CLINICAL STUDY PROTOCOL

X16069

Phase I/II Study of Bendamustine and IXAZOMIB (MLN9708) Plus Dexamethasone in Relapsed/Refractory Multiple Myeloma

Indication: Relapsed/Refractory multiple myeloma
Phase: Phase I/II

Protocol History

Original	10/10/2014
Amendment 1	10/02/2015
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Investigator and Study Center:

Parameswaran Hari, MD, MRCP, MS
Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600
Email address: phari@mcw.edu

Co-Investigator: Binod Dhakal, MD, MS
Assistant Professor of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Sub-I: Ehab Atallah, MD
Associate Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Sub-I: Timothy Fenske, MD
Associate Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Sub-I: Laura Michaelis, MD
Associate Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Sub-I: Karen-Sue Carlson, MD
Assistant Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Sub-I: Marcelo Pasquini, MD
Associate Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Sub-I: Mehdi Hamadani, MD
Associate Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Sub-I: Carlos Arce-Lara, MD
Assistant Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Sub-I: Anita D'Souza, MD
Assistant Professor
Department of Medicine
Division of Hematology and Oncology
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
414.805.4600

Investigational Pharmacy:
Emily Hoefing, Pharm D, BCPS
Froedtert Hospital
9200 W. Wisconsin Ave.
Milwaukee, WI 53226

Research Coordinator:
Daniel Schmoller
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226

Biostatistics:
James Anderson, PhD
Professor
Division of Biostatistics
Medical College of Wisconsin
9200 W. Wisconsin Avenue
Milwaukee, WI 53226

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

PROTOCOL SUMMARY

Study Title: Phase I/II study of bendamustine and **IXAZOMIB** (MLN9708) plus dexamethasone in relapsed/refractory multiple myeloma

Phase: Phase I//II

Total Number of Patients: 28 (Maximum:15 in Phase I and 19 in Phase II [including phase 1 patients treated at recommended phase 2 dosing])

Study Objectives

Primary

- Phase I: To determine the maximum tolerated dose (MTD) of the combination of **IXAZOMIB (**MLN9708) and bendamustine plus dexamethasone in patients with relapsed/refractory multiple myeloma.
- Phase II: To determine the objective response rate(ORR) after four cycles of **IXAZOMIB (**MLN9708) and bendamustine plus dexamethasone.

Secondary

- To determine the overall survival (OS) of patients treated with **IXAZOMIB** (MLN9708) and bendamustine plus dexamethasone.
- To determine the progression free survival (PFS) of patients treated with **IXAZOMIB (**MLN9708) and bendamustine plus dexamethasone.
- To determine the cumulative response rates in patients after 8 cycles.
- To determine the duration of response (DoR).
- To determine the minimal residual disease status (MRD) in patients who achieve a complete response.

Overview of Study Design:

This Phase I/II study is designed to first identify doses of **IXAZOMIB** (MLN9708) and bendamustine that are associated with an acceptable adverse event profile when delivered together in 28 day cycles. Additionally, the study aims to assess the efficacy of the combination in patients with relapsed/refractory multiple myeloma. Responders (stable disease or more), will continue to receive up to 8 cycles total in the absence of further progressive disease.

Dose escalation/de-escalation: Because 4 mg of MLN9708 delivered on days 1, 8 and 15 of a 28 day cycle is known to have an acceptable toxicity profile, as a single agent and in combination with some other agents, the Phase I portion of the study will be designed as follows:

The dose of MLN9708 will be fixed at 4 mg, days 1, 8 and 15.

Dexamethasone administered as 40 mg oral on Days 1, 8, 15 of each 28 day cycle. At physician discretion, patients may be reduced to a minimum of 20mg.

Three doses of bendamustine will be evaluated.

Bendamustine dose levels:

Dose 1: 70 mg/m^2, days 1 and 2
Dose 2: 80 mg/ m^2. days 1 and 2
Dose 3: 90 mg/ m^2, days 1 and 2

A 3+3 design will be employed. At each dose, three patients will be initially evaluated. If no dose limiting toxicities are observed, the bendamustine dose will be increased; if one dose limiting toxicity is observed, three additional patients will be treated at that dose and escalation will occur only of no additional DLTs are observed. A dose at which 2 DLTs are observed in 3 or 6 patients will be judged to be too toxic and the lower dose will be defined as the maximally tolerated dose (MTD).

Should the first dose combination be found to have 2 DLTs in three patients, MLN9708 would be de-escalated to 3 mg, days 1, 8 and 15 (with bendamustine at 70 mg/m^2). If this is achieved with no DLTs, the bendamustine dose will then be escalated to 80 mg/m^2 and then 90 mg/m^2 days 1 and 2.

The Phase I portion of the study is expected to be completed with the enrollment of no more than 15 patients. Should more patients be required, the protocol will be amended.

Design for Phase II portion of study: Once an MTD or a recommended Phase 2 dose (RP2D) for the combination is identified, the plan is to treat additional patients at that dose to assess efficacy and response to treatment. We plan to enroll 14 patients (including those treated at the MTD in Phase I) and continue enrollment only if the observed overall response rate is at least 28.6% (4/14);

If enrollment continues we will treat an additional 5 patients (19 in total) and consider the combination “interesting” for further development only if at least 6/19 patients (35.31%) achieve a response.

From the statistical section:

Enroll 14 patients (including those treated at the MTD in Phase I) and continue enrollment only if the observed response rate is at least 28.6% (4/14);

If enrollment continues, treat an additional 5 patients (19 in total) and consider the combination worthy of further development only if at least 6/19 patients (35.31%) achieve a response.

Study Population:

Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.

2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3. Female patients who:

   - Are postmenopausal for at least one year before the screening visit, OR

   - Are surgically sterile, OR

   - If they are of childbearing potential, agree to practice two effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, 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, postovulation methods] and withdrawal are not acceptable methods of contraception.)

   Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:

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

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

4. Patients must have histologically or cytologically confirmed symptomatic Multiple Myeloma. They must be non-responsive to or ineligible for autologous stem cell transplant, and must progress after prior exposure to both proteasome

inhibitor (bortezomib, carfilzomib) and IMID (lenalidomide or pomalidomide or thalidomide); and refractory/progressive to at least one of the agents and must meet at least one of the following parameters of measurable disease:

1. Measurable levels of monoclonal protein (M protein): > 1 g/dL of IgG or IgM M-protein > 0.5 g/dL, IgA or IgD M protein on serum protein electrophoresis OR > 200 mg/24h of free light chain proteinuria on a 24-hour urine protein electrophoresis, which must be obtained within four weeks prior to registration OR > 10 mg/dL involved free light chain on serum free light chain testing with an abnormal kappa:lambda light chain ratio.

2. Patients with lytic bone disease, defined as at least one lytic lesion that can be accurately measured in at least one dimension.

5. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1 or 2.
6. Patients are eligible after autologous or allogeneic stem cell transplantation. Allogeneic transplantation can be enrolled only if they have no ongoing transplant related side effects. (No GVHD or treatment for GVHD).
7. Patients must be at least two weeks from major surgery, radiation therapy, participation in other investigational trials and have recovered from clinically significant toxicities of these prior treatments
8. Patients must meet the following clinical laboratory criteria:

- Absolute neutrophil count (ANC) ≥ 1,000/mm^3 and platelet count ≥ 75,000/mm^3. Platelet transfusions or G-CSF can be used to help patients meet eligibility criteria but are not allowed within 3 days before study enrollment.
- Total bilirubin < 1.5 × the upper limit of the normal range (ULN), OR, direct bilirubin within normal limits (WNL), when total bilirubin is > 1.5 x the ULN.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 × ULN.
- Calculated creatinine clearance ≥ 30 mL/min.

Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating or have a positive serum pregnancy test during the screening period.

2. Failure to have fully recovered (i.e., ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy except for peripheral neuropathy, which is addressed in exclusion criteria no. 14.

3. Major surgery within 14 days before enrollment.

4. Radiotherapy within 14 days before enrollment. If the involved field is limited (single disease focus not involving pelvis and involving < 36 Gy radiation), seven days will be considered a sufficient interval between treatment and administration of **IXAZOMIB** provided hematologic inclusion parameters are met.

5. Myeloma-related central nervous system involvement.

6. Serious infection within 14 days of study treatment start and has not clinically resolved.

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

8. Systemic treatment, within 14 days before the first dose of **IXAZOMIB**, 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.

9. Active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

10. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

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

12. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of **IXAZOMIB** including difficulty swallowing.

13. Diagnosed or treated for another malignancy where the expected survival is less than two years will be excluded. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

14. Patient has ≥ Grade 2 peripheral neuropathy, or Grade 1with pain on clinical examination during the screening period.

15. Participation in other clinical trials, including those with other investigational agents not included in this trial, within two weeks of the start of this trial and throughout the duration of this trial.

16. Patients that have previously been treated with **IXAZOMIB**, or participated in a study with **IXAZOMIB** whether treated with **IXAZOMIB** or not.

17. Patients with a history of severe chronic obstructive pulmonary disease requiring ongoing oxygen support or those with a resting oxygen saturation < 92% on room air irrespective of the cause.

Duration of Study: The treatment will be given for four cycles (28-day cycles) and up to four more cycles, if there is clinical benefit (no evidence of progression of disease). The study follow up will continue until after the last patient has progressed with myeloma. All patients will be followed for survival.

1. SCHEDULE OF EVENTS

Days	Screening days -21 to -1[1]	Cycle 1 of study q28 days[10, 11]				Cycle 2 and 3 of study q28 days[11]				Cycle 4 of study q28 days[9, 11]				Post treatment follow up phase
		D1	D2	D8	D 15	D1	D2	D8	D 15	D1	D2	D8	D 15	End of study[8]
Study entry assessments														
Informed consent	X													
Demographics	X													
Inclusion/Exclusion criteria	X	X												
Medical history	X													
Medication history	X	X				X				X				X
Physical examination	X	X				X				X				X
ECOG PS	X	X				X				X				X
Vitals[2]	X	X				X				X				X
Height and Weight[12]	X	X				X				X				X
CBC and differential	X	X		X	X	X		X	X	X		X	X	X
Serum chemistry panel[3]	X	X		X	X	X		X	X	X		X	X	X
Serum pregnancy test[4]	X													
Multiple myeloma panel[5]	X	X				X				X				X
Bone marrow aspiration and biopsy[6]	X													X
Survival[7]														X
Treatment 1[13]		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event reporting					Recorded from consent through 30 days after last dose of study drug									

Notes:

1. Screening procedures to occur up to 21 days before Cycle 1 Week 1 Visit, except for serum pregnancy test (within seven days prior to Week 1 Visit). BM aspirates and biopsies performed up to 12 weeks before Cycle 1 Week 1 Visit do not need to be repeated
2. Vital signs: blood pressure, pulse rate, respiratory rate and temperature.
3. Serum chemistries panel: Including albumin, total protein, total bilirubin, ALT, AST, LDH, alkaline phosphatase, bicarbonate, sodium, potassium, chloride, creatinine, BUN and glucose.
4. Females of reproductive potential only.
5. Multiple myeloma panel includes serum protein electrophoresis and immunofixation, 24-hour urine protein electrophoresis and immunofixation, serum-free light chains, quantitative immunoglobulins. For patients who do not have measurable disease in the urine (involved light chain <200 mg/24 hours) at screening, 24-hour urine protein electrophoresis and immunofixation are only to be performed as clinically indicated or to confirm complete remission.
6. Bone marrow aspirate and/or biopsy and cytogenetics will be performed as clinically indicated during the trial.

7. Follow-up will be every eight weeks for the first year or until disease relapse/progression and every 12 weeks for the second year or until disease relapse/progression.
8. Perform end-of-study procedures four weeks after study completion or at time of early withdrawal. If study procedure cannot be performed on the scheduled day, the procedure must be performed within 48 hours.
9. The treatment will be given for a total of four cycles and will be given for four more cycles if response is demonstrated (SD or better). Subsequent cycles will follow the same treatment format and schedules, when performed.
10. Multiple myeloma panel does not need to be repeated at Cycle 1, if the screening panel was performed within one week prior to Cycle 1 Day 1. All other screening assessments performed within 72 hours prior to Cycle 1 Day 1 do not need to be repeated.
11. For all cycles, Day 1 exam, disease and lab assessments may be performed up to 72 hours prior to Day 1. For all cycles and dose dates, a treatment window of $\pm$ 1 day is allowed to accommodate holidays and scheduling conflicts.
12. Height and weight to be performed at screening and follow-up. Weight to be performed on Day 1 of each cycle.
13. Treatment will be as follows: Bendamustine on days 1 and 2, Ixazomib on days 1, 8, and 15, and Dexamethasone on days 1, 8, and 15.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
$5\text{-}HT_3$	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
Ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	Benzodiazepines
CBC	complete blood count
CFR	Code of Federal Regulations
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system

Abbreviation	Term
CO_2	carbon dioxide
CR	complete remission
CRM	continual reassessment method
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	Cradiovascular
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus

Abbreviation	Term
HNSTD	highest nonseverely toxic dose
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression) Progressive disease
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen

Abbreviation	Term
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

2. BACKGROUND AND STUDY RATIONALE

2.1 Scientific Background

2.1.1 Disease Under Treatment

Multiple Myeloma is a neoplastic plasma cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein in the blood or urine and associated organ dysfunction (1). As a result of the development of novel anti-myeloma agents, autologous stem cell transplantation and the supportive care there has been significant improvement in the survival of patients with multiple myeloma (2-4). Multiple myeloma still remains an incurable disease despite advances in these treatment modalities in the recent years (1). The standard of treatment involves induction with novel agents followed by autologous stem cell transplant. Multiple studies have shown that with current induction, there is 35-60% in vGPR or better response rates. Irrespective of induction agents, there is response augmentation of 20% after the autologous stem cell transplantation (3, 5, 6). The median progression free survival with this strategy is more than 50 months and 5 year overall survival is less than 40%. Despite these the great majorities of patients relapse and need effective second line or further therapies. There are few effective salvage regimens available for patients with disease resistant to novel agents. The available options include bortezomib retreatment resulting in the response rates of 40% (7). Lenalidomide and dexamethasone has shown significant improvement in overall response rate (ORR 60.6% vs. 21.9%, $p< 0.001$) complete response rate (CR 15% vs. 2%, $p<0.001$) and median overall survival (OS, 38 m vs. 31.6 m, $p=0.045$) when compared to dexamethasone alone (8).

Bendamustine in Multiple myeloma:

Bendamustine is a bifunctional mechlorethamine derivative with alkylating and anti-purine activities (9). Bendamustine with prednisone in previously untreated multiple myeloma patients had comparable ORR with melphalan and prednisone; however, significantly higher number of patients achieved CR in bendamustine group (32% vs. 13%; $p=0.007$) (10). Bendamustine has shown very promising results in both Phase1 and 2 studies in patients with relapsed/refractory multiple myeloma. In a Phase 1 study, bendamustine at maximum tolerated dose of 100mg/m^2 resulted in ORR of 55% in patients with relapsed multiple myeloma after autologous SCT (11). In a similar group of patients, bendamustine at a lower dose (60mg/m^2), when combined with thalidomide and prednisone, resulted in ORR of 86% (12) . Combination of bendamustine (at MTD of 75 mg/ m^2) with lenalidomide (10 mg/d) and dexamethasone in Phase1/2 study resulted in ORR of 76% (13). There are two Phase1/2

studies looking at the combination of bendamustine with bortezomib in patients with relapsed/refractory multiple myeloma. In one study, 36 patients with relapsed/refractory multiple myeloma and light chain induced renal failure were treated with bendamustine (60mg/m^2), bortezomib (1.3 mg) and prednisone, which resulted in ORR of 67%(14). Similarly, in another Phase I study, 79 patients with relapsed /refractory multiple myeloma were treated with bendamustine (70 mg/^{m2}), bortezomib (1.3 mg/^{m2}) resulted in the ORR of 75.9% (15). Bendamustine, in combination with immunmodulators (IMIDs) or proteasome inhibitor, is active in patients with relapsed/refractory multiple myeloma. *In this study, we seek to improve the efficacy of bendamustine by combining the novel proteasome inhibitor IXAZOMIB (MLN9708) to bendamustine and dexamethasone in patients with relapsed/refractory multiple myeloma.*

2.1.2 Ixazomib (MLN9708)

2.2 Preclinical Experience

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

2.3 Clinical Experience

Ixazomib has been evaluated as an oral single agent in Phase 1 studies that included patients with advanced solid tumors, lymphoma, relapse/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent **IXAZOMIB** and **IXAZOMIB** in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, two Phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating **IXAZOMIB** in combination with Revlimid and Dexamethasone (RevDex) versus placebo/RevDex. Both trials are combining **IXAZOMIB** at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies include evaluation of drug-drug interactions with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetic (PK) of **IXAZOMIB** alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of NDMM are ongoing.

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that **IXAZOMIB** is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations included nausea, thrombocytopenia, diarrhea and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or Phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of antiemetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to **IXAZOMIB**, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to **IXAZOMIB**, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%) and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50%

of patients and is more common when **IXAZOMIB** is given in combination with lenalidomide where rash is an overlapping toxicity.

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

2.4 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that **IXAZOMIB** citrate (measured as the biologically active boronic acid form of **IXAZOMIB** [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by four hours. Oral **IXAZOMIB** citrate is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration (T_{max}) of approximately 0.5 to 2.0 hours and a terminal disposition half-life ($t_{1/2}$) after multiple dosing of approximately 5 to 7 days (16). 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 (17). Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for **IXAZOMIB** using the population PK analysis. Please refer to the current **IXAZOMIB** IB and Safety Management Attachment (SMA) for information on the PK for IV doses of **IXAZOMIB**.

Metabolism appears to be the major route of elimination for **IXAZOMIB**, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that **IXAZOMIB** is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the five major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for **IXAZOMIB** treatment to produce drug-drug interactions (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 or inducer because of the potential for first-pass metabolism when **IXAZOMIB** is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of **IXAZOMIB** in human liver microsomes. Ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and

MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

2.5 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma) have been treated in studies evaluating the oral **IXAZOMIB** formulation. These patients have been treated with different doses of **IXAZOMIB** either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

Table 2-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
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[a]: 4.0 mg fixed (switched to fixed dosing in Phase 2, equivalent to 2.23mg/m^2) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose[a] W
C16010 RRMM N = 200	PO, W, with LenDex versus placebo-LenDex	4.0 mg W
C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W
C16013 RRMM N = 9	PO, W, with LenDex	4.0 mg W

Table 2-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16014 Symptomatic MM N=701	PO, combination with LenDex	**IXAZOMIB** 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=28	PO, combination with Dex	Part A: **IXAZOMIB** 3.0 mg on Day 1 Part B: **IXAZOMIB** 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle
C16017 RR follicular lymphoma N=58	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45	Part A: PO, Day 1 of 15-day cycle Part B: PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
TB-MC010034 RRMM N = 10	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

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

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

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

Overview of the Oral Formulation of Ixazomib

The emerging safety profile indicates that **IXAZOMIB** is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In the four ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral **IXAZOMIB** in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of **IXAZOMIB** 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 **IXAZOMIB** Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 2-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	IV Studies[a] N = 146	Oral Studies[b] N = 491	Total N = 637
General disorders and administration site conditions	**118 (81)**	**363 (74)**	**481 (76)**
Fatigue	89 (61)	223 (45)	312 (49)
Pyrexia	45 (31)	112 (23)	157 (25)
Oedema peripheral	31 (21)	122 (25)	153 (24)
Asthenia	10 (7)	74 (15)	84 (13)
Nervous system disorders	**87 (60)**	**272 (55)**	**359 (56)**
Dizziness	25 (17)	85 (17)	110 (17)
Headache	31 (21)	74 (15)	105 (16)
Neuropathy peripheral	17 (12)	81 (16)	98 (15)
Metabolism and nutrition disorders	**89 (61)**	**267 (54)**	**356 (56)**
Decreased appetite	56 (38)	120 (24)	176 (28)
Dehydration	25 (17)	61 (12)	86 (14)
Hypokalaemia	11 (8)	57 (12)	68 (11)
Blood and lymphatic system disorders	**88 (60)**	**256 (52)**	**344 (54)**
Thrombocytopenia	65 (45)	161 (33)	226 (35)
Anaemia	28 (19)	114 (23)	142 (22)
Neutropenia	16 (11)	103 (21)	119 (19)
Lymphopenia	16 (11)	61 (12)	77 (12)

Table 2-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Skin and subcutaneous tissue disorders	**84 (58)**	**255 (52)**	**339 (53)**
Rash (all terms)	73 (50)	197 (40)	270 (42)
Rash maculo-papular	21 (14)	60 (12)	81 (13)
Rash macular	15 (10)	56 (11)	71 (11)
Musculoskeletal and connective tissue disorders	**78 (53)**	**249 (51)**	**327 (51)**
Back pain	27 (18)	88 (18)	115 (18)
Arthralgia	17 (12)	72 (15)	89 (14)
Pain in extremity	21 (14)	66 (13)	87 (14)
Respiratory, thoracic and mediastinal disorders	**87 (60)**	**228 (46)**	**315 (49)**
Cough	32 (22)	94 (19)	126 (20)
Dyspnoea	31 (21)	80 (16)	111 (17)
Infections and infestations	**48 (33)**	**244 (50)**	**292 (46)**
Upper respiratory tract infection	12 (8)	94 (19)	106 (17)
Psychiatric disorders	**32 (22)**	**151 (31)**	**183 (29)**
Insomnia	14 (10)	89 (18)	103 (16)

Source: Ixazomib Investigator's Brochure Edition 8

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug.
A subject counts once for each preferred term and system organ class. Percentages use the number of treated subjects as the denominator.
[a] Studies C16001 and C16002.
[b] Studies C16003, C16004, C16005, C16006, C16007, C16008, C16009, C16013, C16015, C16017, C16018, and TB-MC010034.

As of 13 April 2015, there are 12 studies actively enrolling patients with multiple myeloma to investigate oral **IXAZOMIB** in combination with standard combination regimens.

The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 2-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Subjects with at Least One Adverse Event	163 (94)
Gastrointestinal disorders	139 (80)
Nausea	65 (38)
Diarrhoea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Oedema peripheral	61 (35)
Asthenia	20 (12)
Nervous system disorders	115 (66)
Headache	28 (16)
Dizziness	34 (20)
Neuropathy peripheral	45 (26)
Metabolism and nutrition disorders	91 (53)
Decreased appetite	25 (14)
Hypokalaemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anaemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular[a]	29 (17)
Rash macular[a]	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)
Dyspnoea	26 (15)

Table 2-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

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

Data from ongoing blinded pivotal trials (C16010) are not included.

a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

The clinical experience with **IXAZOMIB** 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 **IXAZOMIB**, when combined with established therapies, and across the malignancies studied (advanced solid tumors (18), non-Hodgkin's disease, Hodgkin's disease (19), relapsed and/or refractory multiple myeloma [RRMM; (20, 21)], relapsed or refractory systemic light chain amyloidosis [RRAL;(22)], and newly diagnosed multiple myeloma [NDMM; (23-25)]) to date.

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

2.6 Relapsed and/or Refractory Multiple Myeloma

The early development of **IXAZOMIB** in patients with RRMM involves two studies (C16003 and C16004) with similar objectives, but each investigated one of the two dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE.

Study C16003 is an open-label, dose escalation, Phase 1 study of **IXAZOMIB** dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.((26, 27)) Study C16004 is an open-label, dose escalation, Phase 1 study of **IXAZOMIB** dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults

patients with RRMM.((28-30)) Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting and erythema multiforme.

In the dose escalation component of both studies, patients had multiple myeloma that had relapsed following at least two lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were to be enrolled into one of four expansion cohorts, including a relapsed and refractory cohort, a carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a VELCADE-relapsed cohort.

Final study results are currently being analyzed, but preliminary data suggest that **IXAZOMIB** has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated. Please refer to the **IXAZOMIB** IB and SMA for further information.

2.7 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating **IXAZOMIB** in combination with agents commonly used across treatment settings. The development of **IXAZOMIB** in combination with lenalidomide with dexamethasone (LenDex) in patients with NDMM who are transplant eligible or ineligible involves two studies (C16005 and C16008) with similar study designs except for a few key differences, namely the schedules of **IXAZOMIB** and dexamethasone. Ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

All 3 studies are Phase 1/2, with Phase 1 focusing on safety and Phase 2 on efficacy (and further characterization of safety). Please refer to the **IXAZOMIB** IB and SMA for further information.

2.8 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

See the IB for descriptions of the two studies that investigated IV **IXAZOMIB** in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

2.9 Study Rationale

Despite very good response with the novel agents, great majorities of patients with multiple

myeloma relapse and need effective second line or further therapies. There are few effective salvage regimens available for patients with disease resistant to novel agents. The available options include bortezomib retreatment resulting in the response rates of 40%. Lenalidomide and dexamethasone has shown significant improvement in overall response rate (ORR 60.6% vs. 21.9%, p< 0.001) complete response rate (CR 15% vs. 2%, p<0.001) and median overall survival (OS, 38 m vs. 31.6 m, p=0.045) when compared to dexamethasone alone (8). Bendamustine is a bifunctional mechlorethamine derivative with alkylating and anti-purine activities (9). Bendamustine with prednisone in previously untreated multiple myeloma patients had comparable ORR with melphalan and prednisone; however, significantly higher number of patients achieved CR in bendamustine group (32% vs. 13%; p=0.007) (10). Bendamustine has shown very promising results in both Phase1 and 2 studies in patients with relapsed/refractory multiple myeloma. In Phase 1 study, bendamustine at maximum tolerated dose of 100mg/m^2 resulted in ORR of 55% in patients with relapsed multiple myeloma after autologous SCT (11). In a similar group of patients, bendamustine at a lower dose (60mg/m^2) when combined with thalidomide and prednisone resulted in ORR of 86% (12). Combination of bendamustine (at MTD of 75 mg/m^2) with lenalidomide (10 mg/d) and dexamethasone in Phase1/2 study resulted in ORR of 76% (13). There are two Phase1/2 studies looking at the combination of bendamustine with bortezomib in patients with relapsed/refractory multiple myeloma. In one study, 36 patients with relapsed/refractory multiple myeloma and light chain induced renal failure were treated with bendamustine (60mg/m^2), bortezomib (1.3 mg) and prednisone, which resulted in ORR of 67%(14). Similarly, in another Phase I study. 79 patients with relapsed /refractory multiple myeloma were treated with bendamustine (70 mg/m^2), bortezomib (1.3 mg/ m^2) resulted in the ORR of 75.9% (15). Bendamustine, in combination with immunmodulators (IMIDs) or proteasome inhibitor, is active in patients with relapsed/refractory multiple myeloma. In this study, we seek to improve the efficacy of bendamustine by adding **IXAZOMIB** (MLN9708) to bendamustine and dexamethasone in patients with relapsed/refractory multiple myeloma. It is worthwhile to look into the new proteasome inhibitor in combination with bendamustine in relapsed/refractory multiple myeloma. In this study, we seek to combine bendamustine with **IXAZOMIB** (MLN9708), a new proteasome inhibitor in patients with relapsed/refractory multiple myeloma.

2.10 Potential Risks and Benefits

Please refer to the current **IXAZOMIB** IB and SMA.

The clinical benefit of **IXAZOMIB** continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated, as well as those with newly diagnosed MM. It prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of **IXAZOMIB** for the treatment of patients with advanced malignancy.

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

We anticipate additional risks of nausea, diarrhea, cytopenias especially thrombocytopenia, in addition to neuropathy and hepatotoxicity when **IXAZOMIB** (MLN9708) is used in combination with bendamustine.

Rationale for combining Proteasome inhibitor with Bendamustine/Dexamethasone:

The BVD (bendamustine/VELCADE and dexamethasone) combination was able to induce a rapid and high response rate (almost 70%) in a recent study by Rodon et al (31). This compares favorably with those achieved with bortezomib-dexamethasone, showing an ORR between 50% and 54.6% or with lenalidomide-dexamethasone. The best options for future treatment of relapsed MM are likely to consist of triplet combinations, which have, up to now, been reported in only few Phase 3 trials. Ludwig reported the results of 8 cycles of BVD combination in patients with relapsed MM. The ORR was 61%, and a PFS of 10 months, even allowing for the inclusion of patients previously exposed to bortezomib, previously treated with ASCT, and having received more than 1 prior line of therapy (15). Offidani et al. evaluated the BVD regimen in patients treated with ASCT as part of frontline therapy, patients previously exposed to bortezomib,and patients who had experienced more than 1 relapse. The ORR (71.5%) reported by Offidani is identical to the one in study by Rodon et al., while the median PFS was longer (15.5 months) (32). These compare extremely favorably with recently approved agents in this setting — Carfilzomib and pomalidomide. With the widespread use of MPT in frontline in elderly patients and, in the future of Len-Dex, the results by Rodon et al. obtained in a homogenous population of

patients treated at the time of first relapse, suggest that bendamustine, in combination with proteasome inhibitor, could form the basis for future studies.

3. STUDY OBJECTIVES

3.1 Primary Objectives

Phase I -To determine the maximum tolerated dose of the combination of **IXAZOMIB** (MLN9708) and bendamustine plus dexamethasone in patients with relapsed/refractory multiple myeloma.

Phase II - To determine the objective response rate (ORR) after four cycles of **IXAZOMIB (**MLN9708) and bendamustine plus dexamethasone.

3.2 Secondary Objectives

To determine the overall survival (OS) of patients treated with oral **IXAZOMIB** (MLN9708) and bendamustine plus dexamethasone

To determine the progression free survival (PFS) of patients treated with oral **IXAZOMIB** (MLN9708) and benadmustine plus dexamethasone.

To determine the cumulative response rates in patients after 8 cycles.

To determine the duration of response(DoR).

To determine the minimal residual disease status(MRD) in patients who achieve a complete response at the end of the study.

4. STUDY END POINTS

4.1 Primary end point:

MTD of bendamsutine when combined with **IXAZOMIB** plus dexamethasone up to maximum bednamustine dose of 90 mg/m^2.

ORR: CR + PR (IMWG response criteria, Appendix 12.3)

4.2 Secondary end points:

PFS: Measured as time from enrollment to progression of myeloma or death. Patients surviving without progression will be censored at the last follow up.

OS: Measured as time from enrollment to death from any cause.

Cumulative response rate and duration of response

Minimal residual status (MRD)

5. STUDY DESIGN

5.1 Overview of Study Design

This is a Phase I/II, single-arm, open-label, study evaluating the efficacy and safety of the combination of **IXAZOMIB**, bendamustine, and dexamethasone in subjects with relapsed or refractory multiple myeloma, who have previously been treated with proteasome inhibitors or immunomodulators either alone or both. Phase I portion of the study will look into the safety of combination of bendamustine and MLN9708. Subject participation will include a screening period, treatment period, and a follow-up period. The treatment period for all subjects will extend from the first dose of study drug combination on Day 1 Cycle 1 until the completion of four cycles of therapy or up to 8 cycles if a response is observed, PD, unacceptable AE, decision by the subject or by the investigator to discontinue treatment, or death.

On days when more than one study drug is administered, MLN9708 before bendamustine. When possible, dexamethasone should be given prior to MLN9708, as this may lessen the experience of nausea. Subjects will be assigned to a single treatment arm which will consist of:

- Ixazomib initially administered as 4 mg oral on days 1 ,8 and 15 of each 28 day cycle.
- Bendamustine administered after Ixazomib on Days 1 and 2 of each cycle at 70mg/ m^2, 80 mg/^{m2} or 90 mg/m^2 IV during the Phase I portion of the study, and at the MTD or a maximum dose of 90 mg/m^2 IV during the Phase II portion of the study.
- Dexamethasone administered as 40 mg oral or IV on Days 1, 8, 15 of each 28 day cycle. At physician discretion, patients may be reduced to a minimum of 20 mg.

A 3+3 design will be employed. At each dose three patients will be initially evaluated. If no dose limiting toxicities are observed, the bendamustine dose will be increased; if one dose limiting toxicity is observed, three additional patients will be treated at that dose and

escalation will occur only if no additional DLTs are observed. A dose at which 2 DLTs are observed in three or six patients will be judged to be too toxic and the lower dose will be defined as the maximally tolerated dose (MTD).

Should the first dose combination be found to be too toxic, **IXAZOMIB** (MLN9708) would be deescalated to 3 mg oral, days 1, 8 and 15 (with bendamustine at 70 mg/m^2). If this were safe, the bendamustine dose will then be escalated to 80 mg/m^2 and then 90 mg/m^2 days 1 and 2 if found safe. No intra-patient dose escalation is permitted.

DLT observation period will be one cycle from the first dose of MLN9708 and bendamustine on Cycle 1 Day 1 to 28 days after the first dose or the start of Cycle 2. Dose escalation to higher dose level will require the last patient on the previous dose level to be out of DLT observation period.

Once acceptable doses for the combination are identified, the plan is to treat additional patients at the maximally tolerated doses to assess response to treatment.

Phase 2 study:

A Simon 2-stage design will be used for the Phase 2 portion of the study. The study will enroll 14 patients (including those treated at the MTD in Phase I) and continue enrollment only if the observed response rate is at least 28.6% (4/14); If enrollment continues, the study will treat an additional 5 patients (19 in total) and consider the combination “interesting” only if at least 6/19 patients (31.6%) achieve a response.

The study will terminate for futility if there is no objective partial response once 11 patients have been treated at recommended Phase 2 dose (3 up to 6 in Phase I and 5 up to 8 in Phase II).

DSMC will have authority to stop study for any unexpected adverse events during the entire course of the study. During the phase 2 portion of the study, in the event of development of Garde 3-5 non-hematological toxicity in 6 or more (out of 19) patients, the study will be suspended. The DSMC will be asked to review the Grade 3-5 events and their attribution to trial intervention and make a final determination of safety. This would suspend the study 16% of the time when the true rate of Grade 3-5 non-hematological toxicity was 20% but 92% of the time if the true rate was 45%.

Summary of the schedule is as follows:

Cycle (28 days)	Cycle 1 of Study	Cycles 2,3 and 4 of study
Dexamethasone	D1,8,15	D1,8,15
Bendamustine	D1, D2	D1,D2
IXAZOMIB (MLN9708)	D 1, 8, 15	D 1, 8, 15

5.2 Dose Escalation Rules

Dose escalation will proceed as follows:

• If 0 of 3 subjects at a dose level experiences a DLT, dose escalation will proceed, and 3 subjects will be treated at the next dose level.

• If 1 of 3 subjects experiences a DLT, up to 3 more subjects will be enrolled at the same dose level.

• If 1 of 6 subjects experiences a DLT, dose escalation will proceed and 3 subjects will be treated at the next dose level.

• If 2 or more subjects experience a DLT, the prior dose level will be considered the MTD, and the Phase 2 portion of the study will begin at that dose level. However, if 2 or more subjects experience a DLT at the 70 mg/m² dose of bendamustine, then MLN9708 would be deescalated to 3 mg, days 1, 8 and 15 (with bendamustine at 70 mg/m^2). If this is safe, the bendamustine dose will then be escalated to 80 mg/m^2 and then 90 mg/m^2 days 1 and 2 if found safe.

• If the MTD is not achieved, the Phase 2 portion of the study will proceed at 90 mg/m² dose level and 4 mg dose of Ixazomib level which will be considered the recommended Phase 2 dose(RP2D).

• There will be no intrapatient dose escalation

The study team will provide the results from each dosing cohort to the DSMC for review. The study will not enroll any additional patients until the last patient on the previous dose level is out of the DLT observation period and the DSMC has reviewed the cohort's results.

5.3 Number of Patients

A maximum sample size of 28 patients will be enrolled.

After Phase 1 is completed and a recommended Phase 2 dose established, if there are no objective responses in the first 14 pts treated at recommended Phase 2 dose (including those treated at these doses in Phase 1) the study will be terminated for futility.

DSMC will have authority to stop study for any unexpected adverse events during the entire course of the study.

5.4 Duration of Study

The treatment will be given for 4 cycles (28 d cycles) and up to 4 more cycles if there is clinical benefit (stable disease or better). The study follow up will continue until after the last patient has progressed with myeloma. All patients will be followed for survival.

6. STUDY POPULATION

6.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.

2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3. Female patients who:

   - Are postmenopausal for at least 1 year before the screening visit, OR

   - Are surgically sterile, OR

   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR

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

Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following:

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

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

4. Patients must have histologically or cytologically confirmed symptomatic Multiple Myeloma. They must be non-responsive to or ineligible for autologous stem cell transplant, and must progress after prior exposure to both proteasome inhibitor (bortezomib, carfilzomib) and IMID (lenalidomide or pomalidomide or thalidomide); and refractory/progressing to at least one of the agents and must meet at least one of the following parameters of measurable disease:

    - Measurable levels of monoclonal protein (M protein): > 1 g/dL of IgG or IgM M-protein or > 0.5 g/dL IgA or IgD M protein on serum protein electrophoresis OR > 200 mg/24h of free light chain proteinuria on a 24 hour urine protein electrophoresis which must be obtained within 4 weeks prior to registration OR > 10 mg/dL involved free light chain on serum free light chain testing with an abnormal kappa:lambda light chain ratio.

    - Patients with lytic bone disease, defined as at least one lytic lesion that can be accurately measured in at least one dimension.

5. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.

6. Patients are eligible after autologous or allogeneic stem cell transplantation. Allogeneic transplantation can be enrolled only if they have no ongoing transplant related side effects. (No GVHD or treatment for GVHD).

7. Patients must be at least 2 weeks from major surgery, radiation therapy, participation in other investigational trials and have recovered from clinically significant toxicities of these prior treatments
8. Patients must meet the following clinical laboratory criteria:

    - Absolute neutrophil count (ANC) ≥ 1,000/mm^3 and platelet count ≥ 75,000/mm^3. Platelet transfusions or G-CSF can be used to help patients meet eligibility criteria but are not allowed within 3 days before study enrollment.

    - Total bilirubin < 1.5 × the upper limit of the normal range (ULN)), OR direct bilirubin within normal limits (WNL), when total bilirubin is >1.5 x the ULN.

    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 × ULN.

    - Calculated creatinine clearance ≥ 30 mL/min.

6.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating or have a positive serum pregnancy test during the screening period.

2. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy except for peripheral neuropathy, which is addressed in exclusion criteria no. 14.

3. Major surgery within 14 days before enrollment.

4. Radiotherapy within 14 days before enrollment. If the involved field is limited (single disease focus not involving pelvis and involving <36 Gy radiation), 7 days will be considered a sufficient interval between treatment and administration of Ixazomib provided hematologic inclusion parameters are met.

5. Myeloma-related central nervous system involvement.

6. Serious infection within 14 days of study treatment start and has not clinically resolved.

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

8. Systemic treatment, within 14 days before the first dose of **IXAZOMIB**, 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.

9. Active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

10. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

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

12. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of **IXAZOMIB** including difficulty swallowing.

13. Diagnosed or treated for another malignancy where the expected surbvival is less than 2 years will be excluded. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

14. Patient has ≥ Grade 2 peripheral neuropathy, or Grade 1 with pain on clinical examination during the screening period.

15. Participation in other clinical trials, including those with other investigational agents not included in this trial, within two weeks of the start of this trial and throughout the duration of this trial.

16. Patients that have previously been treated with **IXAZOMIB**, or participated in a study with **IXAZOMIB** whether treated with **IXAZOMIB** or not.

17. Patients with a history of severe chronic obstructive pulmonary disease requiring ongoing oxygen support or those with a resting oxygen saturation <92% on room air irrespective of the cause.

7. STUDY DRUG

7.1 Description of Investigational Agents

Ixazomib Capsules

The **IXAZOMIB** drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg and 2.0-, 0.5-, and 0.2 mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink
2.0 mg	Size 2	Swedish orange
0.5 mg	Size 3	Dark green
0.2 mg	Size 4	White opaque

7.2 Study Drug Administration

7.2.1 Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of **IXAZOMIB** should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of **IXAZOMIB** dose (see Section 6.3).

Capsules of **IXAZOMIB** will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 0.2-, 0.5-, and 2.0 mg, or as capsules of 2.3-, 3.0- and 4.0 mg **IXAZOMIB**.

The prescribed administration of **IXAZOMIB** doses in this study is 4mg **IXAZOMIB** in a day 1,8 and 15 cycle.

Patients should be instructed to swallow **IXAZOMIB** capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach. . . Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

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.

Ixazomib Destruction

Investigational **IXAZOMIB** (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.

7.2.2 Bendamustine:

Source and Pharmacology:

Bendamustine (Treanda) is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is cytotoxic in both quiescent and dividing cells.

Bendamustine hydrochloride for injection (Treamda) was the initial formulation used in the study and was available in individual cartons containing amber 8-mL or 20-mL single-use vials. T

In December 2015, the FDA approved a new formulation of Bendamustine (Bendeka Injection). Bendeka is a low-volume and short-time infusion (10 minutes) formulation of bendamustine. It was approved by the Food and Drug Administration based on pharmacokinetic equivalence to the previous available formulation (Treanda). In a pharmacokinetic study, a single IV dose of Bendeka (bendamustine hydrochloride) Injection

(120 mg/m2; administered as a 10 minute infusion), resulted in a higher maximum plasma concentration (Cmax) and equivalent systemic exposure (AUC), compared to a single dose of Treanda (120 mg/m2) infused over 60 minutes.

Since Bendamustine for this study was obtained commercially, the Treanda formulation was used initially. However, with the availability of the new formulation and commercial phasing out of Treanda, the study will switch over to using the newer Bendeka formulation. This formulation is supplied as a 100mg/4mL strength solution multi-dose vials and will obtained commercially. Bendamustine and will not be supplied by the study supporter.

The amount of drug to be administered will be based on BSA calculated using the Mosteller formula. The same BSA will be used for each dose calculation unless the subjects experiences a >10% change in body weight from the weight used for the most recent BSA calculation.

Storage and Stability

BENDEKA (bendamustine hydrochloride) Injection should be stored in refrigerator, 2° to 8°C (36° to 46°F). Bendamustine should be stored in the original containers until the time of use in order to protect the drug from light. Bendamustine contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration. Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) in room light. Drug administration should be completed within the established periods of stability for the admixed solution.

Solution Preparation and Dispensing

Bendamustine hydrochloride for injection is intended for intravenous infusion only after reconstitution. Please follow the reconstitution instructions in the package insert of bendamustine (Bendeka). The volume needed for the required dose should be aseptically withdrawn from the 25 mg/mL solution and immediately transferred to a 50 mL infusion bag of the diluent. The resulting final concentration of bendamustine hydrochloride in the infusion bag should be within 1.85 mg/mL – 5.6 mg/mL. After transferring, thoroughly mix

the contents of the infusion bag. The admixture should be a clear, and colorless to yellow solution

Adverse Effects: Please refer to package insert

Hematologic: neutropenia (Grade 3 or 4 neutropenia in up to 25% of treated patients), thrombocytopenia infrequently requiring transfusions, and anemia.

Infections: increased risk of infections (e.g., pneumonia) and sepsis have been reported following treatment with bendamustine.

Infusion reactions and anaphylaxis: have been reported commonly in clinical trials with symptoms including fever, chills, pruritis, and rash. Rare reports of anaphylactic or anaphylactoid reactions have occurred.

Tumor lysis syndrome: reported in several patients treated with bendamustine, primarily during the first cycle of therapy.

Skin reactions: reported reactions include rash, toxic skin reactions, and bullous exanthema

Elevated LFT's: reported increase in total bilirubin and transaminases in up to 30% of patients in some clinical trials.

Gastrointestinal: frequent reporting of nausea, vomiting, and stomatitis.

Frequent adverse events: asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis; nausea, vomiting, and diarrhea. Hematologic toxicity is very frequent including Grade 3 and 4 neutropenia and thrombocytopenia. Mild elevation of liver function tests (total bilirubin and transaminases).

Less common adverse events: hypersensitivity reactions, skin eruptions, fevers, chills, hypertension, pyrexia, and neutropenic infection.

Nursing/patient implications

Patients require close monitoring during the first infusion for evidence of hypersensitivity reaction, which is an uncommon but serious side effect with bendamustine.

Hematologic toxicity is the primary dose-limiting toxicity, and hematologic nadirs should be expected in the third week of therapy.

Infection, including pneumonia and sepsis, have been reported following treatment with bendamustine, usually in combination with myelosuppression.

Patients with myelosuppression need education regarding monitoring for signs of fever or infection.

Prophylaxis for tumor lysis syndrome should be considered in patients with high tumor burden, or elevated uric acid and/or LDH.

Patients should be educated on supportive measures for management of nausea, vomiting, diarrhea, constipation, and stomatitis.

7.2.3 Dexamethasone:

Source and Pharmacology: Dexamethasone is a synthetic fluorinated glucocorticoid devoid of mineralocorticoid effects. Dexamethasone, 0.75 mg, has potent anti-inflammatory activity equivalent to approximately 5 mg of prednisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Elimination half-lives for the following age groups have been reported to be: infants and children under 2 years of age: 2.3 to 9.5 hours, 8 to 16 years: 2.82 to 7.5 hours, and adults (age not specified): 3 to 6 hours. The biologic half-life is 36- 72 hours. It is primarily metabolized in the liver and excreted by the kidneys.

Formulation and Stability:

Available in 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg tablets; liquid formulations are available in 0.5 mg/5 mL and 0.5 mg/0.5 mL concentration. Inactive

ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, and various dyes. Liquid formulations may include: 5%-30% alcohol, benzoic acid, sorbitol, sodium saccharin, glycerin, purified water, and various dyes. Dexamethasone Sodium Phosphate Solution for Injection is available as 4 mg/mL, 10 mg/mL, 20 mg/mL and 24 mg/mL. Four milligrams of dexamethasone sodium phosphate is equivalent to 3.33 mg of dexamethasone. Vial sizes include 1 mL, 5 mL, 10 mL, 25 mL, and 30 mL and are available in multi-dose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium and propyl paraben, benzyl alcohol, and EDTA.

Guidelines for Administration:

See Treatment and Dose Modifications section of the protocol.

Commercially available from various manufacturers. See package insert for further information

Adverse effects:

Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, cardiomyopathy, CHF, circulatory collapse, edema, hypertension, myocardial rupture (post-MI), syncope, thromboembolism, vasculitis

Central nervous system: Depression, emotional instability, euphoria, headache, intracranial pressure increased, insomnia, malaise, mood swings, neuritis, personality changes, pseudotumor cerebri (usually following discontinuation), psychic disorders, seizure, vertigo

Dermatologic: Acne, allergic dermatitis, alopecia, angioedema, bruising, dry skin, erythema, fragile skin, hirsutism, hyper-/hypopigmentation, hypertrichosis, perianal pruritus (following I.V. injection), petechiae, rash, skin atrophy, skin test reaction impaired, striae, urticaria, wound healing impaired

Endocrine & metabolic: Adrenal suppression, carbohydrate tolerance decreased, Cushing's syndrome, diabetes mellitus, glucose intolerance decreased, growth suppression (children), hyperglycemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary-adrenal axis suppression, protein catabolism, sodium retention

Gastrointestinal: Abdominal distention, appetite increased, gastrointestinal hemorrhage, gastrointestinal perforation, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, weight gain

Genitourinary: Altered (increased or decreased) spermatogenesis

Hepatic: Hepatomegaly, transaminases increased

Local: Postinjection flare (intra-articular use), thrombophlebitis

Neuromuscular & skeletal: Arthropathy, aseptic necrosis (femoral and humoral heads), fractures, muscle mass loss, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents), neuropathy, osteoporosis, parasthesia, tendon rupture, vertebral compression fractures, weakness

Ocular: Cataracts, exophthalmos, glaucoma, intraocular pressure increased

Renal: Glucosuria

Respiratory: Pulmonary edema

Miscellaneous: Abnormal fat deposition, anaphylactoid reaction, anaphylaxis, avascular necrosis, diaphoresis, hiccups, hypersensitivity, impaired wound healing, infections, Kaposi's sarcoma, moon face, secondary malignancy

7.2.4 Definition of MTD:

The MTD is defined as the highest dose of bendamustine, up to a maximum of 90 mg/m², in combination with **IXAZOMIB** and dexamethasone that causes DLT during Cycle 1 in 0 of 3 or 0 to 1 of 6 subjects.

7.2.5 Definition of Dose-limiting toxicity:

Toxicity will be evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0(CTCAEv4). DLT observation period will be one cycle, from the first dose of MLN9708 and bendamustine on cycle 1 day 1 to 28 days after the first dose or the start of cycle 2. Dose escalation to higher dose level will require the last patient on the previous dose level to be out of DLT observation period.

Dose limiting toxicity will be defined as any of the following events that are considered, by the investigator, to be related to therapy with bendamustine and **IXAZOMIB**:

• Grade 4 neutropenia (ANC <500 cells/mm3) lasting more than 7 consecutive days

• Grade 3 neutropenia with fever and/or infection, where fever is defined as an oral temperature ≥38.5°C

• Platelet count <10,000/mm3 or Grade 4 thrombocytopenia (platelet count <25,000/mm3) lasting more than 7 days or Grade 3 thrombocytopenia with clinically significant bleeding

• Grade 3 or greater nausea and/or emesis despite the use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-HT3 antagonist given in standard doses and according to standard schedules.

• Grade 3 or greater diarrhea that occurs despite maximal supportive therapy with loperamide or comparable antidiarrheal agents

• Any other Grade 3 or greater nonhematologic toxicity

• Treatment delay of more than 1 week because of a lack of adequate hematologic or nonhematologic recovery of drug-related toxicities experienced in the previous cycle of treatment.

• Other treatment-related nonhematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require a dose reduction or discontinuation of therapy in Cycle 1.

7.3 Dose-Modification Guidelines

If the first dose of study drug in a cycle is missed due to study-drug-related toxicity or another reason, the start of the cycle is delayed and the next dose will be considered Day 1 of that cycle. All efforts should be made to deliver all study drugs on the specified schedule. If one or more of the drugs must be delayed during a cycle for study-drug-related toxicity or another reason, they must be delivered within 3 days of the scheduled dose; otherwise the dose must be skipped. Subsequent doses during the cycle should remain on schedule based on Day 1 of the cycle. For example, if the Cycle 2, Day 8 dose of **IXAZOMIB** cannot be administered on the scheduled day, it must be delivered no later than Day 11, or it must be skipped. If the Cycle 2, Day 8 dose is delayed to Day 11, the subsequent dose of **IXAZOMIB** should be delivered on Cycle 2, Day 15, as previously scheduled. If a dose is not given, all assessments should be completed and the dose noted as missed.

Bendamustine and Ixazomib:

On the first day of each new treatment cycle and before each **IXAZOMIB**, or bendamustine dose, the subject will be evaluated for possible toxicities that may have occurred after the previous doses(s). Toxicities are to be assessed according to the CTCAEv4.

Any toxicity that requires a treatment delay of more than 2 weeks from the scheduled startof a given cycle will result in the discontinuation of **IXAZOMIB**, bendamustine and dexamethasone. See Table 7-1

Dosage adjustments for hematologic toxicity are outlined in Table 7-1a and 7-1b.

Table 7-1a Ixazomib and Bendamustine Dose Adjustments for Hematologic Toxicities

Criteria	Action
<u>Within-Cycle Dose Modifications</u>	
• If platelet count ≤ 30×10^9/L or ANC ≤ 0.50×10^9/L on a **IXAZOMIB** dosing day (other than Day 1)	• Study treatment should be withheld. • Complete blood count (CBC) with differential should be repeated until the ANC and/or platelet counts have exceeded the prespecified values on at least 2 occasions. • Upon recovery, bendamustine may be reinitiated with 1 dose level reduction and upon recurrence of same toxicity lower **IXAZOMIB** dose to 1 dose level.
<u>Dose Modifications for Subsequent Treatment Cycles</u>	
• Delay up to 2 weeks in the start of a subsequent cycle due to lack of related toxicity recovery • ANC < 1.0×10^9/L, platelet count < 75×10^9/L, related to the investigational agent(s) or other related nonhematologic toxicities > Grade 1 or not to the patient's baseline condition	• Hold both drugs until resolution • Upon recovery, reduce bendamustine first and then **IXAZOMIB** to 1 dose level. • The maximum delay before treatment should be discontinued will be > 2 weeks or at the discretion of the PI.
<u>Dose Modifications for Subsequent Treatment Cycles</u>	
• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle: o If dose was reduced for bendamustine or **IXAZOMIB** within the cycle, start the next cycle at that lowered dose. o If due to toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce **IXAZOMIB** only by 1 dose level at the start of that cycle. o Do not reduce the dose both within a cycle and at the start of the cycle next cycle for the same toxicity.

Table 7-1b Criteria for Related Hematological and Nonhematological Recovery

	To Start a New Cycle (Day 1)	To Redose Within a Cycle (Days 8 and 15)
ANC	ANC must be ≥ 1,000/mm3	ANC must be ≥ 500/mm3
Platelet	Platelet count must be ≥ 75,000/mm3	Platelet count must be ≥ 30,000/mm3
Nonhematological	All other nonhematologic toxicities (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition	Neuropathy must be ≤ Grade 1 (with no pain) Other nonhematologic toxicities should be < Grade 3.

Abbreviation: ANC = absolute neutrophil count.

Treatment modifications due to IXAZOMIB and bendamustine-related AEs are outlined in Table 7-2.

Table 7-2 Ixazomib and Bendamustine Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only (29)
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold **IXAZOMIB** alone until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) (29)
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold **IXAZOMIB** alone until resolution to Grade ≤ 1 without pain or baseline • Reduce **IXAZOMIB** to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated (29)
New or worsening Grade 4 peripheral neuropathy	• Discontinue **IXAZOMIB**	
Grade 2 Rash	• Symptomatic recommendations as per section 7.7	Stevens Johnson Syndrome is a contraindication to further Ixazomib use.

Table 7-2 Ixazomib and Bendamustine Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Grade 3 Rash	• Hold **IXAZOMIB** until resolution to < Grade 2 along with symptom management (first occurrence) • For second or subsequent occurrence of rash dose reduce Ixazomib by one dose level when restarting.	Non resolving Grade 3 rash or any Grade 4 rash will need skin biopsy and stoppage of Ixazomib use.
Nausea, emesis, or diarrhea with maximal prophylaxis ≥Grade 3	• Hold bendamustine and **IXAZOMIB** for up to 2 weeks or until the toxicity returns to ≤Grade 2, and restart at the next lower dose of benadmustine. If treatment is delayed by more than 2 weeks, bendamustine and **IXAZOMIB** must be discontinued. Additional dexamethasone is not permitted as an antiemetic.	
Grade ≥3 nonhematologic toxicity . If not recovered to < Grade 1 or baseline within 4 weeks	• Determine attribution of toxicity. Hold appropriatey attributed agent until resolution to Grade < 1 or baseline • Reduce attributed therapy to next lower dose upon return to < Grade 1 or baseline	Symptomatic recommendations noted in Section 6.7
Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 4 weeks	• Hold attributed therapy until resolution to Grade < 1 or baseline • Reduce attribiuted therapy to next lower dose level	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 nonhematologic toxicities judged to be related either bendamutine or **IXAZOMIB** or both	• Consider permanently discontinuing the drug attributed to cause toxicity	Exceptions are cases in which the investigator determines the patient is obtaining a significant clinical benefit and toxicity has declined to

Table 7-2 Ixazomib and Bendamustine Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
		Grade 2

7.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted in this study. (A drug-drug interaction [DDI] with a strong inhibitor would increase the **IXAZOMIB** and bendamustine exposure and could lead to a higher probability of an AE.):

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

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: Unlike with inhibitors, if there were to be a DDI with an inducer, **IXAZOMIB** exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off **IXAZOMIB**):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba

The following procedures are prohibited during the study.

- Any antineoplastic treatment, including the antihormonal drugs other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression). Patients may be enrolled into a study 2 weeks after

finishing the radiation if they meet eligibility criteria. Study therapy can be interrupted for up to 3 weeks to allow for radiation to symptomatic plasmacytomas/ lytic lesion.

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

7.5 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

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

- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion. **Note additional dexamethsaone is not permitted in the treatment of these symptoms.**

- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice. Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.

- 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.

- Concomitant treatment with bisphosphonates will be permitted, as appropriate.

- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

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

- Prophylaxis for tumor lysis syndrome for high risk is permitted.

7.6 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Pregnancy

It is not known what effects **IXAZOMIB** has on human pregnancy or development of the embryo or fetus. Bendamustine has been assigned to pregnancy category D by FDA. Animal studies have revealed skeletal and visceral malformations (exencephaly, cleft palates, accessory rib, and spinal deformities), decreased fetal body weights, a significant increase in external and internal malformations, as well as embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. There are no controlled data in human pregnancy. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients who:

- Are postmenopausal for at least one year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following:

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

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

7.7 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with **IXAZOMIB** treatment. Infusion reactions and tumor lysis syndrome have been reported with bendamustine. Management guidelines regarding these events are outlined below. Further details of management of **IXAZOMIB** AEs are described in Table 7-2.

Prophylaxis Against Risk of Reactivation of Herpes Infection

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

Nausea and/or Vomiting

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

Diarrhea

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

Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with **IXAZOMIB**, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular

bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of **IXAZOMIB** should be modified per protocol (see Table 7.1).

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

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib and bendamustine administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 7-1). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has

been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib and bendamustine administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 7-1). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

Fluid Deficit

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

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with **IXAZOMIB**. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with **IXAZOMIB**. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors. Further Ixazomib is contraindicated.

Transverse Myelitis

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

Progressive Multifocal Leukoencephalopathy (PML)

One fatal case of progressive multifocal leukoencephalopathy (PML) has been reported with MLN9708 in an oncology patient who had previously received a medication associated with PML. PML is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. It is not known whether MLN9708 may have contributed to the development PML in this patient.

Infusion Reactions (Bendamustine)

Infusion reactions to Bendamsutine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Patients who experience Grade 3 or worse allergic-type reactions should not be rechallenged. Consider measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids in subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions. Discontinue bendamustine for patients with Grade 4 infusion reactions. Consider discontinuation for Grade 3 infusions reactions as clinically appropriate considering individual benefits, risks, and supportive care.

Tumor Lysis Syndrome (Bendamustine)

Tumor lysis syndrome associated with bendamustine treatment has occurred in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol should be used during the beginning of bendamustine therapy in those at high risk for tumor lysis. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly.

7.8 Preparation, Reconstitution, and Dispensing

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

7.9 Packaging and Labeling

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

7.10 Storage, Handling, and Accountability

Ixazomib:

Upon receipt at the investigative site, **IXAZOMIB** should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

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

Bendamustine:

Bendamustine vials should be stored at room temperature (20−25°C [68−77°F]) and protected from light. Bendamustine is stable for 30 months when stored at normal room temperature conditions, 15°C to 30°C (59−86°F). Bendamustine is a cytotoxic anticancer agent and should be handled according to the recommended procedures described in the current edition of the American Society of Health-System Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling cytotoxic drugs.

Dexathemasone:

Dexamethasone should be stored according to commercial labeling guidelines.

7.11 Study Compliance

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

7.12 Termination of Treatment and/or Study Participation

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 patients will be allowed to complete 4 cycles of treatment only (or 8 cycles if any evidence of clinical benefit, SD or better). The

investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Lost to follow-up
- Progressive disease
- Study terminated
- Other

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

8. STUDY PROCEDURES:

8.1 Study procedures:

The Study Flow Chart in Schedule of events summarizes the study procedures to be performed at each required study visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigators.

8.1.1 Administrative procedures:

8.1.1.1 Informed consent:

The investigator must obtain documented informed consent from each potential subject prior to participating in clinical trial.

8.1.1.2 Inclusion/Exclusion criteria:

The inclusion and exclusion criteria will be during screening (up to 21 days before the first dose of study drug). Subjects must continue to meet all eligibility criteria on Day 1 of cycle 1.

8.1.1.3 Demographics:

Subject demographics will be documented during screening and at minimum, will include subject birth date,race and sex.

8.1.1.4 Medical History:

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease (multiple myeloma), for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

8.1.1.5 Medication history:

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before the enrollment. Treatment for the disease (multiple myeloma) for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication. The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 10.

8.1.1.6 Disease (Multiple Myeloma) details and treatments

1. Disease Details

The investigator or qualified designee will obtain prior and current details regarding multiple myeloma status. See Appendices for Multiple Myeloma response criteria.

2.Prior Treatment Details

The investigator or qualified designee will review all prior multiple myeloma treatments including systemic treatments, radiation and surgeries.

8.1.1.7 Study compliance

Subjects will be followed for compliance to allowed concomitant medications and other activity restriction according to section

8.1.2 Clinical Procedures/Assessments

8.1.2.1 Adverse event monitoring(AE) monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs and more frequently if clinically indicated.

Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

8.1.2.2 Physical examination

The investigator or qualified designee will perform a complete physical exam during the screening and other required study visits. Clinically significant abnormal findings should be recorded as medical history.

8.1.2.3 Vital signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of MLN 9708 and bendamustine and at treatment discontinuation. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure.

8.1.2.4 Eastern Co-operative Oncology group(ECOG) group performance scale

The investigator or qualified designee will assess ECOG status (see Appendices) at screening, prior to the administration of each dose of MLN9708 and bendamustine, discontinuation of both drugs and post study visits as specified in the Schedule of events.

8.1.2.5 Multiple myeloma assessment

Multiple myeloma assessment includes peripheral blood and urine quantification of monoclonal protein including serum protein electrophoresis (SPEP), serum immunofixation (IFIX), serum free light chain levels, urine protein electrophoresis (UPEP) and 24-hour urine Bence-Jones protein quantification, and bone marrow examination. These will be performed as specified in the schedule of events. A skeletal bone survey may be completed as clinically indicated.

8.1.3 Other procedures:

Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/ withdrawal should be followed in accordance with the safety requirements outlined in Section 10.- Assessing and Recording Adverse Events. Subjects who complete four cycles of MLN9708 and bendamustine will be considered having completed the study treatment.

After discontinuing treatment, these subjects, if possible, should return to the site for a Safety Follow-up Visit (8.1.4.5) and then proceed to the Follow-Up Period of the study (described in Section 8.1.4.6). Subject will be replaced if he/she drops out in the Phase I portion of study prior to completing the dosing for DLT.

8.1.4 Study definitions

8.1.4.1 Screening

A subject will be considered to be in the "Screening" period from the time he/she signs consent until the date the subject is determined as either "eligible" or "ineligible" (screen failure) by PI or a Co-I. Patients may be consented to this study based on disease eligibility and other criteria at the time of consent, but later removed from the study prior to initiation of MLN9708 and bendamustine if the change of disease status makes the subject "ineligible". In the event that this occurs, the subject will be replaced when the eligibility is again checked on day 1 cycle 1.

8.1.4.2 Enrolled

A subject will be considered to be "Enrolled" onto the study once they have signed consent AND have successfully met all screening criteria, as documented by the inclusion/exclusion document, AND the eligibility criteria has been reviewed and accepted by the PI or a co-I. The date of enrollment will be documented as the date that the PI or a co-I has reviewed and approved the subject's eligibility.

8.1.4.3 Treatment Period

The "Treatment Period" is defined as the first day through the last day of treatment with **IXAZOMIB** (MLN9708) and bendamsutine from first through the fourth cycle (or up to 4 more cycles in responders).

The assessment and reporting period for adverse events (AE) related to the **IXAZOMIB** (MLN9708) and bendamsutine will start from the first dose of each drug administration until 30 days after the last dose administration.

8.1.4.4 On Study

The "On Study period" starts from the day that a subject signs the protocol consent document and subsequently meets the protocol eligibility criteria ("Enrolled"), receives **IXAZOMIB** (MLN 9708) and bendamsutine treatment (8 cycles) and ends 30 days after the last dose of both drugs or prior to this period if one of the following event occurs earlier:

1. Death
2. Lost to follow-up
3. Withdrawal of consent
4. Entry on to a competing trial
5. Multiple myeloma progression/relapse and its treatment or development of new malignancy and its treatment
6. Unacceptable or dose limiting toxicity or complication

Thirty days after the last dose of both drugs, the patient will be considered "off treatment." But they will be followed for the primary and secondary endpoints off treatment until 2 years as mentioned in "Follow Up Period".

8.1.4.5 Post treatment safety follow up visits

The "follow-up period" is defined as the first day a subject is no longer receiving IXAZOMIB (MLN9708) and bendamustine until three years after this date.

The mandatory "end-of-treatment safety follow-up visit" will be performed approximately 30 days after the last dose of IXAZOMIB (MLN9708) and bendamustine or before the

initiation of a new anti-MM treatment, whichever comes first. All AEs that occur prior to the safety follow-up visit should be recorded.

Subjects with an AE of grade >1 will be followed until the resolution of the AE to grade 0-1 or until the beginning of a new anti-MM therapy, whichever occurs first.

SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-MM treatment should also be followed and recorded.

8.1.4.6 Survival follow up

After the "end-of-treatment safety evaluation visit," subjects will be followed for two years. Subjects who have stopped therapy for reasons other than MM relapse/progression will be followed every eight weeks (+/- 2 weeks) for directed follow-up visits for one year or until MM relapse/progression. Subjects will be further followed every 12 weeks (+/- 2 weeks) for the second year or until MM relapse/progression. Once a subject experiences confirmed MM relapse/progression or starts a new anti-MM therapy, the subject moves into the survival follow-up phase and should be contacted (by site visit or telephone) every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

In addition, new primary malignancies that occur during the follow-up period must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose. At the end of year three, study staff will review patient medical records or will contact the patient via telephone to obtain this information regarding possible new primary malignancies.

9. STATISTICAL AND QUANTITATIVE ANALYSES

9.1 Statistical Methods

The section describes the statistical methods to be used to analyze the safety and efficacy as described above in the objectives. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before the database lock. The SAP will include how the variables will be derived, how missing data will be handled and how censoring procedures will be applied for time to event related variables as well as the details on the statistical methods to be used for safety and efficacy analysis. The final clinical study report will discuss deviations from the SAP, if any.

9.2 General considerations

This Phase I/II study is designed to first identify doses of **IXAZOMIB** (MLN9708) and bendamustine when delivered together in 28 day cycles with an acceptable adverse event profile and then to assess the efficacy of the combination in patients with relapsed/refractory multiple myeloma. Responders (stable disease or more), will continue to recieve up to 8 cycles total in the absence of further progressive disease.

9.3 Determination of sample size

This trial will enroll up to 28 patients in total. The actual number of dose cohorts explored will depend upon the safety profile. In the Phase II portion of the study about 19 patients will be treated to look for the response rate.

Simon's 2-stage design allows for early termination of enrollment when there is evidence that a drug or drug combination's anti-tumor activity is too low. The trial is conducted in two stages with an option to stop the trial and not recommend the agent/combination for further development after the first stage. For specified null and alternative hypotheses, significanc3e (α) level and power ($1-\beta$) to detect the alternative hypothesis, a Simon 2-stage design minimizes the expected total sample size when the true response is the null hypothesis response rate.

A Simon 2-stage design for a null response rate of 20%, an alternative response rate of 40%, a significance level less than 15% and power of at least 80%, a Simon 2-stage design is:

Enroll 14 patients (including those treated at the MTD in Phase I) and continue enrollment only if the observed response rate is at least 28.6% (4/14);

If enrollment continues, treat an additional 5 patients (19 in total, including those treated at the MTD in Phase 1) and consider the combination worthy of further development only if at least 6/19 patients (31.58%) achieve a response.

If the true response rate is 20%, the combination would be declared worthy of further development only 14.7% of the time. If the true response rate is 40%, the combination would be declared worthy of further development 80.7% of the time.

These rules mean that the study could be terminated for futility in Phase 2 after 14 patients have been treated at recommended Phase 2 dose (including 6 patients in Phase 1 and 8 in Phase 2), if no objective partial responses are observed.

DSMC will have authority to stop study for any unexpected adverse events during the entire course of the study. During the phase 2 portion of the study, in the event of development of Grade 3-5 non-hematological toxicity in 6 or more (out of 19) patients, the study will be suspended. The DSMC will be asked to review the Grade 3-5 events and their attribution to trial intervention and make a final determination of safety. This would suspend the study 16% of the time when the true rate of Grade 3-5 non-hematological toxicity was 20% but 92% of the time if the true rate was 45%.

A secondary assessment of response will be made excluding those patients who withdraw from protocol therapy without progression from the response assessment.

9.4 Statistical analysis

All statistical analysis will be performed using SAS 9.2 or higher.

9.4.1 Demographics and Baseline characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics for continuous variables, and frequencies and percentages for categorical variables.

9.4.2 Safety analysis

The safety analysis will include all patients who received any study medication. The safety end points will include:

- Incidence of DLTs
- Incidence of AE and AEs considered to be drug related
- Incidence of grade 3 and grade 4 AEs
- Incidence of SAEs
- Laboratory values

The safety analysis will be listed and/or summarized by dose cohort. No inferential statistics will be performed.

All patients who received at least one dose bendamustine and **IXAZOMIB (**MLN9708) will be included in the safety analysis.

The analysis of safety will be based on the frequency of adverse events and their severity for patients in each portion who received at least one dose of study treatment. Worst toxicity grades per patient will be tabulated for select adverse events and laboratory measurements by using NCI CTCAE criteria v4.0.

9.4.3 Efficacy analysis

Two populations will be used in the efficacy analysis, Intent to treat (IIT) and per protocol (PP) populations. The IIT population will include all safety population who provide efficacy assessment, and PP population will include all IIT population without major protocol violations.

The efficacy end points will include:

- Overall response rate(ORR)
- Duration of response

These variables will be analyzed /summarized based on the IIT population as well as PP population as appropriate. The percentages of CR, CR+PR, CR+PR+SD will be presented, as will the median duration of response. The 95% confidence intervals of these percentages will also be presented.

Additional analysis will be performed like

Overall survival (OS)

Progression free survival (PFS)

The primary goal of the Phase II portion of the study is to assess whether the combination identified in Phase I has sufficient anti-tumor activity to warrant further evaluation of the combination. The primary endpoint will be response assessed after 4 cycles of treatment, with patients experiencing progressive disease prior to the completion of 4 cycles classified as non-responders. For the primary assessment of response, any subject who withdraws from protocol treatment prior to completion of 4 cycles of treatment without progression would also be classified as a non-responder.

The 4-cycle response rate (at least partial response) for patients with relapsed/refractory multiple myeloma is about 20%. A true 4-cycle response rate of 40% for the combination of **IXAZOMIB** (MLN9708) and bendamustine would be considered interesting and worthy of

further study. A Simon 2-stage design (see Simon R. Optimal two-stage designs for Phase II clinical trials. Controlled Clinical trials. 10:1-10, 1989) is proposed for the Phase II portion of this study.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event Definition

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

An abnormal laboratory value less than grade 2 lab abnormality will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.2 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- as a substantial disruption of a person’s ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.

- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Reporting Serious Adverse Events

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of **IXAZOMIB**. Any SAE that occurs at any time after completion of **IXAZOMIB** treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator

considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

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

Since this is an investigator-initiated study, the principal investigator Parameswaran Hari also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

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

> **Fatal and Life Threatening SAEs** within 24 hours of the sponsor-investigator's observation or awareness of the event
>
> **All other serious (non-fatal/non life threatening) events** within 4 calendar days of the sponsor-investigator's observation or awareness of the event

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

The sponsor-investigator must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a

guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

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

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 the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

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

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

SAE and Pregnancy Reporting Contact Information

Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

Suggested Reporting Form:

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

10.3 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (provided by Millennium)

11. ADMINISTRATIVE REQUIREMENTS

11.1 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 TAKEDA Quality representative.

For Product Complaints,
• Phone: 1-877-TAKEDA7 (1-877-825-3327) • E-mail: medicalinformation@tpna.com • FAX: 1-800-247-8860 • Hours: Mon-Fri, 8 a.m. – 6 p.m. ET

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

11.2 Data safety monitoring:

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data Safety Monitoring Committee (MCW CC DSMC). The DSMC reviews the research

protocol, informed consent documents and plans for safety and data monitoring. The DSMC will review interim data to detect evidence of efficacy or adverse effects to determine if the trial should continue as originally designed, should be changed or should be stopped based on the data. A copy of the MCW CC Data and Safety Monitoring Plan is attached to the protocol and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study **PI twice annually (or more frequently if needed)** and provide recommendations on trial continuation, suspension or termination as necessary. Since this study is performed under an FDA IND application, the principal investigator will submit individual adverse event reports and IND safety reports to the FDA per FDA regulations CFR 21 Part 312.

As per the Data Safety Monitoring Plan, the DSMC will:

- review interim analysis, if applicable, and determine specific data to be analyzed
- evaluate end point/stop point rules
- review protocol violations and deviations to assess adequacy of study
- enrollment
    - followed eligibility criteria
    - enrollment numbers
    - visit compliance
    - screening failure information
- review IND/IDE information
- discuss investigator or key personnel changes
- evaluate the aggregate analysis of adverse events/serious adverse events.

DSMC Meeting Outcome - The major outcomes following data review include:

- continuing the trial unchanged
- modify the protocols and/or consent form (It may be unethical to continue giving a placebo after a new treatment has been proven to be effective or to continue a new treatment when there is no chance the trial will be positive.)
- terminate the trial

A summary of the MCW CC DSMC responsibilities are as follows: • Review the clinical trial for data integrity and safety

• Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.) Review all DSM reports

• Submit a summary of any recommendations related to study conduct

• Terminate the study if deemed unsafe for patients

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

11.3 Clinical trials management system

Ongoing Study Management:

The study will use the OnCore CTMS for collection and management of data from the Participating Institutions.

Electronic Case Report Forms and Source documents will be entered and uploaded in the OnCore CTMS. Source Documents will include all documents that verify the data collected for eCRF's, AE's and SAE's. (this is only if needed – we will keep a shadow chart here, so the language about source documents can be deleted).

Ongoing Communication with Participating Institution Research Staff

The study staff will receive OnCore CTMS training from the MCW OnCore CTMS Administrator.

11.4 Monitoring

The Cancer Center Clinical Trials Office (CCCTO) is committed to a risk-based and objective-based approach to Quality Assurance reviews to maximize the efficiency and merit of trial oversight. All studies will have the initial Internal Quality Assurance (IQA) Review within the first 3 months of the first subject enrolled on trial. Trials are categorized as low risk, intermediate risk, or high risk at the discretion of the CCCTO Quality Assurance staff. This study has been categorized as High Risk by the MCW Cancer Center Quality Assurance Staff. High Risk studies will be reviewed as follows:

- The study will be reviewed biannually by the MCW Cancer Center Quality Assurance Staff.
- 30% of subject files will be selected randomly for review (max 10 subjects at each

monitoring timepoint).

- Consent, eligibility, adherence to the treatment plan and objective based data will be reviewed for those files selected
- 1 file will be selected randomly for a comprehensive review at each monitoring timepoint.

A letter/report will be provided to the study staff and the DSMC after each IQA review. Necessary corrective action or training will be provided to the staff as needed throughout and following each IQA review. Directed audits may be requested at any time by the CCCTO QA Staff, DSMC, Research Manager, IRB, study staff member, or administrative staff.

12. REFERENCES

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13. APPENDICES

13.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

13.2 Cockcroft-Gault Equation

For males:

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

For females:

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

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

13.3 Response criteria in Multiple myeloma

CR: Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed.

sCR: CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flowcytometry; two consecutive assessments of laboratory parameters are needed.

vGPR: Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component <100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed.

PR: ≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h. If serum and urine M protein are not measurable, ≥50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria. If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥30%. In addition, if present at baseline, ≥50% reduction in size of soft tissue plasmacytomas is required. Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies.

SD: Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed.

PD: Increase of 25% from lowest response value in any of following: Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or; Urine M component (absolute increase must be ≥200 mg/24 h) and/or; Only in patients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) .Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas. Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder. Two consecutive assessments before new therapy are needed.

Source: Paulmbo et al. Journal Of Clinical Oncology 2014; 32:587-600 for International Myeloma Working group.

13.4 Enrollment Worksheet

PI: Parameswaran Hari

Protocol#24991

Phase I/II Study Of Bendamustine And Ixazomib (MLN9708) Plus Dexamethasone In Relapsed/Refractory Multiple Myeloma

Enrollment Worksheet

Subject Name:

Subjects DOB:

Subjects MR#:

Subjects ID #:

Bendamustine: _____mg/m2- Days 1,2 every 28 days

MLN9708: 4mg- Days 1,8,15 every 28 days

Dexamethasone: 40mg Days 1,8,15 every 28 days

Please email a copy of the signed patients consent (signature page) with this enrollment form to IDS when patient has been enrolled in study.

_____

Name of Principal Investigator or Authorized Representative (please print)

_____

Signature of Principal Investigator or Authorized Representative

_____Date