific fusion proteins PLZF-RAR-α, PML-RAR-α, and AML1/ETO [29-32]. DAC inhibitors (DACi) have been shown to induce differentiation, cell cycle arrest or apoptosis in cultured tumor cells, and to inhibit the growth of tumors in animal models [33-39]. In addition, DACi have been shown to induce expression of p21, a key mediator of cell cycle arrest in G1 phase and cellular differentiation [40-43].

Tumor growth inhibition and apoptosis in response to DACi treatment may also be mediated through changes in acetylation of non-histone proteins (e.g., HSP90, p53, HIF-1α, α-tubulin). For example, the chaperone protein HSP90 has been shown to be acetylated in cells treated with DACi [44-46]. Acetylation of HSP90 inhibits its ability to bind newly synthesized client proteins, thus preventing proper client protein folding and function. In the absence of HSP90 function, misfolded proteins are targeted for degradation in the proteasome. Many proteins that require HSP90 association are critical to cancer cell growth, including ErbB1, ErbB2, AKT, Raf, KDR, and BCR-ABL. Acetylation of HSP90 in cells treated with DACi inhibits the chaperone function of HSP90, leading to degradation of the client proteins and eventual cell death.

The potential clinical utility of the use of DACi in cancer therapy was first suggested by the activity of the DACi, sodium phenylbutyrate, against acute promyelocytic leukemia (APL). An adolescent female patient with relapsed APL, who no longer responded to all trans-retinoic acid (ATRA) alone, achieved a complete clinical remission after treatment with a combination of ATRA and the DACi sodium phenylbutyrate [47].

1.2.3 Overview of clinical experience

In clinical studies, both oral and i.v. formulations of panobinostat are being explored for further development. As of 31st December 2009, twenty-six clinical studies, including clinical pharmacology (CP), phase I and phase II trials, as well as one recently started randomized phase III study, have either been completed or are ongoing. In Table 5-1, "completed" studies are studies that have achieved final data base lock; all other studies are identified as "ongoing". A total of 1116 patients were enrolled (248 for i.v. and 868 for oral), received at least one dose of panobinostat, and for whom safety data are available. These patients constitute the safety population.

The most common AEs, regardless of their study drug relationship, concern the gastrointestinal tract (nausea, diarrhea and vomiting mostly of grade 1/2). For the hematopoietic system, the most frequent findings continue to be thrombocytopenia, anemia and neutropenia, mostly of grade 3/4, while febrile neutropenia, as expected, has been noted much more frequently in patients being treated for hematologic malignancies involving the bone marrow. Additional common toxicities include fatigue Grade 3/4 reported with a frequency of 9.2% in an every week (QW) dosing schedule vs 15.7% in an every other week (QOW) dosing schedule.

The most common ECG findings adjudicated by central review included post-baseline increase in frequency of sinus tachycardia, T-waves changes (flat, biphasic, inverted), as well as depressed ST segment findings.

The most frequently encountered laboratory abnormalities in both QW and QOW schedules and regardless of disease, refer to hematological parameters, including decreased WBC, platelet and neutrophil count and hemoglobin. Worsening of these hematologic parameters was more evident for the QW schedule and appears to be dose-dependent. Liver function tests alterations were mostly of grade 1/2 with either schedule, with grade 3 reported at the highest dose of 60 mg TIW QW. Decreasing electrolytes and elevated glucose was mostly grade 1/2 worsening from baseline, but again increased severity (up to grade 3) was seen at the highest dose of 60 mg with the QW schedule.

Thyroid function, as monitored by the measurement of TSH and free T4, did not reveal overt hyper- or hypo- thyroidism, with fluctuations in TSH values being within normal limits.

As the number of patients is quite different across doses, the following rules have been applied to report these events in the tables below: in doses where the number (n) of patients is ≥25 patients, AEs reported in ≥10% of patients are listed; in doses where n is <25 patients, AEs reported in ≥50% of patients are listed. If an AE frequency matches the criteria in one dose category, the frequency of that event is shown for all doses. Since the dosing in this study will follow the three-times-per-week schedule, Table 1-1 below, provides a summary of adverse events that occurred in >15% of the patients at any dose.

Table 1-1All grade adverse events regardless of causality in patients receiving oral panobinostat three-times-a-week every-week (TIW QW)

Primary System Organ Class Preferred term	**20 mg[a] N = 293** **n (%)**	**30 mg[a] N = 22** **n (%)**	**40 mg[a] N = 163** **n (%)**	**60 mg[a] N = 54** **n (%)**
Any primary system organ class	**291(100.0)**	**22(100.0)**	**152(93.3)**	**54(100.0)**
Blood and lymphatic system disorders	**181(61.8)**	**17(77.3)**	**131(80.4)**	**49(90.7)**
Anemia	60(20.5)	9(40.9)	51(31.3)	24(44.4)
Neutropenia	52(17.7)	4(18.2)	38(23.3)	21(38.9)
Thrombocytopenia	122(42.1)	13(59.1)	123(75.5)	31(57.4)
Gastrointestinal Disorders	**232(79.2)**	**21(95.5)**	**137(84.0)**	**53(98.1)**
Abdominal pain	29(9.9)	2(9.1)	23(14.1)	17(31.5)
Constipation	42(14.3)	2(9.1)	27(16.6)	13(24.1)
Diarrhea	150(51.2)	15(68.2)	94(57.7)	42(77.8)
Nausea	132(45.1)	11(50.0)	90(55.2)	34(63.0)
Vomiting	64(21.8)	6(27.3)	62(38.0)	24(44.4)
General Disorders and Site Conditions	**219(74.7)**	**17(77.3)**	**112(68.7)**	**49(90.7)**
Asthenia	50(17.1)	2(9.1)	26(16.0)	11(20.4)
Fatigue	118(40.3)	12(54.5)	66(40.5)	37(68.5)
Edema peripheral	57(19.5)	6(27.3)	24(14.7)	17(31.5)
Pyrexia	59(20.1)	8(36.4)	4(25.2)	20(37.0)
Investigations	**133(45.4)**	**10(45.5)**	**52(31.9)**	**36(66.7)**
Blood creatinine increased	35(11.9)	1(4.5)	9(5.5)	11(20.4)
Weight decreased	42(14.3)	6(27.3)	20(12.3)	17(31.5)
Metabolism and nutrition disorders	**167(57.0)**	**13(59.1)**	**74(45.4)**	**48(88.9)**
Anorexia	45(15.4)	10(45.5)	16(9.8)	24(44.4)
Decreased appetite	43(14.7)	1(4.5)	35(21.5)	12(22.2)

Primary System Organ Class Preferred term	20 mg[a] N = 293 n (%)	30 mg[a] N = 22 n (%)	40 mg[a] N = 163 n (%)	60 mg[a] N = 54 n (%)
Hypokalaemia	31(10.6)	6(27.3)	22(13.5)	24(44.4)
Musculoskeletal and connective tissue disorders	**107(36.5)**	**10(45.5)**	**59(36.2)**	**23(42.6)**
Back Pain	33(11.3)	3(13.6)	14(8.6)	9(16.7)
Nervous system disorders	**142(48.5)**	**13(59.1)**	**70(42.9)**	**36(66.7)**
Dizziness	39(13.3)	3(13.6)	11(6.7)	8(14.8)
Dysgeusia	42(14.3)	6(27.3)	21(12.9)	18(33.3)
Headache	46(15.7)	5(22.7)	27(16.6)	12(22.2)
Respiratory, thoracic and mediastinal disorders	**111(37.9)**	**10(45.5)**	**72(44.2)**	**32(59.3)**
Cough	30(10.2)	5(22.7)	29(17.8)	14(25.9)
Dyspnea	43(14.7)	5(22.7)	23(14.1)	13(24.1)
Skin and subcutaneous tissue disorders	**142(48.5)**	**8(36.4)**	**54(33.1)**	**26(48.1)**
Pruritus	54(18.4)	0(0.0)	13(8.0)	3(5.6)

[a.] Includes patients from [B1101], [B2101], [B2102] Group X and Y, [B2201], [B2202], [B2203], [B2211], [B2212], [E2214]; events occurring in ≥10% of patients A patient with multiple occurrences of an AE in one SOC is counted only once in the AE category

As shown on the above table 1-1, AEs have been reported for 519 patients (97.6% of the safety population) for the QW schedule. The most commonly reported AEs across doses were diarrhea in 301 patients (56.6%), thrombocytopenia in 289 patients (54.3%), nausea in 267 patients (50.2%) and fatigue in 233 patients (43.8%).

Table 1-2All grade adverse events regardless of causality in patients receiving oral panobinostat three-times-a-week every-other-week (TIW QOW)

Primary System Organ Class Preferred term	30 mg[a] N = 28 n (%)	45 mg[a] N = 18 n (%)	60 mg[a] N = 24 n (%)
Any primary system organ class	**28(100.0)**	**18(100.0)**	**24(100.0)**
Blood and lymphatic system disorders	**16(57.1)**	**14(77.8)**	**21(87.5)**
Anemia	5(17.9)	6(33.3)	11(45.8)

Primary System Organ Class Preferred term	30 mg[a] N = 28 n (%)	45 mg[a] N = 18 n (%)	60 mg[a] N = 24 n (%)
Neutropenia	3(10.7)	5(27.8)	10(41.7)
Thrombocytopenia	10(35.7)	10(55.6)	14(58.3)
Gastrointestinal Disorders	**25(89.3)**	**17(94.4)**	**24(100.0)**
Constipation	6(21.4)	3(16.7)	10(41.7)
Diarrhea	15(53.6)	11(61.1)	16(66.7)
Nausea	17(60.7)	9(50.0)	19(79.2)
Vomiting	12(42.9)	6(33.3)	12(50.0)
General Disorders and Site Conditions	**27(96.4)**	**17(94.4)**	**23(95.8)**
Asthenia	5(17.9)	5(27.8)	4(16.7)
Fatigue	18(64.3)	12(66.7)	15(62.5)
Edema peripheral	6(21.4)	5(27.8)	4(16.7)
Pyrexia	11(39.3)	9(50.0)	10(41.7)
Investigations	**14(50.0)**	**8(44.4)**	**11(45.8)**
Weight decreased	10(35.7)	5(27.8)	3(12.5)
Metabolism and nutrition disorders	**22(78.6)**	**9(50.0)**	**18(75.0)**
Anorexia	17(60.7)	6(33.3)	10(41.7)
Hypokalaemia	4(14.3)	3(16.7)	6(25.0)
Musculoskeletal and connective tissue disorders	**16(57.1)**	**7(38.9)**	**13(54.2)**
Arthralgia	3(10.7)	0(0.0)	6(25.0)
Back Pain	3(10.7)	4(22.2)	3(12.5)
Pain in extremity	3(10.7)	2(11.1)	3(12.5)
Nervous system disorders	**17(60.7)**	**6(33.3)**	**14(58.3)**
Headache	7(25.0)	3(16.7)	6(25.0)
Respiratory, thoracic and mediastinal disorders	**15(53.6)**	**8(44.4)**	**17(70.8)**
Cough	5(17.9)	4(22.2)	7(29.2)
Dyspnea	9(32.1)	6(33.3)	6(25.0)

Primary System Organ Class Preferred term	30 mg[a] N = 28 n (%)	45 mg[a] N = 18 n (%)	60 mg[a] N = 24 n (%)
Skin and subcutaneous tissue disorders	**12(42.9)**	**5(27.8)**	**9(37.5)**
Pruritus	5(17.9)	1(5.6)	3(12.5)
Rash	3(10.7)	1(5.6)	4(16.7)

[a.] Includes patients from [B1101], [B2101], [B2102] (Group X and Y), [B2201], [B2202], [B2203], [B2211], [B2212], [E2214]; events occurring in ≥10% of patients A patient with multiple occurrences of an AE in one SOC is counted only once in the AE category

As shown on the above Table 1-2, AEs have been reported for 70 patients (100% of the safety population) for the QOW schedule. The most commonly reported AEs across doses were fatigue and nausea in 45 patients each (64.3% each), diarrhea in 42 patients (60%), thrombocytopenia in 34 patients (48.6%) and anorexia in 33 patients (47.1%).

Of note, the safety profile appears to be qualitatively similar between the two schedules. At present, a quantitative comparison is limited by the significantly different number of patients available in both safety populations.

1.2.4 Human pharmacokinetics

After oral administration, panobinostat is rapidly absorbed with no observed lag phase. Maximum plasma concentrations were generally reached within 1 hour after oral dosing. The absolute bioavailability was 30% (data on file) and the mean (SD) half-life of panobinostat was comparable following i.v. and oral dosing ~15.0 (5) hours. Moderate drug accumulation was observed with oral three-times-a-week schedule but not with the weekly i.v. schedule (1.4-fold drug accumulation with oral three-times-a-week dosing), consistent with the terminal half-life of 15 hours and dosing interval.

Figure 1-1 Mean panobinostat plasma concentration versus time profiles following single oral or intravenous administration

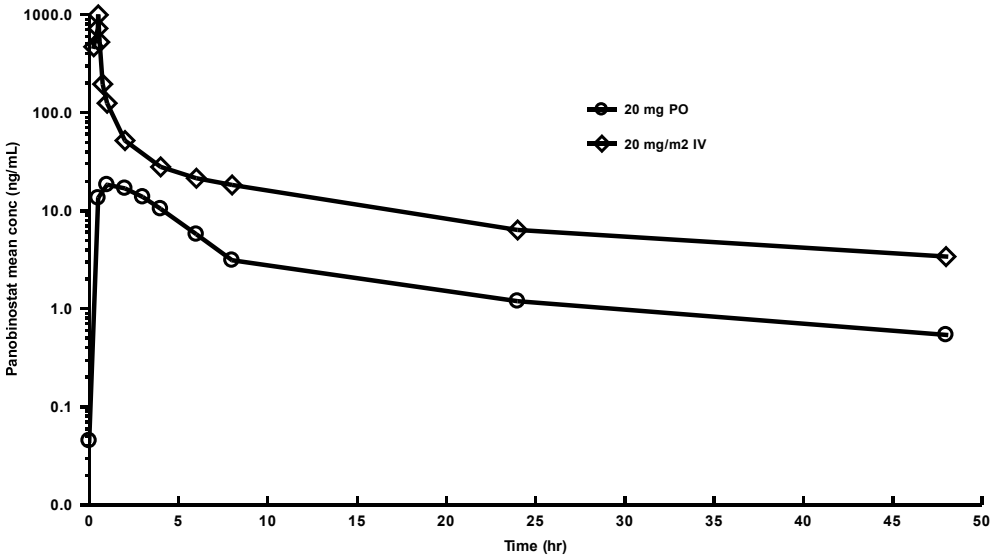


Table 1-3Pharmacokinetic parameters of panobinostat in three ongoing Phase I studies [CLBH589A2101], [CLBH589B2101], and [CLBH589B2102]

Route of administration & Dose (No. of patients following single dose)	Mean (CV%) Single dose C_{max}(ng/mL)	Mean (CV%) Single dose $AUC_{0\text{-}inf}$ (ng*hr/mL)	Mean (CV%) Multiple dose $AUC_{0\text{-}48}$ (ng*hr/mL)
i.v. 20 mg/m^2 (n=31)	**784 (45)**	**1041 (38)**	**n/a**
p.o. 20 mg (n=45)	**22.8 (58)**	**194 (58)**	**258 (65)**
p.o. 30 mg (n=49)	**36.2 (62)**	**267 (54)**	**279 (54)**
p.o. 40 mg (n=24)	**58.0 (59)**	**329 (77)**	**270 (59)**
p.o. 60 mg (n=57)	**66.1 (68)**	**362 (62)**	**306 (50)**
p.o. 80 mg (n=18)	**63.5 (58)**	**397 (49)**	**369 (52)**
n/a: not applicable with weekly i.v. administration			

In vitro experiments suggested that the hepatic oxidative metabolism of panobinostat is mediated primarily by cytochrome P450 (CYP)3A4, and to a lesser extent by CYP2D6 and CYP2C19. In addition to monooxygenation, hydrolysis of the hydroxamic sid chain (M43.5) were also found to be mediated (at least in-part) by the CYPs. These same metabolic pathways, were also observed in the recent human ADME and mass balance study [CLBH589B218].

Dose proportionality

A positive and linear dose-exposure relationship was found following single i.v. administration (1.2 to 20 mg/m^2, Rs = 0.83; p<0.0001). After oral dosing with 15 mg to 80 mg of panobinostat, dose-proportionality analysis indicated that systemic exposure increased nearly dose-proportionally at doses below 60 mg and there is less than proportional increase in AUC after 60 mg and 80 mg doses of panobinostat. It appears that absorption may become limiting at doses ≥ 60 mg of panobinostat.

Food Effect

Influence of food on panobinostat PK was evaluated in patients with advanced cancer who received 20 mg panobinostat twice a week and were randomized to receive panobinostat under fasting, high fat, and normal breakfast conditions [CLBH589B2111]. The overall exposure and inter-patient variability (CV 59%) in 34 patients remained unchanged with or without food, whereas C_{max} was transiently reduced by <45% and T_{max} prolonged by food (i.e., both normal and high fat breakfast). Since food did not alter the overall extent of absorption, food is unlikely to significantly impact panobinostat's systemic exposure in cancer patients. The findings from this formal food effect are consistent with the results from an earlier pilot food effect [CLBH589B2101] arm 1. Therefore, panobinostat can be administered without regard to food in future studies.

1.2.5 Cardiac Safety

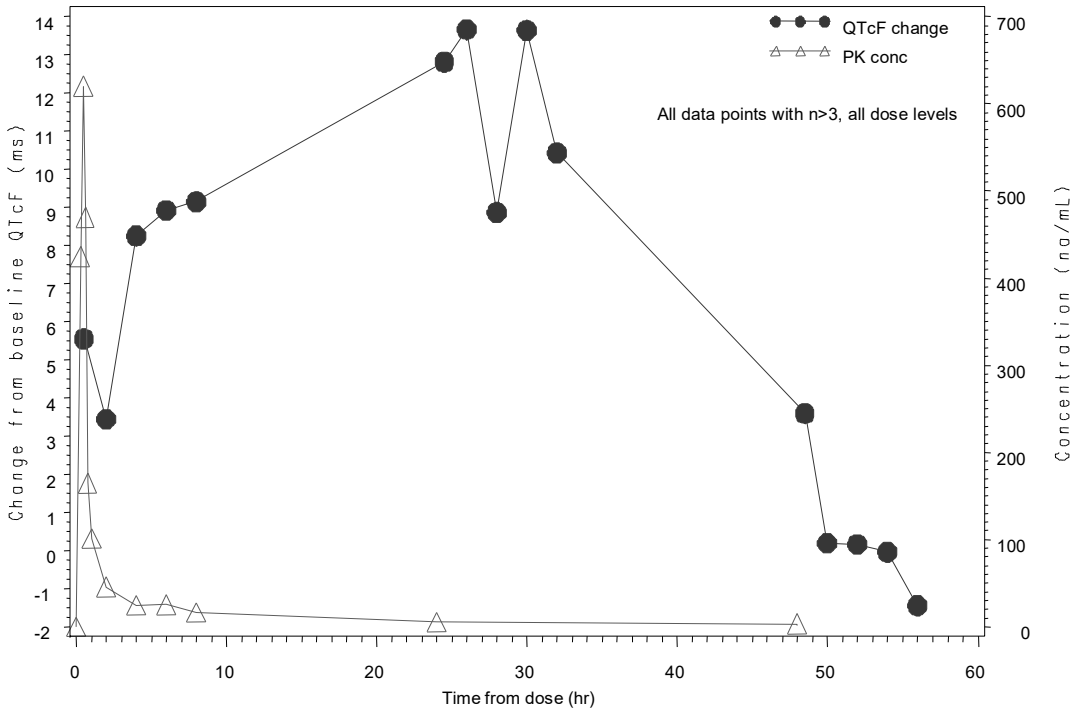
As of 31 December 2009, cardiac safety data were available for 532 patients in the TIW QW dose schedule and 70 patients in the TIW QOW dose schedule. All of these patients underwent intensive pre- and post-dose ECG recording to monitor the occurrence of QTcF changes as well as to capture other ECG abnormalities. There are mounting evidences that the most common finding is a QTcF increase of ≤60 msec (CTCAE grade 1) from baseline in both schedules. The absolute maximal QTcF values remain limited to ≤480 msec (grade 1/2). Higher absolute values are infrequent. Of note a QTcF increase >480 msec has been mostly observed at the highest oral dose of 60 mg given TIW QW. There were no cases of torsade de pointes with either schedule for oral panobinostat.

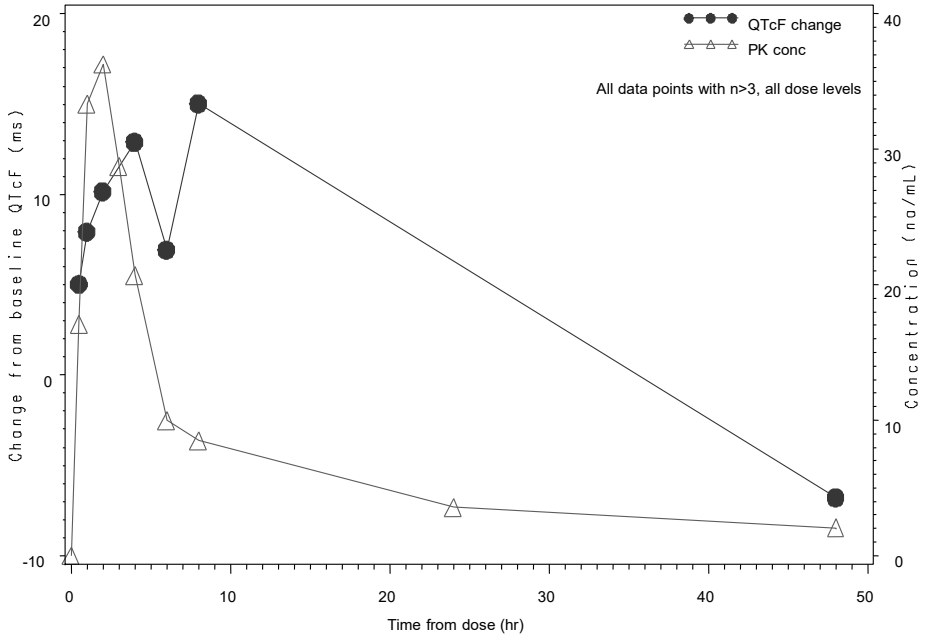
1.2.5.1 Relationship between panobinostat plasma concentrations and QTcF

As presented in Figure 1-2 (i.v.) and Figure 1-3 (po) below, the maximum change of QTcF from baseline does not coincide with the peak plasma concentration-time course of panobinostat for either route of administrations suggesting a possible delayed effect.

It is noteworthy (as shown in Table 1-3) that the mean maximum concentration (C_{max}) and overall exposure (AUC) for the oral formulation is at least 30-fold and 5-fold, respectively lower than that has been seen with intravenous panobinostat. It does not appear that QTcF change is directly related to panobinostat plasma concentrations.

Figure 1-2 QTcF change from baseline over time vs. panobinostat conc-time course following the first intravenous panobinostat weekly doses





1.3 Overview of MLN9708 (Ixazomib)

1.3.1 Scientific Background

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 [48]. In an effort to broaden activity against a wider range of tumor types and increase activity in tumor types where VELCADE has shown activity, Millennium has developed the proteasome inhibitor, MLN9708, formulated for both intravenous (IV) and oral (PO) administration.

1.3.2 Nonclinical Pharmacology

MLN2238 refers to the biologically active, boronic acid form of the drug substance, MLN9708. 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. All doses and concentrations are expressed as the boronic acid, MLN2238.

1.3.2.1 In Vitro Pharmacology

MLN2238 inhibits β5 site 20S proteasome activity in vitro, with a half-maximal inhibitory concentration (IC50) of 3.4 nM. Potency is reduced roughly 10-fold versus β1 (IC50 = 31 nM) and 1,000-fold versus β2 (IC50 = 3500 nM). MLN2238 was also tested for inhibition against a panel of 103 kinases, 18 receptors (neurotransmitter, ion channel, brain and gut receptors), and 9 serine proteases. In all cases, the IC50 values were > 10 μM. Proteasome inhibition results in the accumulation of poly-ubiquitinated substrates within the cell and leads to cell cycle disruption, with concomitant activation of apoptotic pathways and cell death. Consistent with inhibition of β5 20S proteasome activity, MLN2238 demonstrated potent activity against cultured MDA-MB-231 human breast cancer cells in the WST cell viability assay.

1.3.2.2 In Vivo Pharmacology

To determine the activity of MLN2238 in vivo, pharmacodynamic studies were performed in immunocompromised mice bearing either CWR22 human prostate or WSU-DLCL2 (human diffuse large B-cell lymphoma [DLBCL]) tumors. Xenograft tumor pharmacodynamic responses were analyzed by assessing 20S proteasome inhibition and by evaluating levels of the protein markers growth arrest and deoxyribonucleic acid (DNA) damage-inducible protein 34 (GADD34) and activating transcription factor-3 (ATF-3). Increased expression of GADD34 and ATF-3 is indicative of a downstream biological response to proteasome inhibition. After a single dose of MLN2238, a clear dose response was observed in CWR22 xenografts as seen in both tumor 20S proteasome inhibition and in changes in GADD34 and ATF-3 expression. In WSU-DLCL2 xenografts, greater tumor proteasome inhibition and greater elevation of

GADD34 and ATF-3 were observed with MLN2238 compared to bortezomib. Additionally, MLN2238 demonstrated proteasome inhibition in blood, liver, and tumor tissue after a single IV dose of 5, 10, or 14 mg/kg or a single PO dose of 8 or 11 mg/kg to female PHTX-24C (primary colon cancer) tumorbearing NCR nude mice. MLN2238 demonstrated strong antitumor activity in xenograft models derived from human cancer cell lines or primary human tumors. Antitumor activity was demonstrated with subcutaneous (SC) xenografts of CWR22 prostate, LXFE 409 epidermoid lung carcinoma, and 2 lymphoma models (WSU-DLCL2 and PHTX-22L). MLN2238 also showed antitumor activity in a disseminated model of lymphoma (OCI-Ly7-7D1-luc cells inoculated intravenously) and in an intraosseous model using MDA-MB-231 human breast adenocarcinoma cells. In addition, MLN2238 demonstrated antitumor activity in mouse models of plasma cell malignancy (PCM): the iMyc$^{C\alpha}$/Bcl-XL genetically-engineered mouse [GEM] model of de novo PCM and disseminated and intraosseous models of PCM generated by IV and intratibial inoculation of the DP54-Luc iMyc$^{C\alpha}$/Bcl-XL mouse cell line. In the CWR22 xenograft model, significant antitumor activity was seen with both PO and IV dosing, demonstrating that this molecule has antitumor activity when administered via different dosing routes. MLN2238 demonstrated stronger antitumor activity than did bortezomib in the 3 lymphoma models, the lung carcinoma model, and the breast cancer model, and similar antitumor activity to bortezomib in the CWR22 model and the PCM models. In summary, MLN2238 is Millennium's next generation dipeptide boronic acid proteasome inhibitor that potently, reversibly, and selectively inhibits the proteasome. There are several features of MLN2238 demonstrated in mouse xenograft models, such as sustained pharmacodynamic effects and activity in xenograft models that do not respond to bortezomib, that suggest that the biodistribution and activity that of MLN2238 may extend beyond that of VELCADE.

1.3.3 Nonclinical Pharmacokinetics

The pharmacokinetic (PK) properties of MLN2238 were studied in severe combined immunodeficient (SCID) mice bearing human CWR22 tumor xenografts, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Because of the extensive red blood cell (RBC) partitioning of MLN2238, both blood and plasma PK parameters were determined in these studies. MLN2238 had a very low blood clearance (CL) and a moderate blood volume of distribution at steady-state (V_{ss}) after IV administration. The concentration-versus-time curve of MLN2238 displayed a distinct bi-exponential profile, with a steep initial distribution phase and a long terminal $t_{1/2}$ (>24 hr) in all species tested. MLN2238 had higher plasma CL and larger plasma V_{ss} than in blood, largely because of the extensive RBC partitioning. The PK properties of MLN2238 after oral administration were studied in rats and dogs. The plasma oral bioavailability (F) was 41% in rats and nearly 100% in dogs. A clinical prototype formulation of the MLN9708 capsule demonstrated that MLN2238 had excellent oral F and an excellent absorption profile in dogs. In addition, interindividual variability, as measured by %CV, in C_{max} and $AUC_{0\text{-}24hr}$ after oral administration was low to moderate, similar to that after IV administration. The terminal $t_{1/2}$ after oral administration was also similar to that after IV administration. Metabolism appears to be a major route of elimination for MLN2238, and urinary excretion of the parent drug was negligible (< 5% of dose). In vitro in liver microsomes, the metabolism of MLN2238 was high in mice and low to moderate in all other species studied. MLN2238 is metabolized by multiple cytochrome P450 (CYP) isozymes and non-CYP

enzymes and proteins. The rank order of relative biotransformation activity of each of the 5 major human CYP isozymes in the in vivo studies was 3A4/5 (34.2%) >1A2 (30.7%) >2D6 (14.7%) >2C9 (12.1%) >2C19 (negligible). In SD rats, after a single IV dose of [^{14}C]MLN9708, the blood exposure to MLN2238 was the same as that of total radioactivity in the blood, indicating that MLN9708 was completely converted to MLN2238 in vivo and the metabolism of MLN2238 was extremely slow. MLN2238 is neither an inhibitor of CYP isozymes 1A2, 2C9, 2C19, 2D6, and 3A4/5 (IC_{50} >30 μM, with an estimated inhibition dissociation constant [K_i] >15 μM), nor a time dependent inhibitor of CYP3A4/5 (up to 30 μM). 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 CYP3A4/5 or CYP1A2 inhibitor or a strong CYP3A4/5 inducer because of the possible contribution of CYP3A4/5- and CYP1A2-mediated metabolism to the elimination of MLN9708 in humans. Clinical evaluation with CYP3A4/5 as a strong inhibitor or inducer is planned.

1.3.4 Safety Pharmacology

Evaluation of the effect of MLN9708 on cardiovascular (CV), respiratory, and central nervous system (CNS) function was conducted as part of the Good Laboratory Practice (GLP)-compliant repeat-dose toxicology studies. In exploratory safety pharmacology studies, MLN2238 was a weak inhibitor of the cloned cardiac potassium (K+) human ether à-go-go□related gene (hERG) channel in vitro, with an IC50 of 59.6 μM, which exceeds, by approximately 200-fold, the plasma Cmax (111 ng/mL [0.3 μM]) predicted to occur in humans at the optimally efficacious dose after IV administration. In the GLP-compliant, 1-cycle PO toxicology study in beagle dogs, an increase in QTc was seen in male dogs at nontolerated doses, and a potential increase in QTc was seen in male dogs at tolerated doses. However, increased QTc was not seen in female dogs at any dose, despite similar plasma Cmax values. Additionally, in GLP-compliant 2- and 5-cycle IV and 5-cycle PO toxicology studies in beagle dogs, there were no changes in electrocardiograms, heart rate, and waveform intervals (PR, QRS, QT, and QTcV), even though dogs in the IV studies had higher MLN2238 plasma Cmax values than in the 1-cycle PO study. In GLP-compliant PO and IV repeat-dose toxicology studies up to 5 cycles in duration, there were no MLN9708-related effects on clinical signs or physical examination findings indicative of impaired respiratory or CNS function at tolerated doses. These data suggest that MLN2238 has a low potential for cardiovascular, CNS, or respiratory alterations.

1.3.5 In Vivo Toxicology

1.4.1.1 Oral Dosing

After PO administration of MLN2238, the exposures that were tolerated in rats were similar to those tolerated in dogs, indicating similar species sensitivity. Additionally, PO administration for 5 cycles to rats and dogs resulted in higher plasma exposures of MLN2238 on Day 94 than on Day 0, indicating accumulation of MLN2238. Dose-limiting toxicity (DLT) in the GLP-compliant PO toxicology studies up to 5 cycles in duration in rats and dogs was primarily due to effects in the gastrointestinal (GI) and lymphoid systems. Additionally, at doses below those associated with DLT, alterations in leukocyte and coagulation parameters consistent with an

inflammatory response were seen in both rats and dogs, and neuronal degeneration of the sympathetic, dorsal root, and end organ ganglia was seen mainly in dogs (possibly due to higher exposures). All of the effects seen in the GLP-compliant PO toxicology studies in both rats and dogs at tolerated doses were reversible/reversing and can be monitored in the clinic with routine clinical observations (GI disturbances and opportunistic infections secondary to lymphoid depletion), clinical pathology assessments (inhibition of erythropoiesis, thrombocytopenia, and inflammatory leukogram), and neurologic assessment, as are commonly done for patients treated with bortezomib. MLN9708 did not cause significant toxicities that have not been previously observed after dosing with bortezomib,[11] and the neurologic lesions in these studies are similar to what has been described after treatment with bortezomib and are believed to be the cause of the peripheral neuropathy observed in patients treated with bortezomib.

1.4.1.2 Intravenous Dosing

After IV administration of MLN2238, the exposures that were tolerated in rats were similar to those tolerated in dogs, indicating similar species sensitivity. In GLP-compliant IV toxicology studies, the target tissues for dogs and rats were similar and consisted of the bone marrow, peripheral ganglia, intestines, and lymphoid tissues. In addition, kidneys, adrenal and lacrimal glands (rats) and perianal glands (dogs) were also identified as target organs in the 5-cycle studies. The effects seen with the IV studies were largely consistent with the toxicologic effects seen with PO dosing; however, the greater severity/frequency or additional target organs seen with IV dosing were likely a result of the higher exposures relative to PO dosing. DLT was primarily due to GI and lymphoid depletion effects in both rats and dogs, although some of the microscopic features in those organs differed between the species. All of the effects seen in the GLP-compliant IV toxicology studies in both rats and dogs at tolerated doses were reversible/reversing and can be monitored in the clinic. Additionally, these effects were consistent with the toxicities associated with and described after treatment with bortezomib [11].

1.4.2 Genotoxicity

MLN2238 was not mutagenic in a GLP-compliant bacterial reverse mutation assay (Ames assay).

1.3.6 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 a different yet related plasma

cell dyscrasia, systemic light chain (AL) 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 ClinicalTrials.gov and the MLN9708 IB.

1.3.7 Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to 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.[1] 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 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. See the IB for information on the PK for IV doses of MLN9708.

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.

1.3.8 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 1-4 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 the 4 ongoing 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 (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-5 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=146 n (%)
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 102 (70)	Nausea 68 (47); Diarrhoea 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); Anaemia 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 1-6 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) Diarrhoea 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); Anaemia 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)

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.

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 [3], non-Hodgkin's disease, Hodgkin's disease [4], relapsed and/or refractory multiple myeloma [RRMM; 5; 6], relapsed or refractory systemic light chain amyloidosis [RRAL; 7], and newly diagnosed multiple myeloma [NDMM; 8; 9; 10]) 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.

1.3.9 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.[11,12]

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 1-7 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 notrelated 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.[13]

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 1-8 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.

1.3.10 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, diarrhoea, 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 1-9 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%) Diarrhoea (26%) Thrombocytopenia (23%) Upper respiratory tract infection (22%) Anaemia 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, localised infection, gastrointestinal haemorrhage, respiratory syncytial virus (RSV) pneumonia faecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral oedma, asthenia, hyponatraemia vomiting, diarrhoea, 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 haemorrhage, 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.

1.3.11 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).

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

1.3.12 Potential Risks of MLN9708

Safety information from toxicology studies as well as the preliminary safety information gained from clinical Studies C16001, C16002, C16003, C16004, C16005, C16006, C16007, C16008, and C16009 has been used to guide the safety evaluation of MLN9708. As of 30 April 2012, safety data is available for 382 patients who have received multiple cycles of therapy (between 1 and 28 cycles of MLN9708 therapy). Adverse events reported in MLN9708 clinical trials are generally consistent with the class-based effects of proteasome inhibition and are generally similar to what has been previously reported with VELCADE, though the severity of some, for example peripheral neuropathy, is less. While some of the potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed,

dose modification or discontinuation. Each protocol recommends that patients are monitored closely for the anticipated potential toxicities, as well as for any unanticipated toxicities when they receive MLN9708, and for at least 30 days after their last dose.

1.3.12.1 Potential Risks by System Organ Class Include:

- Blood and lymphatic system disorders: Neutropenia, anemia, lymphopenia. Reductions in blood counts may predispose patients to an increased susceptibility to infection (see Infections and infestations below) and anemia. Reticulocytopenia was described in animals and may be associated with anemia.
- Gastrointestinal disorders: Constipation, intestinal obstruction including ileus and intussusception (described in animal studies), abdominal pain.
- General disorders and administration site conditions: Pyrexia, chills, influenza like illness, edema peripheral.
- Infections and infestations: Pneumonia. Lymphopenia may be associated with increased risk of infection, including re-activation of herpes zoster.
- Investigations: Blood creatinine increased (see Renal and urinary disorders below).
- Metabolism and nutrition disorders: Decreased appetite, dehydration, electrolyte imbalance.
- Musculoskeletal and connective tissue disorders: Back pain, myalgia, arthralgia, bone pain, pain in extremity.
- Nervous system disorders: Headache, dizziness, neuropathy peripheral (includes pain, burning sensation, and numbness), and syncope. In addition, autonomic and motor neuropathy may be observed, as both have been reported for VELCADE, another proteasome inhibitor. Posterior reversible encephalopathy syndrome (PRES) has been reported with MLN9708 (this event was reported after the data cut-off date, 30 April 2012). PRES has also been reported for VELCADE (refer to VELCADE for Injection Package Insert).
- Renal and urinary disorders: Renal impairment, renal failures, and renal failure acute have been reported in association with dehydration due to nausea, vomiting, anorexia, and/or diarrhea, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and/or disease progression. In some situations, this has been severe, requiring temporary dialysis.
- Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, upper respiratory tract infection, pneumonitis.
- Skin and subcutaneous tissue disorders: A rare risk is Stevens-Johnson Syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Stevens-Johnson syndrome has also been reported for VELCADE (refer to VELCADE for Injection Package Insert). It is also reported as risk with lenalidomide, an agent used in the treatment of hematologic malignancies including in combination with proteasome

inhibitors. For more information about this risk with lenalidomide refer to the Revlimid (lenalidomide) Package Insert.

- Vascular disorders: Hypotension, orthostatic hypotension.

Other: Acute phase response that may result in fever and metabolic changes (observed only in nonclinical studies). Infrequent incidences of tumor lysis syndrome have also been reported. Supplemental information is provided in the current edition of the IB.

2 Study rationale/purpose

Multiple myeloma refractory to bortezomib and refractory to, relapsed after, or ineligible for IMiDs constitutes an unmet medical need with EFS and OS of 5 and 9 months, respectively, and response and clinical benefit response rates of 24 and 34%, respectively [49]. A recently presented study suggests bortezomib refractoriness of multiple myeloma may be overcome by combination with panobinostat and dexamethasone. Enrolled patients were refractory to their last bortezomib containing regimen and achieved a remarkable response rate of 35% and clinical benefit response rate of 53% [7]. The oral proteasome inhibitor MLN9708 (ixazomib) appears to not only be more convenient than bortezomib but also safer; with an otherwise comparable safety profile it has not caused any severe neuropathy at doses that had single agent activity in relapsed and refractory multiple myeloma when used in a twice a week dosing schedule [10] or administered weekly [9]. The MTD for MLN9708 (ixazomib), when given twice a week (day 1,4,8,11 every 21 days) to patients with relapsed or refractory multiple myeloma was established at 2mg/m2, whereas weekly administration (day 1,8,15 every 28 days) was tolerated at higher doses (MTD 2.97mg/m2) in a comparable patient population [9,10]. Another study used MLN9708 (ixazomib) in a weekly administration schedule (day 1,8,15 every 28 days) in combination with lenalidomide (25mg day 1-21 every 28 days) and dexamethasone (40mg once a week) in newly diagnosed multiple myeloma [8]. This study also found the MTD of MLN9708 (ixazomib) to be at 2.97mg/m2 but recommended 2.23mg/m2 for phase 2 evaluation because of improved tolerance. The most common possibly MLN9708 (ixazomib) related adverse events in these studies were thrombocytopenia, neutropenia, fatigue, and gastrointestinal adverse events including nausea and diarrhea. Gupta et al. analyzed pharmacokinetic data of the active metabolite of MLN9708 (ixazomib) from 4 trials that used either IV or PO dosing. Using a non-linear mixed effects modeling approach he found that body size affected only volume of distribution but not maximal or AUC concentrations [11]. A decision was therefore made by the manufacturer Millennium to use flat dosing in future trials, using 2.3mg, 3mg, and 4mg tablets.
Here we aim to develop an “all oral” regimen of proteasome and histone deacetylase inhibition in combination with dexamethasone for future phase 2 study and as a platform for addition of further drugs.

Phase II extension: Patients in phase I (median age 65, range 50-73, median previous regimens 5, range 2-10) tolerated treatment without DLT and without non-hematologic severe (grade 3 or higher) adverse event according to CTCAE vs.4.03. Three patients developed grade 3 hematologic toxicities (2 neutropenia, 1 thrombocytopenia). Worst diarrhea was grade 1 (n=6), worst nausea grade 2 (n=1) and 4 additional patients developed transient grade 1 nausea. Other possibly panobinostat or ixazomib related grade 1/2 adverse events included thrombocytopenia (n=5), neutropenia (n=3), fatigue (n=2), anemia (n=2), anorexia (n=1) and arthralgia (n=1).

Median QTcF before treatment start was 405 msec (range 378-430) and increased on average by 4.3% (maximally by 13%). One patient developed transient grade 1 QTcF prolongation to 552 msec. No other cardiac adverse events were observed. Of the 11 patients in phase I, one reached PR, two reached MR, and one had stable disease for 6 months. All patients entered the study with disease refractory to their last regimen, and in two of the responding patients (1PR, 1MR) this included a proteasome inhibitor an IMiD, and a glucocorticosteroid (carfilzomib, pomalidomide, dexamethasone in the MR patient, bortezomib, dexamethasone, lenalidomide in the MR patient). Overall, we are encouraged by activity in extensively pretreated patients and by excellent tolerance of this regimen so far. In phase II we aim to extend the study cohort by an additional 20 patients who will be treated until progression or other reasons for discontinuation arise (7.6.1) to strengthen the safety analysis and obtain a more reliable estimate of activity.

3 Study objectives

3.1 Primary Objective

- Define the tolerability and safety of MLN9708 (ixazomib) administered on a day 1,8,15 every 28 day schedule up to 4mg in combination with fixed doses of panobinostat and dexamethasone in patients with relapsed or refractory myeloma.

3.2 Secondary Objective

- Assess response and clinical benefit response rates according to international uniform response criteria and adapted EBMT criteria, respectively (see under 8.1)
- Assess progression-free survival (PFS) and overall survival (OS)

4 Study endpoints:

4.1 Primary endpoints:

- Dose limiting toxicity (phase I) and tolerance according to CTCAE vs. 4.03 (phase I and II)

4.2 Secondary endpoints:

- Response to panobinostat, dexamethasone, ixazomib (MLN9708) will be assessed according to international uniform response criteria and clinical benefit response according to modified EBMT response criteria, comparing myeloma panels obtained at the beginning of each cycle that include SPEP, 24 h UPEP, serum and urine IFEs, and serum free light chains to results at screening. In addition a baseline bone marrow exam and skeletal survey will be obtained and repeated as clinically indicated and for assessment of complete remission (bone marrow).
- Progression-free survival will be measured from study entry to progression or death of any cause, whichever comes first.

- Overall survival for all will be measured from study entry to death from any cause.

5 Overall study design, treatment cycles, and study duration

5.1 Study design and treatment cycles

Phase I: This study will use a modified 3 + 3 design to define the tolerability and safety of MLN9708 (ixazomib) administered to at least 6 patients with relapsed or refractory myeloma on a day 1,8,15 every 28 day schedule at up to 4mg in combination with fixed doses of panobinostat and dexamethasone.

Dose limiting toxicities (DLTs, see under 5.4) will be assessed at the end of the first cycle, on day 28. The trial will accrue up to three patients at any given DL who will need to be assessed for DLTs before the next three patients can be enrolled. Determination of the highest tolerated dose of two tested dose levels will require treatment of at least 6 patients at the respective dose level with no more than one patient developing a DLT.

The first three patients will be treated at DL1. If no patient develops any DLT, the next three patients will be enrolled at DL2. If 1 patient develops any DLT, three additional patients will be enrolled at DL1. If no more than 1 of 6 patients treated at DL1 develops a DLT, the next three patients will be enrolled at DL2. If 2 or more of 2-6 patients treated at DL1 develop DLTs further enrollment will be stopped and a change in the protocol will be discussed. If DL2 opens to enrollment, and 0-1 of the first three patients develop any DLT, additional three patients will be enrolled at DL2 and if no more than 1 of 6 patients treated at DL2 develop any DLT, DL2 will be considered a tolerated MLN9708 dose and further dose escalation will not be done. If 2 of three or up to 6 patients enrolled at DL2 develop any DLT, further enrollment at that dose level will be stopped and enrollment will continue at DL1 unless 6 patients have already been treated at that dose level. If no more than 1 patient treated at DL1 develops any DLT that dose level will be considered tolerated and an intermediate dose level may be discussed. If 2 or more of up to 6 patients treated at DL1 develop a DLT, further enrollment will be stopped and a change in the protocol will be discussed.

Phase II: Twenty additional patients will be treated at target doses of DL2 which has been found to be well tolerated without any DLT in phase I.

5.2 Study duration

Phase I: Patients will remain on study for six 28-day cycles or until criteria for discontinuation (7.6.1) are met, whichever comes earlier. Decisions on subsequent maintenance therapy will at the discretion of the treating physician. If the patient's myeloma is controlled in at least stable disease panobinostat may be continued free of charge to the patient. Follow up after completion of cycle 6 is at the discretion of the treating physician but if panobinostat is continued, monitoring for electrolyte abnormalities, especially potassium and magnesium, at a frequency appropriate for the respective patient, is recommended. This protocol may be amended to

include a formal maintenance phase and/or a phase II portion after review of safety and preliminary efficacy data.
Phase II: Patients will receive therapy according to DL2 and will remain on study until criteria for discontinuation (7.6.1) are met.

5.3 Dose levels

Dose levels are defined in table Table 5-1

Dose level	PO Panobinostat	PO MLN9708 (Ixazomib)	PO Dexamethasone
1	20mg d 1,3,5,15,17,19 q 28 d	3mg d1,8,15 q 28 d	20mg d 1,2,8,9,15,16 q 28 d
2	20mg d 1,3,5,15,17,19 q 28 d	4mg d1,8,15 q 28 d	20mg d 1,2,8,9,15,16 q 28 d

5.4 Dose limiting toxicity

Dose limiting toxicity (DLT) will be assessed during the first cycle and be defined as the following drug-related adverse events according to CTCAE version 4.03 (if an adverse event is attributed to progressive disease, it will not be counted as DLT):

- Grade 4 or higher neutropenia or thrombocytopenia that does not resolve to grade 3 or lower within 7 days after detection while MLN9708 (ixazomib) and panobinostat are held.
- Use of G-CSF or platelet transfusions in cycle one
- Neutropenic fever (with grade 3 or grade 4 neutropenia)
- QTcF increase to $\geq$ 480 msec that persists $\geq$ 7 days after withholding panobinostat and MLN9708
- Any grade 3 or higher non-hematologic adverse events except:
    - Nausea, vomiting, diarrhea, or electrolyte abnormalities that can be reduced to grade 2 with supportive measures within 7 days

Patients who cannot be assessed for DLT due to progressive disease or other reasons will be replaced. Patients who develop a DLT may remain on study.

6 Study population

Patients with relapsed or refractory myeloma after at least two previous regimens including a proteasome inhibitor and an IMiD™ seen at the Cleveland Clinic Taussig Cancer Center will be screened for enrollment. Approximately 700 patients with multiple myeloma are seen each year at this site and approximately 600 have relapsed or refractory myeloma. The study will be offered to our partner institution within the Case Comprehensive Cancer Center, the Seidman Cancer Center of University Hospitals and Case Western University, where approximately 100 patients with relapsed or refractory multiple myeloma are seen each year. Participation is expected and would not alter per patient costs. We have accrued 11 patients to phase I in about 12 months and expect to enroll to phase II at a faster pace since no interruptions for DLT assessments will be required. We anticipate it will take about 18 months to accrue additional 20 patients to phase II. .

6.1.1 Patient population

Eleven patients have been enrolled to phase I and an additional 20 patients are planned for phase two totaling 31 patients for the entire study.

6.1.2 Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion criteria

1. Male or female patients aged ≥ 18 years old
2. Ability to provide written informed consent obtained prior to participation in the study and any related procedures being performed
3. Patients must carry a diagnosis of symptomatic multiple myeloma according to international myeloma working group criteria [50] and have relapsed or refractory disease according to international uniform response criteria and must have previously received therapy with a proteasome inhibitor and an IMiD™ [51,52](see also 6.2).
4. Must have measurable disease defined as any of the following: Serum m-spike ≥ 1g/dL, 24 h urine m-spike of at least 200mg/d, involved serum free light chains ≥ 100mg/L with abnormal serum free light chain ratio, bone marrow plasma cells of at least 30%
5. ECOG PS ≤ 2
6. No gastro-intestinal condition, that in the opinion of the treating physician or the principal investigator significantly limits oral absorption
7. No serious uncontrolled coexisting medical condition

8. Patients must meet the following laboratory criteria:
    - ANC ≥ 1.0 x 10^9/L without use of pegfilgrastim in the preceding 21 days and without non-pegylated G-CSF or GM-CSF within 7 days prior to study entry
    - Hemoglobin ≥ 8 g/dl (may be after transfusion of packed red blood cells or use of erythropoiesis stimulating agents)
    - Platelets ≥ 70x 10^9/L without platelet transfusion 7 days prior to study entry
    - AST and ALT ≤ 2.5 x ULN
    - Serum bilirubin ≤ 1.5 x ULN
    - Serum potassium ≥ LLN and serum magnesium ≥ LLN (electrolyte levels may be achieved with repletion or other supportive medications like potassium sparing diuretics) Creatinine clearance ≥ 30 mL/min according to Cockroft-Gault formula (see Section 22)
    - Clinically euthyroid. Note: Patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism.
9. Baseline MUGA or ECHO must demonstrate LVEF ≥ 45%
10. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 7 days prior to start of study treatment
11. Male patients, even if surgically sterilized (i.e., status post vasectomy), have to either:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study treatment, OR
    - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
    - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.
12. Female patients have to fulfill one of the following:
    - Be postmenopausal for at least 1 year before the Screening visit, OR
    - Be surgically sterile, OR
    - If of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study treatment
    - Oral contraceptives are generally metabolized by CYP3A4. Since the induction potential of panobinostat to induce CYP3A4 is unknown, patients who are using oral contraceptives as a method of contraception, and are sexually active, should use another effective contraceptive method, AND Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR

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

13. At least 7 days must have passed since the last treatment with lenalidomide, pomalidomide, thalidomide, proteasome inhibitors, or low dose cyclophosphamide (up to 50mg daily), at least 21 days must have passed since the last treatment with daratumumab, elotuzumab, investigational therapy and most conventional chemotherapy including cyclophosphamide above 50mg per dose, bendamustine, doxorubicin, cisplatin, and etoposide; and at least 35 days since the last treatment with melphalan.

Exclusion criteria

1. Prior anti-cancer treatment with MLN9708 (ixazomib), HDAC, DAC, HSP90 inhibitors or valproic acid
2. Prior participation in a randomized controlled study that included MLN9708 (ixazomib) in one of the treatment arms independent of whether assigned to MLN9708 (ixazomib) or not
3. Patients who will need valproic acid for any medical condition during the study or within 5 days prior to first panobinostat treatment
4. Female patients who are lactating or have a positive serum pregnancy test during the screening period.
5. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
   - History or presence of sustained ventricular tachyarrhythmia. (Patients with a history of atrial arrhythmia are eligible)
   - Any history of ventricular fibrillation or torsade de pointes
   - Bradycardia defined as HR< 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.
   - Screening ECG with a QTcF > 470 msec (QTcF=QT/$\sqrt[3]{RR}$). If potassium or magnesium blood levels are below normal limits, consider repeating ECG after correction of these electrolytes.
   - Right bundle branch block + left anterior hemiblock (bifascicular block)
   - Patients with myocardial infarction or unstable angina ≤ 6 months prior to starting study drug
   - Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV , uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
6. Impairment of GI function or GI disease that may significantly alter the swallowing absorption of panobinostat and MLN9708

7. Patients with diarrhea > CTCAE (version 4.03) grade 2
8. Patient has ≥ Grade 3 peripheral neuropathy, or ≥ Grade 2 with pain on clinical examination during the screening period.
9. Patients with known metastasis of malignant plasma cells to the central nervous system (if not suspected no specific testing is required)
10. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes or active or uncontrolled infection) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol
11. Patients using medications that have a relative risk of prolonging the QT interval or inducing torsade de pointes if treatment cannot be discontinued or switched to a different medication prior to starting study drug. If an alternative medication that does not risk QT prolongation can safely be used in the opinion of the treating physician and the treatment is changed to that medication, the patient may be enrolled.
12. Patients who have not passed the nadir of bone marrow suppression from previous anti-myeloma therapy yet. If in doubt, serial CBCs with differential should be obtained.
13. The corticosteroids prednisone and dexamethasone may be continued until the day before treatment start if all related adverse events are controlled at CTCAE version.4.03 grade ≤ 1.
14. Patients who have received radiation therapy to more than half of the pelvis or more than half of the spine within ≤ 2 weeks prior to starting study treatment; or who have not yet recovered from side effects of such therapies.
15. Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy
16. Systemic treatment, within 14 days before study enrollment, 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.
17. Ongoing or active systemic infection, known human immunodeficiency virus (HIV) positive, known active hepatitis B virus hepatitis, or known active hepatitis C virus hepatitis.
18. Concurrent diagnosis of another malignancy if either systemic treatment or surgery is expected to be required within 2 years from study entry.
19. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
20. Patients with any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to him/her by the study staff.
21. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment unless the patient is felt to have fully recovered and any antibiotics that are continued are either beta lactam antibiotics or are specifically allowed on study according to 7.7.1

22. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 21 days of the start of this trial and throughout the duration of this trial.

6.2 Definition Relapsed Myeloma and Refractory Myeloma

An ASH/FDA panel has recommended to include clinical criteria to define relapsed myeloma and to separately analyze data for the relapsed as opposed to the refractory group of patients [52]. In accordance with this consensus statement, International Myeloma Working Group diagnostic criteria [50], and the international uniform response criteria [51] the following definitions will be used:

6.2.1 Refractory Myeloma

Biochemical or clinical evidence of loss of disease control within 60 days after the last therapy. Any of the following defines refractory myeloma:

1. Progressive disease (see 8.1.1) on prior therapy
2. Best response to prior therapy was stable disease (see 8.1)
3. Progressive disease (see 8.1.1) within 60 days of the last therapy

6.2.2 Relapsed Myeloma

Not fulfilling criteria for refractory disease and at least one biochemical *and* at least one clinical criterion fulfilled indicating recurrence of disease more than 60 days after the last therapy:

One or more biochemical criteria for recurrent disease:

An **increase of 25% from lowest response value** in **any one or more** of the following, **verified on two consecutive measurements**:

1. Serum M-component (absolute increase must be ≥0.5 g/100 ml) *
2. Urine M-component (absolute increase must be ≥200mg per 24 h)
3. Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >100 mg/l)
4. Bone marrow plasma cell percentage (absolute % must be ≥10%)

AND one or more clinical criteria for recurrent disease:

Any of the following:

1. Definite development of new bone lesions or soft tissue plasmacytomas

2. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of each measurable lesion
3. Development of hypercalcemia (corrected serum calcium >11.5mg / 100ml) that can be attributed solely to the plasma cell proliferative disorder
4. Decrease of hemoglobin by at least 2g/dL below the best independent value (without ESA or blood transfusion for at least 28 days) since the end of previous therapy or new decrease in HgB below 10g/dL or to 2g/dL below the lower limit of normal
5. New increase in serum creatinine to > 2mg/dL, or increase by 2mg/dL attributed to myeloma progression

*: If the starting serum m-protein level is ≥5g/dL an absolute increase of ≥1g/dL, verified on two consecutive measurements, is sufficient as a biochemical criterion for recurrent disease.

7 Treatments

7.1 Investigational therapy

7.1.1 Panobinostat

Panobinostat (also known as LBH589) will be provided by Novartis. Oral panobinostat will be supplied as 5-mg, 15-mg, or 20-mg pink/opaque-colored, hard gelatin capsules.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

During the study, panobinostat will be administered orally as once daily dose of 20 mg. according to the schedule in 5.3.

Patients should be instructed to take their once-a-day oral dose of panobinostat at the same time each morning. Each dose of panobinostat should be taken with an 8 oz / 240 ml glass of water after a meal. Patients should be instructed to swallow the capsules whole and not chew them. Patients must avoid grapefruit or grapefruit juice and seville (sour) oranges during the entire study.

On the days of ECG monitoring, drug administration should be supervised by study center personnel and administration time should be recorded. Subsequently, ECGs should be performed at the predefined time points.)

If the patient forgets to take his/her dose during the morning on scheduled treatment day, then he/she should take panobinostat (LBH589) on that same day within 12 hours after the missed dose if possible. After more than 12 hours, that day's dose should be withheld, and the patient should wait to take LBH589 until the next scheduled treatment day (i.e., patients should be instructed not to try to make-up the missed dose after 12 hours). The patient should then continue treatment with the original dosing schedule

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study should be recorded.

7.1.2 MLN9708 (Ixazomib)

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub investigator(s). Patients should be monitored for toxicity, as necessary, and doses of MLN9708 should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of MLN9708 dose (see under 7.5).

7.1.2.1 MLN9708 (Ixazomib) Administration

Capsules of MLN9708 will be supplied by Millennium as capsules of 2.3 mg, 3.0 mg, and 4.0 mg MLN9708.

The prescribed administration of MLN9708 doses and schedules in this study are outlined in 5.3

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. A total of approximately 8 ounces (240 mL) of water should be taken with each capsule.

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. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

7.1.2.2 MLN9708 Destruction

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

7.1.2.3 Packaging, and Labeling of MLN9708

For blistered material, the capsules are packaged in cold form foil-foil blisters with a paper backing for child-resistance.

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

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

specified by governing regulations. The formulation consists of 0.5-, and 2.0-mg capsules for oral administration.

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). All excursions should be brought to Millennium's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Approval for any patient for take-home medication must be discussed with Millennium in order to ensure the greatest conformity with repackaging, labeling, and patient compliance. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because MLN9708 is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

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

In case of contact with the powder (e.g., from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of MLN9708, including that MLN9708 is to be taken as intact capsules.

7.1.3 Cardiac precautions

All patients must have an assessment of serum potassium, magnesium, and calcium (total corrected for albumin, or ionized calcium) ≤ 72 hours prior to the administration of oral panobinostat on day 1 of cycle 1 and the results must all be ≥ LLN before the first dose of panobinostat is administered. Throughout the study serum biochemistry values including serum potassium, calcium, and magnesium will be monitored closely. On any day and time in which serum potassium, calcium, and magnesium are assessed, if the value is < LLN, then the patient's potassium, calcium, or magnesium should be immediately supplemented following the availability of that laboratory result, in order to minimize the time patients have low values. Patients must then undergo a repeat biochemistry test to demonstrate values ≥ LLN. These values must be ≥ LLN before the patient is re-dosed with oral panobinostat.

Patients must be instructed to not take panobinostat if their most recent biochemistry values demonstrates potassium, calcium, or magnesium < LLN. At a minimum, potassium, magnesium, and calcium will be checked according to the protocol. More frequent testing should be done if clinically indicated, e.g. patient has had prior low values, patient is taking medications (e.g., diuretics) that can result in lowering of their potassium, magnesium, or calcium levels.

7.2 Dexamethasone

Dexamethasone will be prescribed as 4mg tablets and charged to the patient's insurance. Dexamethasone tablets should be taken after breakfast with approximately 8 ounces (240 mL) of water. Missed doses can be made up until 72h from the next planned dose. Adherence will be evaluated together with adherence to investigational therapy.

7.3 Mandatory concomitant therapy

7.3.1.1 Herpes prophylaxis

The risk for shingles is increased with proteasome inhibition and can be decreased with prophylactic acyclovir [53]. All patients will receive prophylaxis with acyclovir 400mg orally twice a day or valacyclovir 1000mg orally once a day. If the creatinine clearance of a patient drops below 30ml/min while a patient is on study, acyclovir should be reduced to 200mg twice a day and valacyclovir to 500mg orally once a day.

7.4 Instructions for Initiation of a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle (cycle 2 and beyond) if:

- ANC $\geq$ 1.0 x 10^9/L (G-CSF and GM-CSF are allowed to achieve this threshold)
- Platelets $\geq$ 50x 10^9/L, without platelet transfusion for $\geq$ 72h
- AST and ALT $\leq$ 3 x ULN
- Serum bilirubin $\leq$ 3 x ULN
- Serum potassium $\geq$ LLN and serum magnesium $\geq$ LLN (electrolyte levels may be achieved with repletion or other supportive medications like potassium sparing diuretics)
- QTcF $\leq$ 480 msec if ECG obtained (mandatory before cycle 2)
- Any non-hematologic drug-related adverse events that may have occurred have resolved to $\leq$ grade 1 or baseline severity. Physician discretion may be used in initiating the next cycle of treatment if the only toxicities that have not resolved to $\leq$ grade 2 severity are dexamethasone-related toxicities.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated at least weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If a prolonged QTcF prevents re-initiation of therapy for more than 7 days the patient will be taken off study. For phase I patients only: If other criteria to initiate a new cycle are not met by 14 days after the planned start of a new cycle patients also go off study.

7.5 Dose modifications for adverse events

7.5.1 Dose reduction guidelines

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drugs. If administration of panobinostat, MLN9708 (ixazomib), or dexamethasone must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to guidelines outlined below. Clinical judgment may be used when deciding which drug to hold or modify in scenarios that are not covered below. Also, if the treating physician feels dose reduction by one level will not suffice to avoid recurrence of an observed profound adverse event, dose reduction by more than one dose level or before the severe adverse event occurs is allowed. If an adverse event is felt not related to study drug but continued use of study drugs may worsen the adverse event, holding the respective study drug until resolution of the adverse event without dose reduction at re-initiation of therapy is allowed. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.03 (CTCAEv4.03, (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf). All interruption or changes to study drug administration must be recoded.

7.5.2 Dose Re-Escalation Guidelines

If an entire cycle was tolerated without need for dose reduction and it is felt that the patient may tolerate a re-escalation of study therapy due to improved disease control or optimized supportive measures, doses may be increased by one level per cycle for either ixazomib (MLN9708) or panobinostat with or without concurrent increase of dexamethasone up to maximally starting dose level.

Table 7-1 Dose modification (DM) levels for adverse events attributed to MLN9708

DM Level	MLN9708 dose modification dependent on starting dose (maintain schedule of administration on day 1,8,15 every 28 days in all DM levels)	
	Starting dose	
0	3mg	4mg
-1	2.3mg	3mg
- 2	Discontinue MLN9708	2.3mg
-3		Discontinue MLN9708

Table 7-2 Dose modification (DM) levels for adverse events attributed to panobinostat

DM Level	Panobinostat dose (maintain schedule of administration on d 1,3,5,15,17,19 q 28 d in all DM levels)
0	20mg
-1	15mg
-2	10mg
-3	5mg
-4	Discontinue panobinostat

Dose modification (DM) levels for adverse events attributed to panobinostat and MLN9708

Modify dosing schedules as outlined in table 7-1 and 7-2 alternating between panobinostat and MLN9708, starting with panobinostat

Table 7-3 Dose modification (DM) levels for adverse events attributed to dexamethasone

DM Level	Dexamethasone
0	20mg d 1,2,8,9,15,16 q 28 d

-1	20mg d 1,8,15,22 q 28 d
-2	16mg d 1,8,15.22 q 28 d
-3	12mg d 1,8,15,22 q 28 d
-4	Discontinue dexamethasone

7.5.3 Dose modifications for study drug-related toxicity (see section 7.5.4 for dose modifications for prolonged QTc):

The criteria for dose modifications for study drug-related toxicity are detailed in table 7-4.

Table 7-4 Criteria for dosing delays, dose-reductions, and re-initiation of treatment due to study drug-related toxicity (excluding QT prolongation)

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
HEMATOLOGICAL TOXICITIES		
Thrombocytopenia	Grade 4 (< 25 x 10^9/L)	Temporarily discontinue panobinostat and MLN9708 dosing until platelets have increased to≥ 50 x 10^9/L, then reduce dose of one of these drugs by one level per cycle starting with panobinostat until panobinostat is at 10mg, then alternate with ixazomib dose reductions

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L)	Temporarily discontinue panobinostat and MLN9708 dosing and consider use of G-CSF or GM-CSF until the ANC has increased to ≥ 0.5 x 10^9/L , then reduce dose of one of these drugs by one level per cycle starting with panobinostat until panobinostat is at 10mg, then alternate with ixazomib dose reductions. If neutropenia was the only reason for dose reduction, consider maintaining the same dose level with prophylactic use of G-CSF or GM-CSF in the next cycle when neutrophil counts decrease below 1 x 10^9/L.
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Temporarily discontinue panobinostat and MLN9708 dosing and consider use of G-CSF or GM-CSF until fever resolved and ANC ≤ grade 2, then reduce dose of one of these drugs by one level per cycle starting with panobinostat until panobinostat is at 10mg, then alternate with ixazomib dose reductions.

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
NON-HEMATOLOGICAL TOXICITIES		
CARDIAC		
Cardiac - Prolonged QT interval**		**Please refer to Section 7.5.4.**
PERIPHERAL NEUROPATHY		
Grade 1-2 with clinically significant impact on quality of life		Consider holding ixazomib (MLN9708) and restarting at reduced level upon satisfactory improvement
Grade 3		Hold ixazomib (MLN9708) and restart at reduced level upon resolution to Grade ≤ 1 or baseline.
Grade 4		Permanently discontinue ixazomib (MLN9708)
RASH		
Grade 2		Symptomatic recommendations as per section 7.6
GASTROINTESTINAL		
Diarrhea	Grade 2 (4-6 stools/day over baseline, etc.) despite the use of optimal antidiarrheal medications	Temporarily discontinue panobinostat and MLN9708 dosing until resolved to ≤ grade 1, or baseline, then restart at unchanged dose levels at the first occurrence. If this adverse event recurs at grade 2 in subsequent cycles reduce dose by one level alternating between panobinostat and MLN9708, starting with panobinostat.
	Grade 3 (≥ 7 stools/day over baseline, etc.) despite the use of optimal antidiarrheal medications	Temporarily discontinue panobinostat and MLN9708 dosing until resolved to ≤ grade 1, or baseline, then reduce dose by one level alternating between panobinostat and MLN9708, starting with panobinostat.

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
	Grade 4 (life-threatening consequences, hemodynamic collapse, etc.) despite the use of optimal antidiarrheal medications	Take patient off study.
Nausea/vomiting	Grade 1 & 2 not requiring treatment or controlled using standard anti-emetics	Maintain dose levels of panobinostat, MLN9708, and dexamethasone.
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Temporarily discontinue panobinostat and MLN9708 dosing until resolved to ≤ grade 1, or baseline, then reduce dose by one level alternating between panobinostat and MLN9708, starting with panobinostat.
FATIGUE		
Fatigue	Grade 3 (fatigue not relieved by rest limiting self-care activities of daily life)	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 2 (fatigue not relieved by rest limiting instrumental activities of daily life), or baseline, then reduce dose by one level alternating between panobinostat and MLN9708, starting with panobinostat.
HEPATIC		
Total Bilirubin	Grade 3-4 (> 3 x ULN)	Temporarily discontinue panobinostat and MLN9708 dosing until resolved to ≤ grade 2, or baseline, then reduce dose by one level alternating between panobinostat and MLN9708, starting with panobinostat.

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
AST/SGOT, ALT/SGPT	> 5-10 x ULN	Temporarily discontinue panobinostat and MLN9708 dosing until resolved to ≤ grade 1 (or ≤ grade 2 if liver infiltration with myeloma is present), or baseline, then: • If resolved within 7 days, then: • restart panobinostat and MLN9708 at unchanged dose levels If resolved in more than 7 days, then reduce dose by one level alternating between panobinostat and MLN9708, starting with panobinostat.
	> 10 x ULN	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then reduce dose by one level alternating between panobinostat and MLN9708, starting with panobinostat.
Other NON-HEMATOLOGICAL TOXICITIES		
Grade 2 with clinically significant impact on quality of life		Consider holding study drug(s) felt to be responsible and restarting at reduced level and/or with improved supportive measures upon satisfactory improvement.
Grade 3		Hold study drug(s) felt to be responsible and restart at reduced dose level upon resolution to Grade ≤ 1 or baseline.
Grade 4		Strongly consider permanently discontinuing study drug(s) felt to be responsible but resuming at reduced dose upon resolution to ≤ grade 1 or baseline is allowed if clinical judgment suggests net benefit from continued treatment.

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**	**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
All dose modifications should be based on the worst preceding toxicity.	
* Common Terminology Criteria for Adverse Events (CTCAE Version 4)	
** It is critical that electrolyte abnormalities be followed closely and corrected prior to dosing	
*** See also concomitant medication Section 7.7	

7.5.4 Dose modifications for prolonged QTcF

All cardiac events should be treated as per the local standard of care and referred to a specialist if clinically indicated. Initial assessments will be made by the treating physician based on the QTc calculated by the ECG machine according to the Bazett formula (QTcB=QT/$\sqrt{}$RR). Any panobinostat dosing or withholding decisions will only be made after calculation of the QTcF according to the following formula QTcF=QT/$\sqrt[3]{}$RR by trained research nurses or the principal investigator. If a patient cannot be dosed due to prolonged QTcF for more than 7 days since last dose, patient should be discontinued from study.

Table 7-5 Dose modifications for prolonged QTcF

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF* of triplicate ECGs. *QTcF: Heart rate corrected QT interval using the Fredericia formula: $\boldsymbol{QTcF = QT\ (msec)/\sqrt[3]{RR}(sec}$		
Pre-panobinostat-dose on cycle 1, day 1: 3 ECGs separated by 5-10 minutes, obtained prior to panobinostat dosing.	Average QTcF > 470 msec	**Check and correct** the patient's serum potassium, magnesium, and calcium immediately, as well as evaluate con-meds that can prolong (or is known to be associated with) QTc interval. Repeat 3 pre-panobinostat-dose ECGs. If the 3 pre-panobinostat-dose ECGs: **Do not meet** criteria again, discontinue patient from study. **Do meet** criteria for dosing; administer study drug treatment.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF* of triplicate ECGs. *QTcF: Heart rate corrected QT interval using the Fredericia formula: $$\boldsymbol{QTcF = QT\ (msec)/\sqrt[3]{RR}(sec}$$		
Pre-panobinostat-dose on day 5, cycle 1, and on day 1 of subsequent cycles: 3 ECGs separated by 5-10 minutes, obtained prior to panobinostat dosing	Average QTcF: ≥ 481 msec to < 500 msec OR > 60 msec increase from baseline average	**Check and correct** the patient's serum potassium, magnesium, and calcium immediately, as well as evaluate con-meds. Delay panobinostat dose at least 3 days, hold MLN9708, and repeat 3 pre-panobinostat-dose ECGs. If the repeat 3 pre-panobinostat-dose ECGs: **Do not meet** pre-panobinostat-dose ECG criteria again, discontinue patient from study. **Do meet** pre-panobinostat-dose ECG criteria for dosing and QT prolongation determined to be related to study drug, resume study drug treatment with a panobinostat dose reduction of 5 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level upon correction of the electrolyte imbalance or discontinuation of the offending con-med. Repeat ECGs - pre-panobinostat-dose (x3), 3-hours post-panobinostat-dose (x3), on the next scheduled panobinostat dosing day.
Pre-panobinostat-dose on cycle 1, day 5 and on day 1 of subsequent cycles: 3 ECGs separated by 5-10 minutes, obtained prior to panobinostat dosing	Average QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, and calcium immediately. **Discontinue** patient from study therapy. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: Omit panobinostat and next MLN9708 dose. On the next scheduled panobinostat dosing day continue at the same dose level. Repeat ECGs - pre-panobinostat-dose (x3), 3-hours post-panobinostat-dose (x3), on the next scheduled dosing day.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF* of triplicate ECGs. *QTcF: Heart rate corrected QT interval using the Fredericia formula: $$QTcF = QT\ (msec)/\sqrt[3]{RR}(sec$$		
Post-panobinostat dose on cycle 1, days 1 and 5: 3 ECGs separated by 5-10 minutes, obtained 3 hours +/- 0.5 hours after panobinostat dosing:	Average QTcF ≥ 481 msec to < 500 msec OR > 60 msec increase from baseline	**Check and correct** the patient's serum potassium, magnesium, and calcium immediately, as well as evaluate con-meds. **Monitor ECG hourly** or by telemetry until at least 2 consecutive hourly ECGs performed at least 6 hours post dose show QTcF < 481. Next scheduled panobinostat dosing day: repeat 3 pre-panobinostat-dose ECGs. If these 3 pre-panobinostat-dose ECGs: Do not meet pre-panobinostat-dose ECG criteria for dosing (average QTcF ≤ 480 msec), discontinue patient from study. Do meet pre-panobinostat-dose ECG criteria for dosing (average QTcF ≤ 480 msec) and QT prolongation determined to be related to study drug, resume study drug treatment with a panobinostat dose reduction of 5 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level if responsible con-meds could be stopped and any electrolyte abnormalities are corrected. Repeat ECGs - pre-panobinostat-dose (x3), 3-hours post-panobinostat-dose (x3) on the next scheduled dosing day.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF* of triplicate ECGs. *QTcF: Heart rate corrected QT interval using the Fredericia formula: $$QTcF = QT\ (msec)/\sqrt[3]{RR}(sec$$		
	Average QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, and calcium immediately. **Discontinue** patient from study therapy and monitor ECG hourly or by telemetry until at least 2 consecutive hourly ECGs performed at least 6 hours post dose show QTcF < 480. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: omit panobinostat and MLN9708 dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-panobinostat-dose (x3), 3-hours post-panobinostat-dose (x3), on the next scheduled dosing day.

7.6 Management of Clinical Events

Infections

Mild infections may be treated with concurrent oral antibiotics of the beta-lactam class, with azithromycin or levofloxacin, or with other antibiotics taking possible pharmacokinetic interactions with panobinostat and MLN9708 into account. Infections that are associated with fever (temperature 38C on two consecutive measurements or one temperature of 38.5 C or higher) or with other concerning clinical signs or symptoms require holding all study drugs until the infection is controlled.

Nausea and/or Vomiting

Standard anti-emetics, including 5-HT_3 antagonists, are recommended for emesis occurring upon treatment initiation; prophylactic anti-emetics may also be considered. Dexamethasone should not be administered as an anti-emetic. Fluid deficits should be corrected before initiation of study drug and during treatment.

Diarrhea

Diarrhea should be managed according to standard clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficits should be corrected before initiation of treatment and during treatment.

Erythematous Rash With or Without Pruritus

As with VELCADE, rash with or without pruritus has been reported with MLN9708, primarily at the higher doses tested. The rash may range from some erythematous areas to macular and/or small papular bumps that may or may not be pruritic over a few areas of the body or more generalized, or it may have been transient and resolved either spontaneously or with standard symptomatic measures such as oral or topical antihistamines. Prophylactic measures should also be considered if a patient develops a rash (e.g., using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (e.g., prednisone ≤ 10 mg per day or equivalent) is permitted. A rare risk is Stevens-Johnson Syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice.

Thrombocytopenia

Thrombocytopenia has been reported with MLN9708 and panobinostat. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. MLN9708 administration should be modified as noted as per dose modification recommendations in Table 3-2 and Table 7-4 when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts.

Neutropenia

Neutropenia has been reported with MLN9708 and panobinostat. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. GM-CSF and G-CSF may be used to shorten neutropenic periods and to maintain dose level of study drugs if neutropenia is the only reason for dose reduction according to table Table 7-4 and at the discretion of the treating physician.

Fluid Deficits

Dehydration should be avoided because MLN9708 and panobinostat may cause vomiting, diarrhea, and dehydration. Two cases of acute renal failure have been reported in patients treated at or above the MTD with IV administration of MLN9708. There has been no treatment-related renal failure reported in patients treated with PO MLN9708. Fluid deficits should be corrected before initiation of study drug and during treatment. Until further information is available, intake of NSAIDs while on this protocol should be avoided.

Hypotension

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

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES) has been reported with MLN9708. While this case ultimately resolved, PRES has also been reported rarely with another proteasome inhibitor, VELCADE. PRES is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Prompt diagnosis and initiation of antihypertensive and anticonvulsant therapy are important to prevent irreversible end-organ damage.

7.6.1 Study drug discontinuation

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued, the reason will be recorded in the source documents and within ONCORE.

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

1. Disease progression, this always requires removal from study
2. Adverse event(s)
3. Abnormal laboratory value(s)
4. Abnormal test procedure result(s)
5. For phase I patients only: Dosing delay of > 21 days (= unable to receive study therapy for 22 days including any therapy held during a cycle)
6. For phase I patients only: Delay of a cycle by > 14 days from the intended day of the next scheduled dose, counted from the start of the previous cycle.

7. Protocol violation
8. Subject withdrew consent
9. Lost to follow-up
10. Administrative problems
11. New anti-myeloma therapy started
12. Study Termination
13. Death

7.6.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to a possibly study-drug related adverse event or abnormal laboratory value must be followed until resolution to CTCAE V 4.03 grade 2 or 30 days post last study drug administration, whichever comes first.

If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. All patients will be followed for adverse events and serious adverse events for at least 4 weeks following the last dose of any study drug.

7.7 Other concomitant medications

Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including IV bisphosphonates and drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- Any medications listed in Section 19 which may cause QTc prolongation or inducing torsades de pointes should not be used.
- Any medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias.
- No other investigational therapy should be given to patients
- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Leukocyte growth factors (e.g. G-CSF and GM-CSF) are not to be administered systematically but may be prescribed by the investigator for severe neutropenia if this is thought to be appropriate, see also for guidance under table 7-4..
- Medications known to be substrates of the isoenzyme CYP2D6 should be used with caution with panobinostat as panobinostat can inhibit isoenzyme CYP2D6 at low micromolar ranges. Please refer to Section 21 for the list of CYP2D6 substrates. .
- Concomitant use of CYP3A4 inhibitors with panobinostat should be used with caution due to a potential increase in panobinostat exposure during concomitant treatment with these drugs.

- Oral contraceptives are generally metabolized by CYP3A4. Since the induction potential of panobinostat to induce CYP3A4 is unknown, patients who are using oral contraceptives as a method of contraception, and are sexually active, should use another effective contraceptive method.

7.7.1 Summary of commonly used allowed supportive concomitant medications

While a heightened awareness about possible pharmacokinetic and pharmacodynamic interactions should be maintained with any medication used concomitantly with study drugs the following are generally considered safe due to lack of reported interaction or large therapeutic window despite possible interaction:

- HT3 blockers (with caution, D/C if followed by QTcF prolongation), metoclopramide, and prochlorperazine
- Loperamide, diphenoxylate/atropine
- Azithromycin, levofloxacin, pefloxacin, ofloxacin, tosufloxacin, difloxacin, temafloxacin, fleroxacin, acrosoxacin, and nalidixic acid are allowed
- Acetaminophen and opioid analgesics other than methadone
- Regular orange juice and dihydropyridine calcium channel blockers (e.g. amlodipine, felodipine, nicardipine, nifedipine) are allowed
- IV bisphosphonates
- G-CSF, GM-CSF: Their use is allowed and should follow institutional practice and guidance outlined in table 7-4, alternative usage may be reviewed with Millennium and Novartis.
- Erythropoietin will be allowed in this study. Its use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.

7.7.2 Summary of prohibited concomitant medications and supplements

The following contains commonly used medications that should not be used during this study due to either pharmacokinetic interactions or pharmacodynamically based increased risk for adverse events. It is not inclusive. See Sections 19-21 for more information.

- Grapefruit or grapefruit juice and seville (sour) oranges (regular orange juice is allowed)

- Non-steroidal anti-inflammatory agents (NSAIDs) should be avoided if possible due to risk for kidney dysfunction in myeloma but if clinical judgement strongly argues for their use patients can remain on study while receiving NSAIDs
- Other antineoplastic agents
- Other investigational agents
- Aprepitant
- All Class IA antiarrhythmics: quinidine, procainamide, disopyramide, any other class IA antiarrhythmic drug
- All Class III antiarrhythmics: amiodarone, sotalol, bretylium, disopryramide, dofetilide, ibutilide, any other class III antiarrhythmic drug
- Calcium channel blockers: diltiazem, verapamil
- The following Antibiotics: Erythromycin, clarithromycin, telithromycin (azithromycin is allowed), enoxacin, sparfloxacin, ciprofloxacin, voriconazole, ketoconazole, and posaconazole
- Antipsychotics/antidepressants: thioridazine, mesoridazine, chlorpromazine, pimozide, fluvoxamine, nefazodone
- Antimalarials: halofantrine, chloroquine
- Miscellaneous drugs: arsenic trioxide, astemizole, bepridil, domperidone, levomethadyl, methadone, pentamidine, droperidol
- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole
- 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 procedures are prohibited during the study:

- Any antineoplastic treatment with activity against MM except for drugs in this treatment regimen.

- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).Platelet transfusions can be given as clinically indicated but eligibility for starting a new cycle needs to be determined after at least 72 h without platelet transfusion and eligibility for inclusion in this trial needs to be determined after at least 7 days without platelet transfusion. Adjuvant hormone therapy for breast or prostate cancer.

7.7.3 Anti-coagulant therapy

Panobinostat and MLN9708 therapy is commonly associated with mild to moderate degree of thrombocytopenia. This may lead to an increase in the risk of bleeding with concomitant sodium warfarin (Coumadin®). It is recommended that patients who require anticoagulation therapy while on panobinostat therapy use low molecular weight heparin (LMWH). However, if the use of LMWH is not feasible, patients on sodium warfarin may continue such therapy while on study but for such patients, a close and frequent monitoring of the coagulation parameters, including PT/INR should be followed and they should be maintained within a therapeutic range. The dose of sodium warfarin may be adjusted as needed while on study.

7.8 Precautions and Restrictions

- Fluid and electrolyte deficits should be corrected before and throughout treatment.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) risk for nephrotoxicity is increased in patients with multiple myeloma, underlying kidney dysfunction, and dehydration. NSAIDs should generally be avoided in patients with multiple myeloma, especially if other risk factors co-exist.

7.9 Contraception Requirements

The effects of MLN9708 and panobinostat on human pregnancy or development of the embryo or fetus are unknown. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet the following eligibility criteria:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, for at least 28 days before starting study drug through 90 days after the last dose of study treatment.
    - The 2 methods of reliable contraception must include 1 highly effective method and 1 additional effective (barrier) method. Females of childbearing potential must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

      Highly effective methods:

        - Intrauterine device (IUD)
        - Hormonal (injections, implants)
        - Tubal ligation
        - Partner's vasectomy

      Additional effective methods:

        - Male condom
        - Diaphragm
        - Cervical Cap

Male patients, even if surgically sterilized (i.e., status post vasectomy), must meet the following eligibility criteria:

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study treatment if their partner is of childbearing potential, even if they have had a successful vasectomy.

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

7.9.1 CYP2D6 Substrates

In in vitro assays, panobinostat was shown to inhibit the cytochrome P450 isoenzyme CYP2D6 at low micromolar ranges, thereby suggesting a potential risk of drug-drug interactions with concomitant medications that are also metabolized by CYP2D6. A clinical drug-drug interaction study with dextromethorphan (a CYP2D6 probe drug) and panobinostat is currently ongoing in cancer patients. In the meantime, medications that are known to be CYP2D6 substrates should be used with caution when given concomitantly with panobinostat. Patients must be carefully monitored for signs of toxicity as a result of concomitant medication which may require dose titration or reduction of the CYP2D6 substrate as medically necessary. Please see Appendix 1 and refer to the following website: http://medicine.iupui.edu/flockhart/table.htm for a list of substrates of CYP2D6.

7.9.2 Drugs that can inhibit/induce CYP3A4/5

7.9.2.1 Drugs that can inhibit CYP3A4/5

Panobinostat is metabolized in vitro by CYP3A4/5. A clinical drug-drug interaction study with ketoconazole and panobinostat has recently been completed. The less than 2-fold increase in panobinostat AUC upon co-administration with ketoconazole suggests that CYP3A contribution to the total clearance of panobinostat is low. The observed interaction is not considered clinically relevant, as panobinostat doses at least 2-fold greater than 20 mg (40 and 60 mg) have been safely administered in patients. CYP3A4 inhibitors should have no major impact on the exposure of panobinostat and may be co-administered when medically necessary.

7.9.2.2 Drugs that are potent CYP3A4/5 inducers

As it is with other medications that are metabolized by CYP3A4, clinical judgment is to be exercised when potent CYP3A4 inducers are concomitantly taken with panobinostat.

7.10 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

8 Visit schedule and assessments

Table 8-1 Schedule of Assessments*

Examinations	Screening	Cycle 1			Cycles 2 and beyond		Study exit [8]
	D-7 to D1	D1	D5	Weekly	D 1	Weekly	
Informed consent	X						
Background information [1]	X						
Inclusion/exclusion criteria	X						
Bone marrow examination [2]	X						
Skeletal survey [3]	X						
Echocardiogram or MUGA scan [3]	X						
Vital signs [4]		X		X	X		X
History & Physical examination	X	X		X	X		X
ECG [5]	X	X	X		X[5]		
CBC/Diff	X	X		X	X	X[10]	X
PTT, INR	X						
CMP,, magnesium	X	X		X	X	X[10]	X
Response parameters SPEP, 24h UPEP, sFLCs, serum and urine IFE	X				X		X
TSH, free T3, FTI	x				Cycle 4X[9]		X
Pregnancy testing [6]	X				X		
Compliance review/drug calendar [7]					X		X

* Unless noted otherwise all visits and assessments should occur on the scheduled day +/- 3 days but a new cycle may not begin unless ECG and electrolyte assessment has been completed within 24h prior to day one dosing and criteria are met for the start of a new cycle (7.4).

1) Background information. The treating physician is responsible for comprehensive assessment of background information as it relates to eligibility for this trial. The following will be recorded on the CRFs: Year and month symptomatic myeloma was diagnosed, cytogenetic findings at diagnosis (karyotype, FISH, gene expression profile as available), beta 2 microglobulin, serum albumin, and LDH levels at diagnosis, number of prior therapies, and responses to prior therapies. Past medical history, past surgical history, and allergies as recorded in patient's charts 6 month prior to enrollment and all concomitant medications at the time of enrollment will also be recorded.

2) Bone marrow examinations: In general this will only be done once at screening or within 28 days prior to study entry but for patients who appear to have reached a complete remission based on blood and urine studies it will be repeated for confirmation. Patients who have measurable disease only in the bone marrow will have bone marrow examinations after cycle 2 and at the end of the study. Additional bone marrow examinations may be obtained as clinically indicated. 3) Skeletal survey and left ventricular ejection fraction determination by Echocardiogram or MUGA scan: Within 28 days prior to study entry.

4) Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position

5) ECGs:

- On Screening: One ECG
- On day 1 and 5 of cycle 1: Pre-dose: One ECG, Post-dose at 3 hours ± 0.5 hour: One ECG
- On day 1 of cycle 2: Pre-dose: One ECG
- Additional ECGs as detailed under 7.5.4 may be necessary if QTcF prolongation prevents dosing of panobinostat and MLN9708 or if felt clinically necessary for other reasons

6) Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of study drugs on day 1 of cycle 1. The pregnancy test should be repeated in week 1 of every cycle (except for cycle 1).

7) Compliance review / study calendar: Nurses review medication compliance based on study calendar patients fill out.

8) Study exit: Visits and assessments at study exit should occur within 3 days prior and 7 days after the end of the previous cycle or within 7 days after the decision to remove the patient from study. If grade $\geq$ 3 non-hematologic adverse events or grade 4 neutropenia or thrombocytopenia are present at study exit, the respective adverse events should be followed weekly until resolution to grade 2 for non-hematologic adverse events and grade 3 for neutropenia and thrombocytopenia or until 30 days from last treatment have elapsed.

9) Thyroid function tests should be obtained at study entry, at about 3 months from study entry, ideally after the third 28-day cycle, whenever there is clinical suspicion for hypothyroidism, and at the completion of this study unless it has been obtained within 30 days prior to study exit.

10) Weekly CBC/diff, CMP, and magnesium until completion of cycle 2, then as clinically indicated

8.1 Efficacy / response assessments and criteria

Baseline assessments must occur within ≤ 7 days of protocol therapy initiation as indicated in Section 8, schedule of assessments. Response assessments include serum protein electrophoresis (SPEP), serum free light chains (sFLCs), 24 h urine protein electrophoresis with m-spike (24h UPEP), serum and urine immunofixation, and, for confirmation of complete remission and to monitor asecretory myeloma; bone marrow examinations.

Efficacy assessments are scheduled to occur after each cycle except for bone marrow examinations which are done only for confirmation of complete remission (once) and in patients

with measurable disease restricted to bone marrow plasma cell percentage, where bone marrow is obtained after cycle 2 and at study completion.

All response categories require two consecutive blood and urine assessments (bone marrow biopsies do not need to be repeated) and no evidence for progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required for response assessment but should be obtained when there is clinical suspicion for progressive bone disease. The time point myeloma response parameters first fall into respective response levels is recorded as the time a response is achieved once a consecutive set of tests confirmed the response. For response categories ≥ PR the confirmatory test may be obtained at any time but will generally be obtained at the start of the next cycle unless there is a clinical reason to obtain earlier; for MR consecutive tests have to confirm MR over a period of at least 6 weeks.

Complete response (CR)	Negative immunofixation of serum and urine (or normal sFLC ratio if the only measurable disease outside of the bone marrow is by sFLCs) and disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow
Stringent CR (sCR)	CR as defined above plus normal sFLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% or greater reduction in serum M-component plus urine M-component <100mg per 24 h or >90% reduction in the difference between involved and uninvolved serum free light chains if this is the only measurable disease outside of the bone marrow
Partial response (PR)	≥50% reduction of serum M protein and reduction in 24-h urinary M protein by ≥90% or to <200mg per 24 h, if the serum and urine M protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved sFLC levels is required in place of the M protein criteria, if the only measurable disease is in the bone marrow, a ≥50% reduction in bone marrow plasma cells is required, provided the baseline percentage was ≥30%. In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is required.
Minor response (MR)	≥25% but ≤49% reduction of serum M protein and reduction in 24 h urine M protein by 50–89%, which still exceeds 200mg per 24 h. In addition to the above criteria,

	if present at baseline, 25–49% reduction in the size of soft tissue plasmacytomas is also required. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable disease (SD)	Not meeting criteria for sCR, CR, VGPR, PR, MR, or progressive disease (see under 5.9.1).

8.1.1 Progressive Disease

Progressive disease (PD) is defined according to the international uniform response criteria (Durie et al. Leukemia 20:1467-73, 2006, ERRATUM Durie et al. Leukemia 21:1134, 2007) and requires any of the following, confirmed on two consecutive assessments:

An **increase of 25% from lowest response value** in **any one or more** of the following:

- Serum M-component (absolute increase must be ≥0.5 g/100 ml) *
- Urine M-component (absolute increase must be ≥200mg per 24 h)
- Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >100 mg/l)
- Bone marrow plasma cell percentage (absolute % must be ≥10%)

And / or:

- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium >11.5 mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder

*: If the starting serum m-protein level is ≥5g/dL an absolute increase of ≥1g/dL, verified on two consecutive measurements, is sufficient to define progressive disease.

The decision as to when to repeat the assessment to document progressive disease will be left at the discretion of the treating physician, there is no need to wait until the next scheduled response assessment.

9 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, vital signs, ECOG performance status, and the regular physical examinations and ECG assessments.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. CTCAE v4.03 can be accessed on the NIH/NCI website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf))

9.1.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigators' Brochures for panobinostat and MLN9708 or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

9.1.2 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position

9.1.3 Physical examination

Physical examination will be performed which must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system).

Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

9.1.4 Laboratory evaluations

Laboratory evaluation should be done at baseline (within ≤ 72 hours prior to dosing prior to the first administration of study drugs, during the course of the study and at the time of the study treatment completion visit. Results must be reviewed prior to administering panobinostat (LBH589) and ixazomib (MLN9708). More frequent examinations may be performed if medically indicated; results should be recorded.

Hematology

Hematology must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential. The coagulation profile includes a prothrombin time or International Normalized Ratio (INR) and activated partial thromboplastin time.

Blood chemistry

Biochemistry includes the following parameters: BUN, creatinine, sodium, potassium, chloride, CO_2 (HCO_3), glucose, calcium, albumin, total protein, total bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT, and magnesium (where indicated in 8). If total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed.

Thyroid function test

Thyroid Stimulating Hormone (TSH), free T3, and FTI will be measured at baseline, about 3 months after study entry (+/- 14 days), at the study completion, and as deemed clinically necessary during the course of the study.

9.1.5 Serum pregnancy test

All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of study drugs on day 1 of cycle 1. The pregnancy test should be repeated in week 1 of every cycle (except for cycle 1). Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered “of non-childbearing potential”.

9.1.6 ECG

See Section 7.1.3 (Cardiac precaution) Section 7.5.4 (Dose modification for prolonged QTc) for guidelines on the required close monitoring of patients’ serum biochemistry values (in particular, potassium and magnesium) and the requirement for rapid correction of low values).

A screening 12-lead ECG will be performed to assess study eligibility. Additional 12-lead ECGs will be performed at a minimum at scheduled time points as indicated in Section 8. For all patients, a 12-lead ECGsmust be performed on cycle 1 day 1 prior to the first administration of

study drugs or within 24 hours prior to that day. This is necessary to get an accurate baseline QTcF calculation.

Table 9-1 Cardiac assessment monitoring schedule

Cycle	Day of cycle	ECG monitoring [a]
	Screening [b]	Single ECG to assess eligibility
Cycle 1	1, 5	Pre-dose: Single 12 lead ECG
	1, 5	3 hours post dose: Single 12 lead ECG
Cycle 2	1	Pre-dose: Single 12 lead ECG
[a] Refer to Table 6-7 for the recommended dose modifications due to QTc interval prolongation [b] The screening ECGs will be analyzed locally to assess eligibility of the patient. (Note: the mean QTc interval at baseline must be ≤ 470 msec for the patient to be eligible for participation in the trial) Note: If no significant QTcF prolongation is noted during the first 4 cycles, the QTc monitoring is no longer required and may be performed at the Investigator's discretion, if medically indicated.		

9.1.6.1 Performance status

Performance status will be assessed according to the ECOG Performance Status Scale:

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

9.1.6.2 Special tests

No special tests will be obtained. Routine standard myeloma tests will be obtained as outlined in Section *8*.

9.2 Drug levels and pharmacokinetic assessments

No pharmacokinetic studies are planned.

10 Safety monitoring

10.1 Novartis Instructions for rapid notification of serious adverse events

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form as outlined per contractual agreement; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E) are included in the contractual agreement. The original copy of the SAE Report Form and the fax confirmation sheet should be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or

continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

10.2 Millennium Instructions for rapid notification of serious adverse events

All serious adverse events (SAEs) (regardless of expectedness or causality) must be reported to Millennium Pharmacovigilance (or designee). See also Novartis Instructions for rapid notification of serious adverse events for the reporting of SAEs.

The sponsor-investigator is responsible to meet all regulations and requirements applicable to the sponsor-investigator.

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 must be reported to Millennium Pharmacovigilance (or designee). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

This is an investigator-initiated study. The principal investigator, Jason Valent (who may also sometimes 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.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.7) must be reported by the sponsor- to the Millennium Pharmacovigilance or designee by faxing the SAE Report using the US FDA MedWatch 3500A Form :

> **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

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 4.0 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.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance or designee from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to Millennium Pharmacovigilance. Millennium Pharmacovigilance (or designee) may request follow-up information to a reported SAE or serious pretreatment event, which the sponsor-investigator will be responsible for providing to Millennium Pharmacovigilance or designee.

Millennium will provide a sample SAE Report Form representative of the information Millennium Pharmacovigilance may request in follow-up.

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

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

Intensity for each AE, including any lab abnormality, will be determined by using the NCI CTCAE, version 4.0 as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html

Relationship to study drug administration 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 study product(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 **FAX Number 1-800-963-6290**

Email: TakedaOncoCases@cognizant.com

Reporting Form:

- US FDA MedWatch 3500A:

- http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

10.3 Any other form deemed appropriate by the sponsor-investigatorAdverse 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

10.4 Millennium Rules for Monitoring of Adverse Events and Period of Observation

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

- AEs will be reported from the first dose of MLN9708 through 30 days after administration of the last dose of MLN9708. In addition, skeletal-related events that occur during the follow-up periods must be reported from the first dose of MLN9708 through death or termination of the study by the sponsor-investigator or Millennium.

- Serious pretreatment events will be reported to Millennium Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of MLN9708.

- Related and unrelated SAEs will be reported to Millennium Pharmacovigilance or designee from the first dose of MLN9708 through 30 days after administration of the last dose of MLN9708. 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). In addition, new primary malignancies that occur during the treatment or follow-up periods must be reported, regardless of causality to study regime. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee). Follow up for detection of second primary malignancies beyond the planned study is not required; however, if the sponsor-investigator learns about the occurrence of a second primary malignancy in one of the study subjects within 3 years after the last study drug administration he must report the event to Millennium Pharmacovigilance (or designee).

10.5 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is participating in this study, or within 28 days of the subject's last dose of MLN9708, are considered immediately reportable events. Study drug(s) is to be discontinued immediately. Millennium or designee must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance. The pregnancy must be followed for the final pregnancy outcome. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to MPI/PPD Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.
The Sponsor-Investigator will follow the female subject until completion of the pregnancy, and must notify MPI/PPD Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Sponsor-Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to MPI/PPD Drug Safety immediately by facsimile, or other appropriate method, as soon as possible but no later than 5 calendar days of the Sponsor-Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Sponsor-Investigator suspects is related to the in utero exposure to the IP should also be reported to MPI/PPD Drug Safety immediately by facsimile, or other appropriate method, as soon as possible but no later than 5 calendar days of the Sponsor-Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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

10.6 Millennium 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 PPD (refer to Section 8.2).

10.7 Serious Adverse Events

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general conditionNote that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

10.8 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis (and Millennium, see under 10.5) within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous

or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the panobinostat any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

11 Protocol amendments, or changes in study conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis, Millennium, and the sponsor-investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Novartis and Millennium. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

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

12 Data review and management

12.1 Data Management

12.2 Analyses and Reporting

Oncore will be used for data entry and analysis. Data will be analyzed and reported in abstract form after the last patient has completed the first cycle and a full manuscript will be submitted once the last patient has gone off this up to 6 month duration study. In addition, interim

reports may be submitted as abstracts.Data Safety Monitoring PlanThis protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

12.3 Study Monitoring

Internal monitoring by quality control teams of the Cleveland Clinic Taussig Cancer Institute and the Seidman Cancer Center of University Hospitals of Case Western University will occur as per Case Comprehensive Cancer Center standard operating procedures for monitoring of investigator initiated trials QA-8.1.0.

12.3.1 Investigator Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by Novartis and Millennium or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Novartis and Millennium so that the accuracy and completeness may be checked.

13 Statistical methods

13.1 Datasets to be Analyzed

13.1.1 Primary objectives and endpoints

13.1.1.1 Dose limiting toxicity

This study will use a 3 + 3 design (see under 5) to estimate whether select doses of MLN9708 up to a maximal target dose, chosen based on available data from other studies, are tolerated when combined with fixed doses of panobinostat and dexamethasone. Tolerance will be based on the ratio of patients developing dose limiting toxicity (DLT). Dose increase is allowed if 0 or 3 patients or 1 of 6 patients develop DLTs, while confirmation of a given dose level as tolerated requires treatment of at least 6 patients with no more than one patient developing a DLT.

Dose limiting toxicity (DLT) will be assessed during the first cycle and be defined as the following drug-related adverse events according to CTCAE version 4.03 (if an adverse event is attributed to progressive disease, it will not be counted as DLT):

- Grade 4 or higher neutropenia or thrombocytopenia that does not resolve to grade 3 or lower within 7 days after detection while MLN9708 (ixazomib) and panobinostat are held.
- QTcF increase to ≥ 480 msec that persists ≥ 7 days after withholding panobinostat and MLN9708
- Any grade 3 or higher non-hematologic adverse events except:
  - Nausea, vomiting, diarrhea, or electrolyte abnormalities that can be reduced to grade 2 with supportive measures within 7 days

Patients who cannot be assessed for DLT due to progressive disease or other reasons will be replaced.

13.1.1.2 Safety

Data from all subjects who receive any protocol therapy will be included in the safety analyses. Subjects who entered the study and did not receive any protocol therapy and had this confirmed, will not be evaluated for safety. Adverse events will be recorded during the entire study, weekly during the first cycle, and at the start of each cycle for subsequent cycles. Toxicity will be graded according to CTCAE v.4.0 whenever possible and reported in a descriptive way.

13.1.2 Secondary objectives and endpoints

13.1.2.1 Response

The response rate (RR= sCR+CR+VGPR+PR) and clinical benefit response rate (CBRR=sCR+CR+VGPR+MR) will be calculated for the entire study group, and for individual dose levels. Since the number of patients treated at any given dose level will be small, any report will mainly list the number of responses but may also mention the percentage of patients achieving a response.

13.1.2.2 PFS and OS

Progression-free survival will be measured from study entry to progression or death of any cause, whichever comes first. Overall survival for all will be measured from study entry to death from any cause. Due to small sample size and limit of treatment duration to six months only observed PFS and OS will be reported for patients participating in phase I. For patients who enter on phase II the Kaplan-Meier method will be used to estimate PFS and OS.

14 Procedures and instructions

14.1 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and Millennium and prior to any outside submission. Novartis and

Millennium must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' and Millennium's responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and Millennium and, in accord with the trial contract and shall not permit disclosure of Novartis or Millennium confidential or proprietary information.

14.2 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis and Millennium in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

14.3 Discontinuation of study

Novartis and Millennium reserve the right to discontinue any study under the conditions specified in the clinical trial agreement.

15 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis and Millennium standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, the Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis and Millennium before study initiation. Any

amendments to the protocol, other than administrative ones, must be reviewed by Novartis and Millennium and approved by this committee.

15.2 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

15.3 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 and/or Novartis or a designee or disposal of the drug (if applicable and if approved by Millennium and/or Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

15.4 Record Retention

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

16 USE OF INFORMATION

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

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

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18 Appendices

19 Medications which have a risk of causing Torsades de pointes ventricular arrhythmia should be avoided

Patients who are currently receiving treatment of the medications in Table 19-1 and cannot either discontinue from this treatment or switch to an alternative medication prior to enrollment in a panobinostat clinical study, will be excluded from the study. Patients may not begin panobinostat treatment with any of the medications listed in Table unless this is discussed with the Sponsor and an approval is granted by the Sponsor. The sponsor may agree to temporarily discontinue panobinostat treatment (e.g., for 72 hours) during administration with these drugs or withheld medications in Table 19-1 for at least 72 hours when panobinostat is to be administered.

NOTE: It is of great importance to avoid combining drugs listed below in Table 19-1 and Table 20-1 (CYP3A inhibitors) especially in the presence of electrolyte abnormalities, notably decreased potassium or magnesium levels commonly associated with diuretic usage.

In generally, medications listed in Table 19-1 should be avoided while medications listed in Tables 20-1 and Table 21-1 are to be used with caution when co-administered with panobinostat. Please select the most stringent recommendation for concomitant medications (i.e., to be avoided) which are common among the tables (e.g., erythromycin, clarithromycin)

Table 19-1 Medications which have a risk of causing Torsades de pointes to be avoided

All **Class IA antiarrhythmics** • **quinidine** • **procainamide** • **disopyramide** • **any other class IA antiarrhythmic drug**
All **Class III antiarrhythmics** **amiodarone** **sotalol** **bretylium** **disopryramide** **dofetilide** **ibutilide** **any other class III antiarrhythmic drug**
Antibiotics **Macrolide antibiotics*** • **erythromycin** • **clarithromycin** • **telithromycin** **Quinolone antibiotics***

sparfloxacin
Antipsychotics **thioridazine** **mesoridazine** **chlorpromazine** **pimozide**
Antimalarials • **halofantrine** • **chloroquine**
Miscellaneous drugs • **arsenic trioxide** • **astemizole** • **bepridil** • **domperidone** • **levomethadyl** • **methadone** • **pentamidine** • **droperidol**
***Note: azithromycin, levofloxacin, pefloxacin, ofloxacin, tosufloxacin, difloxacin, temafloxacin, fleroxacin, acrosoxacin, and nalidixic acid are allowed.**

This is not a comprehensive list of medications which may prolong the QT interval or have a risk of causing Torsades de pointes. This list of medications was developed in collaboration with an external cardiology consultant, and represents those medications which are deemed to have an unacceptable risk of co-administration with panobinostat.

The following website may be referenced as a supplemental guide for drugs which have been associated with Torsades de pointes or prolonging the QT interval but at this point lack substantial evidence for causing Torsades de pointes:

http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm#.

Medications listed on the website which do not appear in Table 19-1 above may be used with caution at the discretion of the investigators.

The serotonin ($5HT_3$) antagonists, often used as antiemetics, such as ondansetron dolasetron, (also are known CYP2D6 substrates, see Table 21-1), or granisetron have been associated with Torsades de points and QT prolongation but have not been shown to cause Torsades de pointes. Therefore, $5HT_3$ antagonists are not per se prohibited but close monitoring for signs and symptoms of QT prolongation is recommended. Caution is to be exercised when using these or other agents that may prolong QT intervals in combination with panobinostat.

20 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

Panobinostat is a substrate of CYP3A4 with minor involvement of CYP2D6, and CYP2C19 in *in vitro* evaluation of its metabolism. Thus, a clinical drug-drug interaction study was conducted using ketoconazole, a strong CYP3A inhibitor, in combination with panobinostat in study CLBH589B2110.

Multiple ketoconazole doses at 400 mg increased C_{max} and AUC of panobinostat by 1.6- and 1.8-fold, respectively, but with no change in T_{max} or half-lives in 14 cancer patients. The less than 2-fold increase in panobinostat AUC upon co-administration of a strong CYP3A inhibitor is considered a weak drug inhibition and not clinically relevant, as panobinostat doses at least 2-fold greater than the evaluated 20 mg dose (i.e., 40 mg and 60 mg) have been safely administered in patients. Thus, co-administration of panobinostat with a moderate or weak CYP3A inhibitor is allowed. However, clinical monitoring of signs and symptoms of panobinostat treatment related adverse events is recommended when long-term (≥ 1 week) concomitant administration of any strong CYP3A inhibitors and panobinostat is medically indicated or investigated in a clinical study.

Patients with impaired liver function (as defined by NCI CTEP criteria)[1] are recommended not to receive panobinostat concomitantly with strong CYP3A inhibitors because potential interaction has not been established in this population.

Table 20-1 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

Macrolide antibiotics* • **clarithromycin** • **telithromycin** • **troleandomycin** • **erythromycin**
Antifungals (azoles)* • **ketoconazole** • **itraconazole** • **fluconazole**
Antidepressants • **nefazodone**
Calcium channel blockers* • **diltiazem** • **verapamil**
HIV protease inhibitors: • **indinavir** • **nelfinavir** • **ritonavir**

• **saquinavir**
Miscellaneous drugs or products • **aprepitant** • **grapefruit product or juice**
*** azithromycin, regular orange juice and dihydropyridine calcium channel blockers (e.g. amlodipine, felodipine, nicardipine, nifedipine) are allowed.**

This is not a comprehensive list of medications which may inhibit CYP3A4/5. Additional updated versions with moderate and weak CYP3A inhibitors, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs

21 Medications which are known CYP2D6 substrates to be used with caution

Panobinostat was also shown to be a CYP2D6 inhibitor (K_i 0.17 μM) *in vitro*. Thus, clinical drug-drug interaction study with panobinostat as CYP2D6 inhibitor and dextromethorpan as CYP2D6 substrate was recently conducted in study CLBH589B2109.

Multiple panobinostat doses increased C_{max} and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold respectively, but with no change in T_{max} in 17 cancer patients. An approximately 2-fold increase in dextromethorphan AUC upon co-administration with panobinostat indicated that *in vivo* CYP2D6 inhibition of panobinostat is weak.

As the study was conducted using a sensitive CYP2D6 substrate which resulted in a weak inhibition, drugs with a large therapeutic index such as anti-emetics, anti-hypertensives, and anti-depressants are generally safe to be co-administered with panobinostat.

Patients should be carefully monitored for potential signs and symptoms of toxicity and may require dose titration or dose reduction of a sensitive CYP2D6 substrate which also have a narrow therapeutic window (e.g., the ratio of toxicity exposure is ≤ 2-fold higher than the efficacious or therapeutic exposure).

Table 21-1 Medications which are known CYP2D6 substrates to be used with caution

Beta blockers (listed below):	**Antipsychotics** (listed below):
carvedilol	aripiprazole
metoprolol	haloperidol
propafenone	perphenazine
timolol	risperidone
Antidepressants (listed below):	thioridazine
amitriptyline	zuclopenthixol
chlormipramine	amphetamine

desipramine	alprenolol
imipramine	bufuralol
fluoxetine	chloropheniramine
paroxetine	**Antiarrhythmics** (listed below):
venlafaxine	quinidine
bupropion	lidocaine
duloxetine	mexiletine
Antiemetics (listed below):	propafenone
dolasetron	**Others**:
ondansetron	oxycodone
metoclopramide	codeine
	hydrocodone
	terbinafine
	promethazine
	tamoxifen
	tramadol

This is not a comprehensive list of CYP2D6 substrates. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs Synold TW, Takimoto CH, Doroshow JH, Gandara D, Mani S, Remick SC, Mulkerin DL, Hamilton A, Sharma S, Ramanathan RK, Lenz HJ, Graham M, Longmate J, Kaufman BM, Ivy SP. Dose-Escalating and Pharmacological Study of Oxaliplatin in Adult Cancer Patients with Impaired Hepatic Function: A National Cancer Institute Organ Dysfunction Working Group Study, Clin Cancer Res. 2007 *13;* 3660

22 Cockroft-Gault estimation of CrCl

Cockcroft-Gault estimation of creatinine clearance (CrCl):

(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

(**Males**)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

(**Females**)

22.1.1 Millennium Pregnancy Reporting Form

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS) Page 1 of 4

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: _____

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS) Page 2 of 4

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

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

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:_____

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

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: _____

Summary of Changes:

April 24, 2014: Amendment 1

- Cover page: added Dr. Campagnaro as UH investigator
- Section 7.6.1: pg. 61 changed CRF to Oncore
- Section 8: pg. 69 -70 changes on the schedule of assessments and foot notes for some additional clarifications
- Pgs. 76-87 administrative changes brought to our attention

May 6, 2014: Amendment 2

- Table 7.5 pg. 57 the parameters for QTCF was changed to >=481 since it would otherwise contradict parameters to start a new cycle (7.4; QTCF <=480 = grade 1).
- Table 8.1 pg. 69 myeloma parameters removed from day 1 cycle one in schedule of assessments (table 8.1) since they are already included in screening (day -7 to 1) and do not need to be repeated for any safety concerns

June 18, 2014: Amendment 3

- Section 10.4 pg. 82 Added: Follow up for detection of second primary malignancies beyond the planned study is not required; however, if the sponsor-investigator learns about the occurrence of a second primary malignancy in one of the study subjects within 3 years after the last study drug administration he must report the event to Millennium Pharmacovigilance (or designee).

December 26, 2014: Amendment 4

Cover: Replaced Dr. Campagnaro with Dr. William as UH PI

1. **5.4: Dose Limiting Toxicities: Pg. 42**
    - Use of G-CSF or platelet transfusions in cycle one
    - Neutropenic fever (with grade 3 or grade 4 neutropenia)

2. **6.1.2: Inclusion/Exclusion: Pg. 45 and 46**
    - Updated Inclusion Criteria # 12
    - added Inclusion criteria # 13
    - Updated Exclusion Criteria # 1
    - Added # 2
    - Updated #'s 5, 6 and 9
    - deleted Exclusion criteria # 11 (was added to Inclusion)

3. **7.1.3: Cardiac Precautions – Pg. 51**

- deleted phosphorus

4. **7.4: Instructions for Initiation of a New Cycle: Pg. 52**
   - Platelets ≥ 50x 10^9/L, without platelet transfusion for ≥ 72h

5. **7.5.4: Dose Modifications for Prolonged QTcF: Pg. 58-63**
   - Tables Updated

6. **7.6.1: Drug Discontinuation: Pg. 66**
   - Dosing delay of > 21 days (= unable to receive study therapy for 22 days including any therapy held during a cycle)
   - Delay of a cycle by > 14 days from the intended day of the next scheduled dose, counted from the start of the previous cycle.

7. **7.7.2: Summary of Prohibited Concomitant Medications and Supplements: Pg. 68**
   - Non-steroidal anti-inflammatory agents (NSAIDs) should be avoided if possible due to risk for kidney dysfunction in myeloma but if clinical judgement strongly argues for their use patients can remain on study while receiving NSAIDs
   - Platelet transfusions can be given as clinically indicated but eligibility for starting a new cycle needs to be determined after at least 72 h without platelet transfusion and eligibility for inclusion in this trial needs to be determined after at least 7 days without platelet transfusion.

8. **8.0: Visit Schedule and Assessments: Pg. 73**
   - Added Physical Exam at Screening
   - Deleted Weekly ECGs (typo)
   - Updated ISTAT BMP info.
   - Updated CMP info.
   - Footnote #5 regarding ECGs updated

9. **9.1.6: ECG Assessments: Pg. 79**
   - Updated tables for ECG from 3 to 1

10. **10.0: Safety Monitoring: Pg. 81-88**
    - Multiple updates for Novartis and Millennium Reporting Requirements

June 3, 2015: Amendment 5

- **Cover:** Replaced Dr. William with Dr. Malek as UH PI

- **Pg. 3 Dose Levels:** Patient may continue on Panobinostat behind cycle 6 if disease is at least stable disease free of charge.
- **Pg. 39 Section 5.2: Study Duration:**
    - If the patient's myeloma is controlled in at least stable disease panobinostat may be continued free of charge to the patient. Follow up after completion of cycle 6 is at the discretion of the treating physician but if panobinostat is continued, monitoring for electrolyte abnormalities, especially potassium and magnesium, at a frequency appropriate for the respective patient, is recommended.
    - This protocol may be amended to include a formal maintenance phase and/or a phase II portion after review of safety and preliminary efficacy data.
- **Pg. 69 Visit Schedule and Assessments**
    - Deleted iSTAT BMP weekly and made CMP weekly instead

September 23, 2015: Amendment 6

- Page 1 Increase # of patients to an additional 20 in the Phase 2
- Section 2 Page 40 Rationale for Phase 2
- Section 6 Page 44 Study Population
- Section 6.1.2 Page 44-46 Inclusion Criteria items 3, 8 and 13
- Section 6.1.2 Page 48 Exclusion Criteria item 21
- Section 8 Page 74-75 Visit schedule and assessments

July 18, 2016: Amendment 7

- **Pg. 43 Inclusion Criteria #13 (Added Dara and Elot)** At least 7 days must have passed since the last treatment with lenalidomide, pomalidomide, thalidomide, proteasome inhibitors, or low dose cyclophosphamide (up to 50mg daily), at least 21 days must have passed since the last treatment with daratumumab, elotuzumab, investigational therapy and most conventional chemotherapy including cyclophosphamide above 50mg per dose, bendamustine, doxorubicin, cisplatin, and etoposide; and at least 35 days since the last treatment with melphalan.
- **Pg. 50 Section 7.4 Instructions for Initiation of a New Cycle (these were previously deleted in Amendment 6, however we missed a section**
    - **Deleted:** total serum calcium [corrected for serum albumin] or ionized calcium ≥LLN
    - **Clarified:** QTcF ≤ 480 msec if ECG obtained (mandatory before cycle 2)

March 1, 2017: Amendment 8

- Cover Page: Adding NCT #

- Footer: Updated
- Addendum: Summary of Changes

April 3, 2017

- Cover Page: PI from Dr. Reu to Dr. Valent
- Footer Updated