CLINICAL STUDY PROTOCOL

A Phase I/II Study of PiC-D (Ixazomib in Combination with Pomalidomide, Clarithromycin and Dexamethasone) in Patients with Relapsed or Refractory Multiple Myeloma

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

PROTOCOL SIGNATURE PAGE

Protocol Number: UCDCC#253

Protocol Title: A Phase I/II Study of PiC-D (Ixazomib in Combination with Pomalidomide, Clarithromycin and Dexamethasone) in Patients with Relapsed or Refractory Multiple Myeloma

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

_____
Date

PROTOCOL SUMMARY

Study Title: A Phase I/II Study of PiC-D (Ixazomib in Combination with Pomalidomide, Clarithromycin and Dexamethasone) in Patients with Relapsed or Refractory Multiple Myeloma

Phase: I/II

Number of Patients: Up to 52

Phase I: Up to 12

Phase II: 40 (including patients in Phase I that received the Phase II dose)

Study Objectives:

Phase I Primary Objectives

- To establish the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) for PiC-D therapy (pomalidomide, ixazomib, clarithromycin and dexamethasone) in patients with multiple myeloma who are proteasome inhibitor and lenalidomide pretreated.

Phase I Secondary Objectives

- To evaluate the safety and tolerability of PiC-D therapy.
- To characterize the pharmacokinetics (PK) in plasma of oral ixazomib in combination with pomalidomide, clarithromycin and dexamethasone
- To assess preliminary evidence of clinical activity.
- To assess the effects of PiC-D therapy on quality of life (QOL).
- To assess the effects of PiC-D therapy on immune status (phenotypic analysis and cytokine profiling) in future research.

Phase II Primary Objectives

- To determine the Complete Response (CR) and stringent CR (sCR) rate for PiC-D therapy in patients with multiple myeloma who are proteasome inhibitor and lenalidomide pretreated.

Phase II Secondary Objectives

- To evaluate the safety of PiC-D therapy.

- To determine the Overall Response Rate (ORR: CR, sCR, Partial Response (PR), and Very Good Partial Response (VGPR)).
- To determine the Clinical Benefit Rate (CBR: Minimal Response (MR) + ORR).
- To determine the Disease Control Rate (DCR: Stable disease (SD) + CBR).
- To determine the Duration of Response (DOR) in patients achieving a PR or better.
- To determine the Time to Next Treatment (TNT).
- To determine progression free survival (PFS) and overall survival (OS).
- To assess the effects of PiC-D therapy on quality of life (QOL).

Phase II Correlative Objective

- To assess the effects of PiC-D therapy on immune status (phenotypic analysis and cytokine profiling) in future research.

Overview of Study Design:

This is a Phase I/II, non-randomized, open label, study in patients with relapsed or refractory multiple myeloma to evaluate the safety and efficacy of PiC-D therapy (pomalidomide, ixazomib, clarithromycin and dexamethasone).

The Phase I portion of the study will utilize a 3+3 dose escalation design to determine the maximum tolerated dose (MTD) of clarithromycin in combination with ixazomib, pomalidomide, and dexamethasone. One clarithromycin dose levels are planned (250 mg BID on Days 1-21), with an additional cohort for de-escalation (250 mg QD on Days 1-21) if unacceptable toxicity occurs at the first dose level, for a total of up to 12 patients.

Once the recommended phase 2 dose (RP2D: based on the MTD) of clarithromycin has been determined, the Phase II portion of the study will be initiated. The Phase II portion of the study will utilize the Simon's optimal 2-stage design to determine the complete response (CR) and stringent CR (sCR) rate of PiC-D therapy

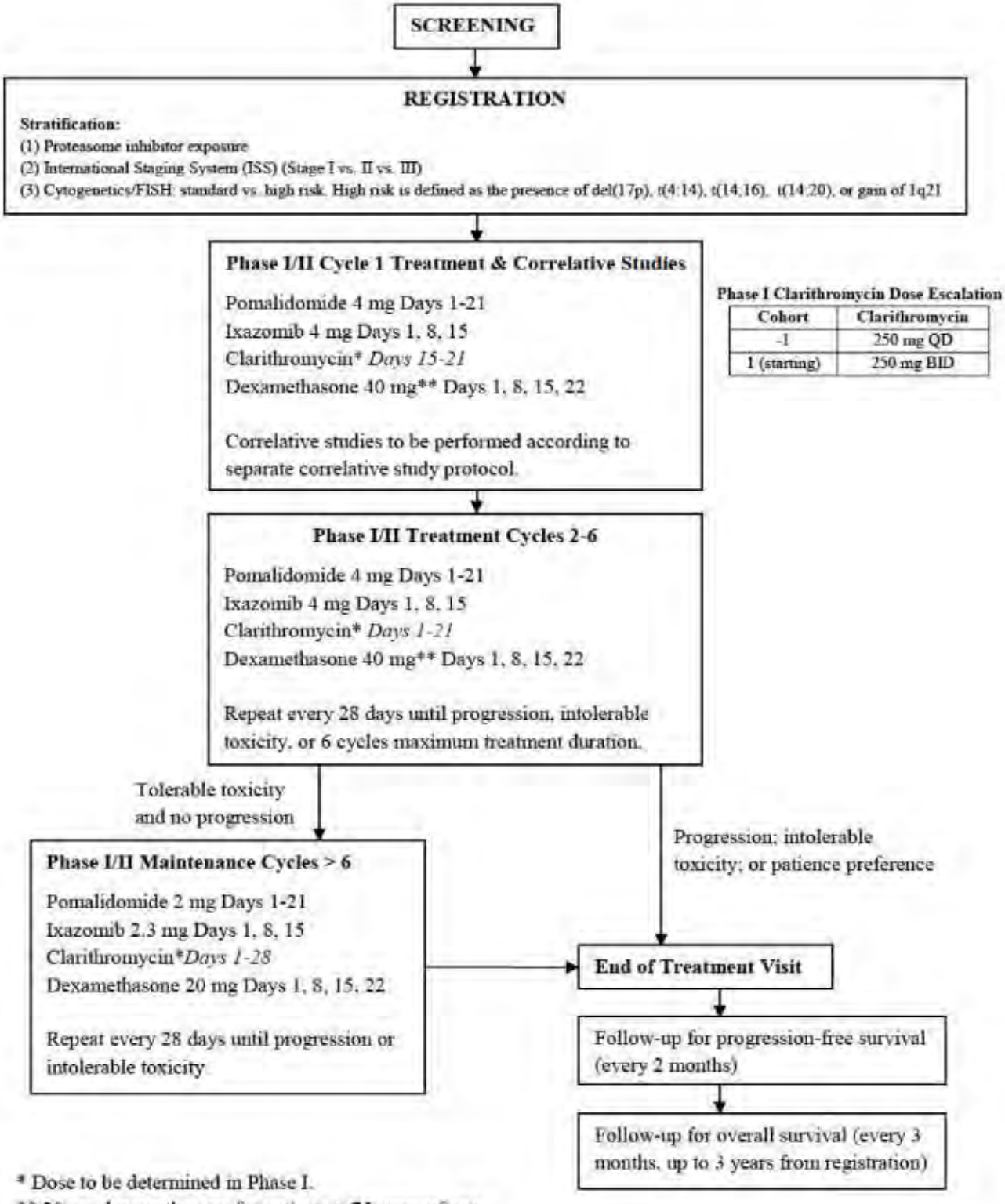
Study Population:

Adult patients with biopsy-confirmed diagnosis of multiple myeloma that have proteasome inhibitor and lenalidomide pretreated disease, defined as progression while on therapy or within 6 months of coming off therapy with both agents either sequentially or concurrent, and who meet all other eligibility criteria will be enrolled in this study.

Duration of Study:

Accrual: 24 months
Follow-up: 36 months

STUDY OVERVIEW DIAGRAM



* Dose to be determined in Phase I.
** 20 mg dexamethasone for patients > 75 years of age.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the plasma concentration versus time Curve
BCRP	Breast Cancer Resistance Protein
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CL	Clearance
C_{max}	single-dose maximum (peak) concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CYP	Cytochrome P_{450}
DDI	Drug-Drug Interaction
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	United States Food and Drug Administration
FLC	Free Light Chain
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
HIV	Human Immunodeficiency Virus

Abbreviation	Term
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IMiD	Immunomodulatory Drug
IRB	Institutional Review Board
IV	Intravenous; intravenously
IMWG	International Myeloma Working Group
ISS	International Staging System
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	Multiple Myeloma
MR	Minimal Response
MRI	Magnetic Resonance Imaging
MRP2	Multidrug Resistance associated Protein
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	Newly Diagnosed Multiple Myeloma
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PD	Progressive Disease (disease progression)
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	Partial Response
QD	*quaque die*; each day; once daily
QOL	Quality of Life
RP2D	Recommended Phase 2 Dose
RRMM	Relapse/Refractory Multiple Myeloma
SAE	serious adverse event
sCR	Stringent Complete Response
SD	Stable Disease
SMA	Safety Management Attachment
$t_{1/2}$	terminal disposition half-life
TEAE	Treatment Emergent Adverse Event

Abbreviation	Term
T_{max}	single-dose time to reach maximum (peak) concentration
TNT	Time to Next Treatment
TTP	Thrombotic Thrombocytopenic Purpura
ULN	Upper Limit of the Normal range
VGPR	Very Good Partial Response
WBC	white blood cell

1. BACKGROUND AND STUDY RATIONALE

1.1 Overview of Multiple Myeloma

Multiple myeloma (MM) is a disseminated malignant proliferation of plasma cells and plasmacytoid cells at multiple sites in the bone marrow and is characterized by secretion of abnormal immunoglublins (Igs) [Palumbo 2011]. The age-adjusted incidence in the United States (US) is 5.4/100,000 and is comparable to that of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL; 5.7/100,000). According to the Surveillance Epidemiology and End Results (SEER) database, 22,350 new cases of multiple myeloma were estimated for the US in 2013, with an estimated 10,710 deaths from the disease [SEER 2013].

The emergence of new therapies over the last decade, particularly immunomodulatory agents (IMiDs; e.g., thalidomide and lenalidomide) and proteasome inhibitors (PIs; e.g., bortezomib), has significantly improved the prognosis for patients with multiple myeloma with a recently published study estimating a current median overall survival (OS) of 6.1 years from diagnosis [Kumar 2013]. Lenalidomide, thalidomide and bortezomib have become components of frontline therapy and are being integrated into induction, consolidation and maintenance regimens (associated with frontline therapy and/or stem cell transplantation), including IMiD/bortezomib combinations (lenalidomide/bortezomib/dexamethasone and thalidomide/bortezomib/ dexamethasone). Despite high initial response rates and prolonged progression-free survival (PFS) with these regimens, almost all patients eventually relapse [Cavallo 2012]. Treatment for relapsed or refractory disease typically includes regimens that maintain IMiDs and/or PIs as a foundation.

1.2 Relapsed and Refractory Multiple Myeloma

Although the treatment for relapsed and refractory multiple myeloma includes numerous regimens, there is no proven "best" regimen or standard of care. Options are limited in patients who are dual-refractory to lenalidomide and bortezomib, and this remains an unmet medical need. Carfilzomib, a second-generation proteasome inhibitor, has demonstrated promise in this patient population. In a phase II study, 266 patients with heavily pre-treated multiple myeloma were treated with single-agent carfilzomib [Siegel 2012]. In this trial, 95% of treated patients were refractory to their last treatment regimen, 99.6% of patients had received prior bortezomib-containing therapy, 94% had received prior lenalidomide-based treatment, and 64% of patients were refractory to prior bortezomib- and lenalidomide-based therapy. Importantly, the overall response rate (ORR, or ≥ PR rate) was 23.7%, the median duration of response (DOR) was 7.8 months, progression-free survival 3.7 months, and overall survival 15.6 months. Of note, for those with lenalidomide- and bortezomib-refractory disease, the ORR and median OS were only 15.4% and 11.9 months, respectively. Novel therapies for this refractory patient population are greatly needed.

1.3 Pomalidomide and Dexamethasone

Pomalidomide, a thalidomide analogue, is an immunomodulatory agent that displays similar anti-angiogenic activity, but far greater anti-proliferative and immunomodulatory activity compared to the parent drug [Payvandi 2004]. In *in vitro* cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the in vitro umbilical cord model.

1.4 Non Clinical Toxicity

Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of 12 monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of the exposure in patients at the recommended dose of 4 mg/day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study.

Pomalidomide was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames test), the in vitro assay using human peripheral blood lymphocytes, and the micronucleus test in orally treated rats administered doses up to 2000 mg/kg/day.

In a fertility and early embryonic development study in rats, drug-treated males were mated with untreated or treated females. Pomalidomide was administered to males and females at doses of 25 to 1000 mg/kg/day. When treated males were mated with treated females, there was an increase in post-implantation loss and a decrease in mean number of viable embryos at all dose levels. There were no other effects on reproductive functions or the number of pregnancies. The lowest dose tested in animals resulted in an exposure (AUC) approximately 100-fold of the exposure in patients at the recommended dose of 4 mg/day. When treated males in this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

1.4.1 Pharmacokinetics

Absorption
Following administration of single oral doses of pomalidomide, the maximum plasma concentration (C_{max}) for pomalidomide occurs at 2 and 3 hours post-dose. The systemic exposure (AUC) of pomalidomide increases in an approximately dose proportional manner. In patients

with multiple myeloma who received pomalidomide 4 mg daily alone or in combination with dexamethasone, pomalidomide steady-state drug exposure was characterized by AUC(T) of 400 ng·h/mL and C_{max} of 75 ng/mL. Following multiple doses, pomalidomide has an accumulation ratio of 27% to 31%.

Distribution
Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours post dose (~T_{max}) after 4 days of once-daily dosing at 2 mg. Human plasma protein binding ranges from 12% to 44% and is not concentration dependent. Pomalidomide is a substrate for P-glycoprotein (P-gp).

Metabolism
Pomalidomide is primarily metabolized in the liver by CYP1A2 and CYP3A4. *In vitro*, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6.

Elimination
Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with multiple myeloma. Pomalidomide has a mean total body clearance (CL/F) of 7-10 L/h.

Following a single oral administration of [^{14}C]-pomalidomide (2 mg) to healthy subjects, approximately 73% and 15% of the radioactive dose was eliminated in urine and feces, respectively, with approximately 2% and 8% of the radiolabeled dose eliminated unchanged as pomalidomide in urine and feces.

1.4.2 Clinical Experience Multiple Myeloma

In 2013, pomalidomide was approved by the United States Food and Drug Administration (FDA) for the treatment of relapsed/refractory myeloma patients that have failed at least two prior therapies including lenalidomide and bortezomib.

Pomalidomide was initially shown to have high activity when combined with low-dose dexamethasone in 38 patients with previously treated and/or refractory multiple myeloma with an overall response rate of 63% [Lacy 2009]. Toxicity consisted primarily of myelosuppression, with grade 3 or 4 anemia (5%), thrombocytopenia (3%), and neutropenia (32%).
A phase 2, multicenter, randomized open-label study assessed the safety and efficacy of pomalidomide and low-dose dexamethasone in patients with relapsed multiple myeloma that were refractory to their last myeloma therapy and had received lenalidomide and proteasome

inhibitor [Richardson 2014]. A total of 221 patients were randomized to receive pomalidomide 4 mg, once daily for 21 of 28 days, until disease progression, alone and in combination with low-dose dexamethasone (40 mg/day given only on Days 1, 8, 15, and 22 of each 28-day cycle for patients aged 75 years or younger, or 20 mg/day given only on Days 1, 8, 15, and 22 of each 28-day cycle for patients aged greater than 75 years). In the pomalidomide alone group or pomalidomide combined with low-dose dexamethasone, median progression free survival (PFS) was 4.2 and 2.7 months (hazard ratio = 0.68, P = .003), overall response rates (ORR) were 33% and 18% (P = .013), median response duration was 8.3 and 10.7 months, and median overall survival (OS) was 16.5 and 13.6 months, respectively. Refractoriness to lenalidomide or resistance to both lenalidomide and bortezomib did not affect outcomes with this treatment (median PFS 3.8 months for both; ORRs 30% and 31%; and median OS 16 and 13.4 months). Grade 3-4 neutropenia occurred in 41-48% of patients and no grade 3-4 peripheral neuropathy was reported.

Pomalidomide was also shown active in combination with proteasome inhibitors in patients with heavily pretreated and/or refractory myeloma wherein patients previously exposed to both lenalidomide and bortezomib were treated with pomalidomide and carfilzomib. Early response assessment demonstrated that, in 27 of 32 enrolled patients, there were 2 VGPR, 7 PR, 6 MR, 8 SD, and 4 PD for a ≥ MR rate of 56% [Shah 2012].

1.5 Clarithromycin

Macrolide antibiotics have been used for many years to modulate the metabolism of steroids and have weak immune modulating effects. Clarithromycin is a macrolide antibiotic that has been shown to also have immunomodulatory properties partially mediated through suppression of IL-6, increases in the Th1/Th2 ratio and modulation of other cytokines [Durie 1997]. In addition it has also been shown to increase the AUC (area under the time concentration curve) of concomitantly administered steroids.

Clarithromycin has been reported to possess direct anti-neoplastic activity in hematologic as well as solid tumors. In a phase II study, clarithromycin in combination with thalidomide and dexamethasone induced a response rate of over 90% in patients with multiple myeloma. Patients who were refractory to thalidomide/dexamethasone also responded to the addition of clarithromycin [Morris 2008]. In another phase II study, Niesizky *et al* demonstrated very high overall response rates (ORR 90%), with a sCR + CR rate of almost 40%, in newly diagnosed multiple myeloma patients treated with clarithromycin (Biaxin®), lenalidomide, and high dose dexamethasone (BiRD) regimen [Niesvizky 2008]. Francesa *et al* verified this data using low dose dexamethasone [ASH 2009, abstract # 2868].

Mark *et al* also reported a study of the combination of clarithromycin with pomalidomide, and dexamethasone for the treatment of 114 heavily pre-treated patients [Mark 2013]. The proportion

of patients who were refractory to lenalidomide, refractory to bortezomib, and double (lenalidomide + bortezomib) refractory were 85%, 79%, and 68% respectively. The ORR in the entire cohort and double-refractory subgroup were 61.4/ 6.4%, stringent complete remission (sCR): 4.4/4%, complete response (CR): 0.9/1.3%, very good partial response (VGPR): 14.9/11.5%, partial response (PR): 41.2/38.5%, minimal response (MR): 7/9%, stable disease (SD): 21.9/21.8%, progressive disease (PD), respectively. Median overall survival (OS) has not been reached with 68 patients (57%) alive at last follow-up. After a mean follow up time of 11.9 months, 40 patients (34%) remain free from progression, with a median progression free survival of 8.1 months (95% CI: 5.1, 9.8). Median duration of response (DOR) was 9.3 months (95% CI: 7.2, 16.1). Median PFS, DOR, OS were not significantly different in the double-refractory subgroup at 6.3 (95% CI 4.7, 8.7; p = 0.21), 8.6 (95% CI 6.5, 16.1; p = 0.87), and 16.8 months (95% CI 12.4, 28.7; p = 0.11) respectively. The most common grade 3 and 4 toxicities were neutropenia (49%), thrombocytopenia (39%), anemia (27%), pneumonia (10%), fatigue 8%, and muscular weakness 7%.

1.5.1 Pharmacokinetics and Drug Metabolism

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, clarithromycin tablets may be given without regard to food.

In non-fasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1 to 2 mcg/mL with a 250 mg dose administered every 12 hours and 3 to 4 mcg/mL with a 500 mg dose administered every 8 to 12 hours. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 to 12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 mcg/mL and has an elimination half-life of 5 to 6 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 mcg/mL), and its elimination half-life is about 7 to 9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3 to 4 days.

After a 250 mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250 mg (125 mg/5 mL) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10% to 15% of the dose with either a 250 mg or a 500 mg tablet administered every 12 hours.

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500- or 1000-mg doses of clarithromycin every 12 hours, steady-state clarithromycin C_{max} values ranged from 2 to 4 mcg/mL and 5 to 10 mcg/mL, respectively.

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function.

1.6 Ixazomib (MLN9708)

Ixazomib (MLN9708: Millennium Pharmaceuticals, Inc., Cambridge, MA) is a selective, orally bioavailable proteasome inhibitor currently in phase II clinical development. Upon exposure to aqueous solutions or plasma, ixazomib rapidly hydrolyzes to MLN2238, the biologically active form. Similar to bortezomib, MLN2238 is a boronic acid analog; however, it is distinct from bortezomib since preclinical data demonstrates it has a shorter proteasome dissociation half-life, as well as improved pharmacokinetics, pharmacodynamics, and antitumor activity in xenograft models versus bortezomib. Pre-clinical studies have demonstrated synergistic activity when ixazomib is added to lenalidomide [Chauhan 2011]. A recent Phase I/II study in patients with previously untreated multiple myeloma demonstrated that ixazomib could be safely added to lenalidomide and dexamethasone with a phase II dose of 4 mg administered weekly for 3 weeks when given in combination with 25 mg of lenalidomide (days 21 out of 28) demonstrated that this was a safe and potentially efficacious regimen [Kumar 2012].

1.6.1 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB).

1.6.2 Clinical Experience

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have 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 include 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 anti-emetics 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.

1.6.3 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 4 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 [Gupta 2010]. 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 [Gupta 2011]. 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 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 CYPs and non-CYP enzymes/proteins. At clinically relevant concentrations of ixazomib, in vitro studies using human cDNA-expressed CYP isozymes showed that no specific CYP isozyme predominantly contributes to ixazomib clearance. At concentrations exceeding those observed clinically (10 µM), ixazomib was metabolized by multiple CYP isoforms with

estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%) and 2C9 (<1%). In contrast, at 0.1 µM and 0.5 µM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP–mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor would be expected. In addition, ixazomib is neither a reversible nor a time-dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.

In a recently concluded, phase 1 DDI study, the PK of ixazomib (C_{max} and $AUC_{0\text{-}last}$) was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor (Study C16009, Arm 5); hence, no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. These findings are explained by the in vitro metabolism data indicating the lack of a discernible contribution of CYP-mediated metabolism at clinically relevant ixazomib concentrations. As discussed earlier, no CYP isoforms have been identified to contribute meaningfully to ixazomib metabolism at clinically relevant concentrations and CYP3A contribution to total metabolism was highest across all CYP isoforms when characterized at a supratherapeutic concentration of 10 µM. Therefore, based on the totality of information from the clinical clarithromycin DDI study and the in vitro CYP phenotyping data, it can be concluded that ixazomib PK is not likely to be altered upon co-administration with any CYP isoform-selective inhibitor, including strong CYP1A2 inhibitors. Consistently in the population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. Ixazomib may be a weak affinity substrate of P-gp but not of breast cancer resistance protein (BCRP) or multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of P-gp, BCRP, or MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.
Further details on these studies are provided in the IB.

1.6.4 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, non-hematologic 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 1-1 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
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 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, non-hematologic 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 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	Oral Single Agent Total n = 201 n (%)
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhoea	88 (44)
Vomiting	77 (38)
Constipation	46 (23)
Abdominal pain	33 (16)
General disorders and administration site conditions	151 (75)
Fatigue	103 (51)
Pyrexia	51 (25)
Oedema peripheral	27 (13)
Asthenia	31 (15)
Nervous system disorders	92 (46)
Headache	29 (14)
Dizziness	26 (13)
Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)
Decreased appetite	64 (32)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)
Anaemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash macular[a]	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnoea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

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

As of 27 March 2013, there are 5 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 1-3 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)
Diarrhea	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)
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 [Chow 2012], non-Hodgkin's disease, Hodgkin's disease [Assouline 2012], relapsed and/or refractory multiple myeloma [RRMM; Lonial 2012a; Kumar 2011], relapsed or refractory systemic light chain amyloidosis [RRAL; Merlini 2012], and newly diagnosed multiple myeloma [NDMM; Kumar 2012; Richardson 2012a; San Miguel 2012]) to date.

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

1.6.5 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involves 2 studies (C16003 and C16004) with similar objectives, but each investigated 1 of the 2 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. [Richardson 2011, Lonial 2012b]. 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 [Kumar 2012#816, Kumar 2012#8034, Kumar 2013]. 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 2 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 1 of 4 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.

1.6.6 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 2 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.

1.6.7 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

See the IB for descriptions of the 2 studies that investigated IV ixazomib in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.7 Study Rationale

We hypothesize that the addition of ixazomib to clarithromycin, pomalidomide, and dexamethasone will significantly enhance the anti-myeloma properties of the pomalidomide clarithromycin and dexamethasone regimen and can result in higher CR, sCR rates, and PFS beyond the 8 months that was reported in the recent Mark *et al* abstract [Mark 2013]. The rationale for this hypothesis is based on the reported synergistic effects of bortezomib when added to other IMiDs [Mitsiades 2003; Richardson 2010].

We anticipate a rapid reduction in disease a control of tumor burden early in the course of therapy. Perhaps this multi-agent regimen will allow for a limited number of cycles in the induction phase when used as conditioning pre-transplant. It is also possible this novel regimen will be shown to prolong PFS and OS in this highly treatment refractory patient population.

It is also noteworthy that this will be an entirely oral regimen, a convenience that would be expected to positively impact the quality of life of our myeloma patients. To this end we will incorporate both the Cancer Therapy Satisfaction Questionnaire and the EORTC QLQ – MY20 questionnaire into patient assessments.

1.8 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA for potential adverse events and the product labels for pomalidomide, clarithromycin, and dexamethasone.

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, and 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.

Clinical benefit was achieved in 68.4% of patients with heavily treated relapsed/refractory multiple myeloma using a clarithromycin, pomalidomide, and dexamethasone regimen. Response to this regimen is rapid and sustained at 8 months in the majority of subjects. Overall response rates and progression free survival are favorable when considering historical and currently available therapies.

Because the pomalidomide, ixazomib, and clarithromycin are either partially or completely metabolized in the liver, there is the potential for increased hematologic and non-hematologic toxicity. Therefore, a phase I clarithromycin dose escalation component has been incorporated into the protocol to determine the recommended phase 2 dose.

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

2. STUDY OBJECTIVES

2.1 Phase I Primary Objectives

- To establish the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) for PiC-D therapy (pomalidomide, ixazomib, clarithromycin and dexamethasone) in patients with multiple myeloma who are proteasome inhibitor and lenalidomide pretreated.

2.2 Phase I Secondary Objectives

- To evaluate the safety and tolerability of PiC-D therapy.
- To characterize the pharmacokinetics (PK) in plasma of oral ixazomib in combination with pomalidomide, clarithromycin and dexamethasone
- To assess preliminary evidence of clinical activity.
- To assess the effects of PiC-D therapy on quality of life (QOL).
- To assess the effects of PiC-D therapy on immune status (phenotypic analysis and cytokine profiling) in future research.

2.3 Phase II Primary Objectives

- To determine the Complete Response (CR) and stringent CR (sCR) rate for PiC-D therapy in patients with multiple myeloma who are proteasome inhibitor and lenalidomide pretreated.

2.4 Phase II Secondary Objectives

- To evaluate the safety of PiC-D therapy.
- To determine the Overall Response Rate (ORR: CR, sCR, Partial Response (PR), and Very Good Partial Response (VGPR)).
- To determine the Clinical Benefit Rate (CBR: Minimal Response (MR) + ORR).
- To determine the Disease Control Rate (DCR: Stable disease (SD) + CBR).
- To determine the Duration of Response (DOR) in patients achieving a PR or better.
- To determine the Time to Next Treatment (TNT).
- To determine progression free survival (PFS) and overall survival (OS).
- To assess the effects of PiC-D therapy on quality of life (QOL).

2.5 Phase II Correlative Objectives

- To assess the effects of PiC-D therapy on immune status (phenotypic analysis and cytokine profiling) in future research.

3. STUDY ENDPOINTS

3.1 Phase I Primary Endpoints

- To establish the MTD and RP2D.

3.2 Phase I Secondary Endpoints

- Proportion of patients experiencing treatment-emergent adverse events (description, grade [CTCAE v4.03], seriousness, and relatedness).
- Overall Response Rate, Clinical Best Response, Disease Control Rate, Duration of Response, Time to Next Treatment, Progression Free Survival, Overall Survival.
- Cancer Therapy Satisfaction Questionnaire and EORTC QLQ-MY20 scores.
- Change in immune phenotype and cytokine profile over time (future research).

3.3 Phase II Primary Endpoints

- CR + sCR.

3.4 Phase II Secondary Endpoints

- Proportion of patients experiencing treatment-emergent adverse events (description, grade [CTCAE v4.03], seriousness, and relatedness).
- Overall Response Rate.
- Clinical Best Response.
- Disease Control Rate.
- Duration of Response.
- Time to Next Treatment.
- Progression Free Survival, Overall Survival.
- Cancer Therapy Satisfaction Questionnaire and EORTC QLQ-MY20 scores.

3.5 Phase II Correlative Endpoints

- Immune modulation with and without the addition of clarithromycin (future research).

4. STUDY DESIGN

4.1 Overview of Study Design

This is a Phase I/II, non-randomized, open label, multicenter study in patients with relapsed or refractory multiple myeloma to evaluate the safety and efficacy of PiC-D therapy (pomalidomide, ixazomib, clarithromycin and dexamethasone). Adult patients with biopsy-confirmed diagnosis of multiple myeloma that have proteasome inhibitor and lenalidomide pretreated disease, and who meet all other eligibility criteria will be enrolled in this study.

Patients will be stratified according to (1) Proteasome inhibitor exposure (progression on therapy vs. progression within 6 months after completion of therapy), (2) International Staging System (ISS) (Stage I vs. II vs. III), and (3). Cytogenetics/FISH: standard vs. high risk. High risk is defined as the presence of del(17p), t(4:14), t(14;16), t(14:20), or gain of 1q21.

The Phase I portion of the study will utilize a 3+3 dose escalation design to determine the maximum tolerated dose (MTD) of clarithromycin in combination with ixazomib, pomalidomide, and dexamethasone (see Section 4.1.1 and 4.1.2). One clarithromycin dose level is planned (250 mg BID on Days 1-21), with an additional cohort for de-escalation (250 mg QD on Days 1-21) if unacceptable toxicity occurs at the first dose level, for a total of up to 12 patients.

Once the recommended phase 2 dose (RP2D: based on the MTD) of clarithromycin has been determined, the Phase II portion of the study will be initiated. The Phase II portion of the study will utilize the Simon's optimal 2-stage design to determine the complete response (CR) and stringent CR (sCR) rate of PiC-D therapy. Patients from the Phase I component of the study who were treated at the RP2D will be included in the Phase II analysis.

Treatment cycles are 28 days in length. In both the Phase I and II portions of the study, Cycle 1 will consist of pomalidomide (4 mg) on Days 1-21, dexamethasone (40 mg for patients of age $\leq$ 75, 20 mg for patients of age > 75) on Days 1, 8, 15, and 22, and ixazomib on Days 1, 8, and 15. Clarithromycin will be held during the initial 2 weeks of the first cycle to assess its impact on immune parameters and will be administered on Days 15-21. Correlative immune studies will require peripheral blood collection at baseline, Day 15 of Cycle 1, Day 1 of subsequent cycles, and at the end of treatment. Pharmacokinetics will be performed on Day 1 and Day 15 after ixazomib dosing in the first 9 patients or until 3 patients have been treated.

Treatment Cycles 2-6 will consist of all PiC-D study drugs.

PiC-D therapy:

- **Pomalidomide** 4 mg oral, daily on Days 1-21.
- **Ixazomib** 4 mg oral, on Days 1, 8, and 15.
- **Clarithromycin** oral, on Days 1-21 at the respective doses for Phase I and Phase II.
- **Dexamethasone** 40 mg oral (20 mg for patients > 75 years of age), on Days 1, 8, 15, and 22.

On PK sampling days, cycle 1 days 1 and 15 (phase 1) and cycles 2-3 day 1 (phase 2), clarithromycin will be administered immediately prior to pomalidomide and ixazomib.

Treatment will be administered for 6 cycles unless the patient experiences disease progression, unacceptable toxicity, or withdraws consent. Patients who are responding after 6 cycles and do not have grade 3 or 4 toxicity will continue on maintenance therapy.

Maintenance therapy will consist of pomalidomide 2 mg daily on Days 1-21, dexamethasone 20 mg on Days 1, 8, 15, and 22, ixazomib 2.3 mg on Days 1, 8, and 15, and clarithromycin on Days 1-28 at the RP2D or 250mg BID whichever is lower.

Clinic visits and laboratory measurements will be performed throughout treatment as shown in the Schedule of Events. Patients will be assessed with monthly physical exam, complete blood count, Serum protein electrophoresis (SPEP), and serum free light chain (SFLC). Response assessments will occur monthly and will be determined by the local investigator according to the International Myeloma Working Group (IMWG) criteria (see Appendix 13.2).

Health-related quality of life will also be evaluated monthly during treatment, at the end of treatment and at 2 and 3 years after study registration using the Cancer Therapy Satisfaction Questionnaire and the EORTC QLQ–MY20 questionnaire.

An end of treatment visit will occur within 4-6 weeks after receiving the last dose of study treatment. Patients who discontinue study treatment prior to disease progression will continue to be assessed for disease progression during the follow-up period. All patients will be followed for survival.

The follow-up period will consist of visits approximately every 2 months until disease progression. Thereafter, survival information and data regarding start of new treatment (if applicable) are required approximately every 3 months (± 1 month) until 3 years following study registration.

4.1.1 Phase I Determination of Maximum Tolerated Dose (MTD)

Dose escalation will be performed in serial patient cohorts. Patients will receive study drugs according to the dose level cohort to which they are assigned according to Table 4-1. Treatment cycles are 28 days.

Table 4-1 Phase I Dose Escalation Regimen

Dose Level	Dose			
	Clarithromycin* Days 1-21	Pomalidomide Days 1-21	Ixazomib Days 1, 8, 15	Dexamethasone Days 1, 8, 15, 22
-1	250 mg QD	4 mg	4 mg	40 mg (20 mg if age > 75)
1 (starting level)	250 mg BID	4 mg	4 mg	40 mg (20 if age > 75)

- Cycle 1: *Clarithromycin administration will be delayed for two weeks for correlative studies and will only be administered on Days 15-21.
- Cycles 2-6: All drugs will be administered as described in Table 4-1.

Maintenance therapy: will consist of pomalidomide 2 mg daily on Days 1-21, dexamethasone 20 mg on Days 1, 8, 15, and 22, ixazomib 2.3 mg on Days 1, 8, and 15, and clarithromycin on Days 1-28 at the dose level in which the patient enrolled (or lower if modifications were needed).

Dose escalation (opening of a new cohort of patients) will be based on the dose-limiting toxicities (DLTs) encountered during the DLT assessment period, as outlined in Table 4-2. DLTs are defined in Section 4.1.2.

Table 4-2 Dose Escalation Design

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level. If 0 of the 1st 3 patients at the highest dose level (250 mg BID of clarithromycin) experience a DLT, then this dose level will be expanded with 3 more patients.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose. *If this occurs at Dose Level 1, Dose Level -1 will be the first de-escalation step.*
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. If this dose level is 250 mg BID of clarithromycin then this will be the MTD. Three (3) additional subjects may be enrolled so that a total of six subjects are evaluated at this dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose or at the highest planned dose	This is the MTD (highest dose of clarithromycin tested in which fewer than 33% of patients experience a DLT and at least 6 patients have been treated at that dose and are evaluable for dose-escalation decisions). The MTD will be the recommended Phase 2 dose, provided that other safety considerations are acceptable.

4.1.2 Definition of Dose-Limiting Toxicity (DLT)

The DLT assessment period is defined as the first day of study treatment through the end of Cycle 2.

Toxicities are to be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0). A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

Dose Limiting Toxicity (DLT) is defined as any of the following adverse events considered by the investigator to be related or possibly related to one of the study drugs:

- Grade 3 thrombocytopenia with hemorrhage and/or requiring transfusion.
- Grade 4 thrombocytopenia regardless of duration.
- Grade 3 thrombocytopenia lasting ≥ 21 days.
- Grade 3 thrombocytopenia with potentially life-threatening morbidity.

- Grade 3 neutropenia lasting ≥ 21 days (despite the use of growth factors).
- Grade 4 neutropenia lasting ≥ 7 days (despite the use of growth factors).
- Grade 3 or 4 neutropenia with potentially life-threatening morbidity.
- Grade 4 other hematologic toxicity (with the exception of lymphopenia).
- Grade 3 or 4 non-hematologic toxicity, including neuropathy
- Grade 3 nausea, vomiting and diarrhea are considered a DLT only if they persist ≥ 24 hours despite optimal supportive care

Patients that experience a Grade 3 or 4 dose limiting toxicity will hold treatment until the toxicity has resolved to ≤ Grade 2. Resumption of treatment will follow the dose modification guidelines in Section 6.2.

4.2 Number of Patients

The Phase I portion will enroll up to 12 patients depending on the occurrence of DLTs. The Phase II portion will enroll 40 patients (including those treated in the phase I component at the RP2D). Enrollment is defined as having initiated study treatment.

4.3 Duration of Study

It is anticipated that this study will last for approximately 5 years, including a 24-month enrollment period, and an additional 3 years follow-up from the last patient enrolled.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

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

2. Male or female patients 18 years or older.

3. Patients must have a confirmed biopsy diagnosis of a *multiple myeloma*

4. Submission of original biopsy for review and verification by hematopathologist at local institution.

5. Patients must have measurable disease according to International Myeloma Working Group (IMWG) criteria (see Appendix 13.2). Measurable disease includes at least one of the following criteria:

- Serum M-protein ≥ 1.0 g/dL, and/or
- Urine M-protein ≥ 200 mg/24 hours, and/or
- Involved serum free light chain ≥ 10 mg/dL (≥ 100 mg/L) AND an abnormal serum free light chain ratio, and/or
- Baseline marrow burden or myeloma of at least 30%.

6. Disease that has progressed after treatment with both a proteasome inhibitor and lenalidomide (either sequentially or concurrent). Progressive disease is defined as any of the following:
   - An increase of ≥25% from lowest response value in any of the following:
     - Serum M-protein (absolute increase must be ≥0.5 g/dL) AND/OR:
     - Urine M-protein (absolute increase must be ≥200 mg/24 hours) AND/OR:
     - For patients without a measurable serum or urine M-protein but measurable disease by serum free light chain testing: Difference between the involved and uninvolved serum free light chain level (absolute increase must be ≥10 mg/dL) AND/OR:
     - For patients without a measurable serum or urine M-component or serum free light chain level: % marrow involvement with myeloma (absolute increase must be ≥10%). AND/OR:
   - Definite development of new bone lesions or extramedullary plasmacytomas or definite increase in the size of existing bone lesions or extramedullary plasmacytomas AND/OR:
   - Hypercalcemia (corrected serum calcium > 11.5 mg/dL) attributable to myeloma (e.g. not due to omitted doses of biophosphonate).

7. Life expectancy of greater than 3 months.

8. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2. (see Appendix 13.3).

9. Disease free of prior malignancies for > 5 years with exception of patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

10. Patients must meet the following clinical laboratory criteria:
    - Absolute neutrophil count (ANC) ≥ 1,000/mm^3 and
    - Platelet count ≥ 50,000/mm^3.
      Note: Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
    - Total bilirubin ≤ 2.0 × the upper limit of the normal range (ULN).

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN.
- Calculated creatinine clearance ≥ 30 mL/min (see Appendix 13.4).

11. 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 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, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

12. 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 [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

5.2 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. Treatment with clarithromycin, anti-myeloma therapy including investigational agents or plasmapheresis within 15 days prior to treatment in this study.

3. Failure to have fully recovered (i.e., ≤ Grade 1 toxicity or to patient's clinical baseline) from the reversible effects of prior chemotherapy.

4. Major surgery within 14 days before enrollment.

5. Radiotherapy within 14 days before enrollment.

6. Central nervous system involvement.

7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

8. 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.

9. Systemic treatment within 14 days before the first dose of study drugs, or concurrent use, with any of the following:
    - strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin);
    - strong inhibitors of CYP3A (telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole);
    - strong CYP3A4 inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, or St. John's Wort).

10. Known ongoing or active systemic infection, active hepatitis B or C virus infection.

11. Patients with HIV infection may be eligible provided they meet the following:
    - No history of AIDS-defining conditions or other HIV related illness
    - CD4+ cells nadirs > 350/mm^3
    - Treatment sensitive HIV and, if on anti-HIV therapy, HIV viral load < 50 copies/mm^3

      Please note: HIV+ patients who enroll on this study may need to modify their anti-retroviral therapy prior to receiving protocol therapy if they are on strong inducers or potent inhibitors of cytochrome P450 3A4. Adverse events in HIV+ patients will be reported separately.

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

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

14. Previous allergic reaction to an immunomodulatory drug (IMiD).

15. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of study drugs including difficulty swallowing.

16. Patient has ≥ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.

17. Previous treatment with ixazomib or pomalidomide.

6. TREATMENT PLAN

6.1 Study Drug Administration

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

6.1.1 Ixazomib Administration

The prescribed administration of ixazomib doses in this study is 4 mg ixazomib on Days 1, 8, and 15 in Cycles 1-6 in a 28 day cycle. The ixazomib dose administered in the maintenance phase of this study is 2.3 mg ixazomib on Days 1, 8, and 15 in a 28-day cycle.

- Proteasome inhibitor-based therapy is associated with an increased risk of herpes zoster reactivation. As such, it is suggested that patients on treatment with ixazomib are required to receive herpes zoster reactivation prophylaxis (e.g. valacyclovir 500 mg orally twice daily or its equivalent) but it will up to the discretion of the treating physician.

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Ixazomib drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

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.

6.1.2 Pomalidomide Administration

The prescribed administration of pomalidomide doses in this study is 4 mg pomalidomide on Days 1-21 in a 28 day cycle. The pomalidomide dose administered in the maintenance phase of this study is 2 mg pomalidomide on Days 1-21 in a 28-day cycle.

- Given the increased risk of venous thromboembolic events with the use of pomalidomide and dexamethasone, thromboprophylaxis is required while patients are on protocol therapy and should consist of either aspirin (81 mg or 325 mg daily), a prophylactic dose of low molecular weight heparin (e.g. enoxaparin 40 mg SC daily), warfarin targeting an INR of 2-3, or other equivalent. Thromboprophylaxis should be held in the presence of ≥ grade 3 thrombocytopenia. For patients with poor oral intake and frequent ≥ grade 3 thrombocytopenia, low molecular weight heparin is preferred over warfarin.

Pomalidomide should be taken once daily at about the same time each day when it is scheduled. The capsules should not be opened, broken, or chewed. Pomalidomide should be swallowed whole with water.

Instruct patients that if they miss a dose of pomalidomide, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take pomalidomide at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

Care should be exercised in handling of pomalidomide. Pomalidomide capsules should not be opened or crushed. If powder from pomalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If pomalidomide contacts the mucous membranes, flush thoroughly with water.

Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

6.1.3 Clarithromycin Administration

The prescribed administration of clarithromycin doses in the Phase I component of this study is dependent on the dose level in which patient enrolls (see Section 4.1.1). Dose levels include 250 mg BID (level 1), and 250 mg QD (level -1). Clarithromycin will be administered on Days 15-21 in Cycle 1 and on Days 1-21 in Cycles 2-6 in a 28-day cycle. The prescribed administration of clarithromycin doses in the Phase II component of this study will be determined in the Phase I component. The clarithromycin dose administered in the maintenance phase of this study is at the respective doses for Phase I and Phase II on Days 1-28.

Clarithromycin tablets may be taken with or without food.

Instruct patients that if they miss a dose of clarithromycin, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take clarithromycin at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

Clarithromycin may interact with some drugs; therefore patients should be advised to report to their doctor the use of any other medications.

6.1.4 Dexamethasone Administration

The prescribed administration of dexamethasone doses in this study is 40 mg dexamethasone for patients ≤ 75 years of age and 20 mg for patients >75 years of age on Days 1, 8, 15, and 22 in a 28 day cycle.

The dexamethasone dose administered in the maintenance phase of this study is 20 mg (irrespective of age) on Days 1, 8, 15, and 22 in a 28-day cycle.

Dexamethasone should be taken with food.

Instruct patients that if they miss a dose of dexamethasone, they may still take it as soon as they remember. Warn patients not to take 2 doses to make up for the one that they missed. 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.

Dexamethasone may interact with some drugs; therefore patients should be advised to report to their doctor the use of any other medications.

6.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

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

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be > 50,000/mm^3.
- All other non-hematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition.

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 7 days. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-

cited criteria, delay therapy and continue to re- evaluate. For dosing recommendations upon recovery, refer to Section 6.3.

If the start of a new treatment cycle is delayed for > 21 days as a result of toxicities at least possibly related to study treatment, the patients will be discontinued from study treatment.

6.3 Dose Modification Guidelines

Study drug dose modifications may change depending on the disease and combination with other drug(s). If a new combination study, an attempt should be made to integrate dose modifications for the combination for each AE.

Any patient who receives treatment on this protocol will be evaluable for toxicity. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments for adverse events deemed related to study drug by the investigator should be made according to the system showing the greatest degree of toxicity. Doses may be adjusted for adverse events related to study medications not listed below at the discretion of the investigator. These dose modification guidelines apply to treatment during cycles 1-6 as well as the "maintenance phase".

6.3.1 Dose Modifications for Ixazomib

Refer to Table 6-1 for Ixazomib dose levels and Tables 6-2, 6-3 for treatment modification guidelines.

Table 6-1 Ixazomib Dose Levels

Dose Level	Ixazomib Days 1, 8, 15
Starting Dose	4.0 mg
-1	3.0 mg
-2	2.3 mg
-3	Discontinue

Table 6-2 Ixazomib Dose Adjustments for Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count $\leq 30 \times 10^9$/L or ANC $\leq 0.50 \times 10^9$/L on an ixazomib dosing day (other than Day 1)	• Ixazomib dose should be withheld. • Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts are $\leq$ Grade 2 on at least 2 occasions. • Upon recovery, ixazomib may be reinitiated at the current dose level. Subsequent $\geq$ Grade 3 toxicity will result in 1 dose level reduction after recovery.
Dose Modifications for Subsequent Treatment Cycles	
• Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.3.1 • ANC < 1.0×10^9/L, platelet count < 50×10^9/L, or other non-hematologic toxicities > Grade 1 or not to the patient's baseline condition	• Hold ixazomib until resolution $\leq$ Grade 2 • Upon recovery, reduce ixazomib 1 dose level. • The maximum delay before treatment should be discontinued will be 28 days or at the discretion of the PI.
Dose Modifications for Subsequent Treatment Cycles	
• 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 within the cycle, start the next cycle at that same dose. o If due to toxicity timing, i.e., after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib 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 for the same most severe toxicity.

Table 6-3 Ixazomib 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
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold study drug until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold study drug until resolution to Grade ≤ 1 without pain or baseline • Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 2 Rash	• Symptomatic recommendations as per section 6.7	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Grade 3 non-hematologic toxicity judged to be related to study drug	• Hold study drug until resolution to Grade < 1 or baseline	Symptomatic recommendations noted in Section 6.7
If not recovered to < Grade 1 or baseline within 4 weeks	• Reduce study drug 1 to next lower dose upon return to < Grade 1 or baseline	
Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 4 weeks	• Hold study drug until resolution to Grade < 1 or baseline • Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 non-hematologic toxicities judged to be related to study drug	• Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

Once ixazomib is reduced for any toxicity, the dose may not be re-escalated.

6.3.2 Dose Modifications for Pomalidomide

Refer to Table 6-4 for dexamethasone dose levels and Tables 6-5 for treatment modification guidelines.

Table 6-4 Pomalidomide Dose Levels

Dose Level	Pomalidomide Days 1-21
Starting Dose	4 mg
-1	3 mg
-2	2 mg
-3	1 mg

Table 6-5 Pomalidomide Treatment Modifications (Delays, Reductions, and Discontinuations) Due to Toxicities

Toxicity	Action
Neutropenia	
• ANC <500 per mcL or febrile neutropenia (fever more than or equal to 38.5°C and ANC <1,000 per mcL)	• Interrupt pomalidomide treatment, follow CBC weekly
• ANC return to more than or equal to 500 per mcL	• Resume pomalidomide treatment at 3 mg daily
• For each subsequent drop <500 per mcL	• Interrupt pomalidomide treatment
• Return to more than or equal to 500 per mcL	• Resume pomalidomide treatment at 1 mg less than the previous dose
Thrombocytopenia	
• Platelets <25,000 per mcL	• Interrupt pomalidomide treatment, follow CBC weekly
• Platelets return to >50,000 per mcL	• Resume pomalidomide treatment at 3 mg daily
• For each subsequent drop <25,000 per mcL	• Interrupt pomalidomide treatment
• Return to more than or equal to 50,000 per mcL	• Resume pomalidomide treatment at 1 mg less than the previous dose
Other Grade 3 or 4 toxicities	• Interrupt pomalidomide treatment if felt to be the offending agent • Restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion.

6.3.3 Dose Modifications for Clarithromycin

Refer to Table 6-6 for clarithromycin dose levels and Tables 6-7 for treatment modification guidelines.

Table 6-6 Clarithromycin Dose Levels

Phase I component Dose Level	Clarithromycin Days 1-21	Phase II component Dose Level
-1	250 mg QD	RP2D to be determined in the Phase I component. Dose levels used for reductions will remain the same.
1 (Starting Dose)	250 mg BID	

Table 6-7 Clarithromycin Treatment Modification Guidelines for Adverse Events

Adverse Event Criteria	Action
Grade ≥ 3 Loss of appetite	• Reduce one dose-level
Grade ≥ 3 Abdominal pain	• Reduce one dose-level
Grade ≥ 3 Nausea*	• Reduce one dose-level
Grade ≥ 3 Diarrhea*	• Reduce one dose-level
Grade ≥ 3 Dyspepsia	• Reduce one dose-level
Grade ≥ 3 Hepatic failure	• Discontinue clarithromycin
Grade ≥ 3 Anaphylaxis	• Discontinue clarithromycin
*Grade 3 nausea, vomiting and diarrhea are considered a DLT only if they persist ≥ 24 hours despite optimal supportive care	

6.3.4 Dose Modifications for Dexamethasone

Refer to Table 6-8 for dexamethasone dose levels and Tables 6-9 for treatment modification guidelines.

The starting dose for dexamethasone is 40 mg for patients ≤ 75 years of age, 20 mg for patients >75 years of age.

Table 6-8 Dexamethasone Dose Levels

Dose Level	Dexamethasone Days 1, 8, 15, 22 *(age ≤ 75)*	Dexamethasone Days 1, 8, 15, 22 *(age > 75)*
1 (Starting Dose)	40 mg	20 mg
-1	20 mg	12 mg
-2	12 mg	8 mg
-3	8 mg	Not applicable

Table 6-9 Dexamethasone Treatment Modifications (Delays, Reductions, and Discontinuations) Due to Adverse Events

Adverse Event Criteria	Action
Grade ≥3 Dyspepsia	• Delay dexamethasone until recovery to Grade 1, then restart at 1 dose level decreased
Grade ≥3 Edema	• Delay dexamethasone until recovery to Grade 1, then restart at 1 dose level decreased
Grade 2 psychiatric (agitation, anxiety, delirium, depression, hallucinations, mania, personality change, psychosis, or confusion)	• Delay dexamethasone until recovery to Grade 1, then restart at 1 dose level decreased
Grade ≥3 psychiatric (agitation, anxiety, delirium, depression, hallucinations, mania, personality change, psychosis, or confusion)	• Discontinue dexamethasone
Grade ≥3 Hyperglycemia	• Delay dexamethasone until recovery to Grade 1, then restart at 1 dose level decreased
Grade ≥3 generalized muscle weakness	• Delay dexamethasone until recovery to Grade 1, then restart at 1 dose level decreased
Grade ≥3 non-hematologic toxicity not specified above	• Delay dexamethasone until recovery to Grade 1, then restart at 1 dose level decreased
Grade 4 non-hematologic toxicity not specified	• Discontinue dexamethasone

6.4 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 exposure and could lead to a higher probability of an AE.):

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

Systemic treatment with any of the following metabolizing enzyme inducers must 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

The following procedures are prohibited during the study.

- Any antineoplastic treatment with activity against MM, other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day

6.5 Permitted Concomitant Medications and Procedures

All blood products and concomitant medications such as antibiotics, antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until the end of treatment visit will be recorded in the medical records.

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted ***except during Cycle 1 of treatment in the Phase I portion of the study***. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Millennium Clinical or Medical Representative. 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.

- 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.

6.6 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.
- Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Contraception and Pregnancy

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

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of 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 postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or
- 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 for the female partner] and withdrawal are not acceptable methods of contraception.)

Because of the risk of embryo-fetal toxicity, pomalidomide is only available through a restricted program call POMALYST REMS.

- Patients must sign a Patient-Prescriber agreement form and comply with the requirements to receive pomalidomide. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements, and participate in monthly telephone surveys. Males must comply with the contraception requirements.
- Pomalidomide is available only from pharmacies that are certified in POMALYST REMS™ program.
- Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS™ program.
- Provide patients with the telephone number and Web site for information on how to obtain the product.

6.7 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB.

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.

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

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (e.g., 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 administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-2/6.3). 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 administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 6-2/6.3). 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.

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.

6.8 Treatment Compliance

Study drugs 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.

The appropriate amount of drug tablets for one cycle of study treatment will be provided to patients to be self-administered at home. Patients will be asked to fill out diary to record study drug administration.

Patients will be asked to bring the remaining trial medication at the end of each cycle to the investigative site for a compliance check. The remaining tablets will be counted by the investigator/site staff and recorded. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. At the end of each cycle, any remaining medication will be collected. If the patient is eligible for further treatment, a new supply study medication must be dispensed.

6.9 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 investigator also has the right to withdraw patients from the study for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Patient demonstrates disease progression;
- Patient experiences unacceptable toxicity;
- Start of a new treatment cycle is delayed for > 28 days as a result of toxicities at least possibly related to study treatment;
- Patient receives alternative treatment;
- Treating physician judges continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant;
- Patient is lost to follow-up;
- The study is terminated.

At the time of withdrawal from study treatment, all study procedures outlined for the End of Treatment visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and case report form (CRF).

7. STUDY PROCEDURES

7.1 Descriptions of Study Assessments

7.1.1 Informed Consent

All patients must provide written informed consent before any study related screening procedures can be used.

7.1.2 Demographics

Demographic profile will include date of birth, gender, race, and ethnicity.

7.1.3 Medical History and Physical Exam

Complete medical, surgical and oncology history (*e.g.*, date of initial diagnosis, stage and extent of disease, previous anti-tumor therapy including response to, and disease status at inclusion of study) as well as history of infections should be obtained at screening. Additional histories will be obtained as indicated in the schedule of events.

A complete physical examination should include the evaluation of general appearance; evaluation of head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, neurological, and genitourinary systems. A complete physical examination will be done at Screening, Day 1 of each Cycle, and at the End-of-Treatment visit. A symptom-directed physical examination may be performed on other visits.

7.1.4 Vital Signs, Weight, and Height

Vital sign measurements include blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, and temperature. Measurement of height will only be done at screening, and will be used to calculate body surface area (BSA) using weight obtained when designated in the schedule of events.

7.1.5 Performance Status

ECOG performance status will be assessed when designated (see Appendix 13.3).

7.1.6 Concurrent Medications

All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, received by patients from the first dose of study treatment until 28 days after the last study dose (or until the start of a new treatment, whichever comes first) will be recorded in the patient's electronic medical record. If a reportable adverse event deemed related to study drug occurs within 28 days after last study dose and the patient has not started a new treatment, recording of concomitant medications related to the treatment of that adverse event should continue until resolution of the adverse event.

7.1.7 ECG

12-lead ECG will be taken at screening. Additional ECGs may be performed if clinically indicated.

7.1.8 Quality of Life Assessments

Quality of life will be assessed with the Cancer Therapy Satisfaction Questionnaire and the EORTC QLQ-MY20 questionnaire (see Appendices 13.5 and 13.6). QOL will be assessed at baseline, Day 1 of Cycle 2 and all subsequent cycles and maintenance cycles, at the end of treatment, and during follow-up. During the follow-up period, the QOL questionnaires will be obtained at approximately 2 years and 3 years after the date of the patient's baseline assessment.

7.1.9 Laboratory Parameters

Laboratory examinations to be performed are presented in Table 7-1. Hematology and serum chemistries must be performed within 24 hours of the scheduled study drug administration. Pregnancy test must be done within 10-14 days of study initiation and again within 24 hours prior to initiation of pomalidomide. Pregnancy test must be performed weekly during the first month, then monthly thereafter in women with regular menstrual cycles (or every 2 weeks in women with irregular menstrual cycles). A new cycle of pomalidomide cannot be dispensed until a negative pregnancy test is confirmed.

Table 7-1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hemoglobin, hematocrit, platelet count (plts), white blood cell count (WBC), differential.
Serum Chemistries	
Complete Metabolic Panel	Glucose, blood urea/blood urea nitrogen (BUN),creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin.
Other	Magnesium, phosphorus, LDH, uric acid
Coagulation	Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT).
Pregnancy test	β-HCG testing in urine or serum in women of childbearing potential.
CD4+ count, **HIV viral load**	CD4 count and percentages will be quantified. HIV viral load studies will be performed using an assay with a limit of detection of 50 copies/mm^3 or less.
β2-microglobulin	Serum levels of β2-microbulin will be determined at baseline.
PK	Ixazomib levels will be measured pre-dose, and at 0.5, 1, 1.5, 2, 4, 8, and 24 hours (phase 1) after dosing ixazomib during cycle 1 days 1 and 15 in the first 9 patients or until at least three patients have been treated at the clarithromycin MTD – Section 13.8. Ixazomib levels will be measured 2-6 hours after dosing ixazomib (phase 2) on day 1 during cycles 2 and 3 of therapy.
Proteasome inhibition	Proteasome inhibition will be measured pre-dose and at 2, 4, 8, and 24 hours (phase 1) after dosing ixazomib during cycle 1 days 1 and 15. Proteasome inhibition will also be measured 2-6 hours after dosing ixazomib (phase 2) on dose day 1 during cycles 2 and 3 of therapy.

The investigator should complete additional evaluations of laboratory tests as clinically

indicated. Any abnormal findings from these investigations need to be reported as an Adverse Event.

7.1.10 Radiographic Tumor Assessments

Baseline scans can include either: 1) a CT or MRI, or 2) a whole body FDG-PET scan and diagnostic CT performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness. Baseline scans are NOT required for those patients who do not have documented or suspected measurable extramedullary plasmacytomas at the time of enrollment. Baseline scans are required ≤ 42 days prior to registration for those with known or clinically suspected measurable extramedullary disease. Measurable extramedullary disease is required prior to starting maintenance treatment and at the end of treatment if not performed within the last eight weeks, unless study treatment was stopped due to disease progression. The same imaging modality initially used to measure disease at baseline should be used over the course of the study to document response/progression.

7.1.11 Skeletal survey

A baseline skeletal survey should be completed ≤ 42 days prior to registration. A repeat skeletal survey will be obtained to confirm a CR or sCR. Otherwise, the skeletal survey should be repeated as clinically indicated.

7.1.12 Bone marrow aspiration & biopsy with cytogenetics/FISH

Bone marrow aspiration & biopsy with cytogenetics should be completed ≤ 100 days prior to registration to determine: 1) Marrow burden of myeloma. Note: flow cytometry should NOT be used to assess marrow burden of disease. Marrow burden should be determined by aspirate differential and CD138 immunohistochemistry. 2) Fluorescent in situ hybridization testing for the following high-risk cytogenetic abnormalities: t(4;14), t(14;20), t(14;16), del(17p) and gain of 1q21 (positivity defined by the individual probe and testing facility). Plasma cell purification prior to FISH testing is strongly recommended. A repeat bone marrow aspirate and biopsy should be performed within 14 days after CR or sCR is documented.

7.1.13 M-protein assessments

M-protein assessments includes serum protein electrophoresis (SPEP), serum immunofixation, serum free kappa and lambda light chain levels, quantitative serum IgG, IgA and IgM, urine protein electrophoresis (UPEP) and immunofixation. Follow-up assessments will be performed every 2 months after completion of treatment until disease progression or for up to 3 years after the last patient has been enrolled. At these follow-up assessments, patients are followed for disease status, survival, long-term toxicities, and second malignancies. Once a patient progresses, disease assessments are no longer required.

7.2 Screening/Baseline Procedures

To be completed within 14 days of registration:

- Medical history and physical exam
- Demographics
- Vital signs, height, weight
- ECOG Performance Status assessment
- Concurrent medications assessment
- CBC with differential, platelets *(within 24 hours prior to drug administration)*
- CD4+ count, HIV viral load
- Serum chemistries *(within 24 hours prior to drug administration)*
- PT, PTT
- Pregnancy test in women of child-bearing potential *(within 10-14 days of registration)*
- β2-microglobulin
- M-protein assessments

To be completed within 28 days of registration:

- ECG
- QOL questionnaires

To be completed within 42 days of registration:

- Radiologic tumor measurements
- Skeletal survey

To be completed within 100 days of registration:

- Bone marrow aspiration & biopsy with cytogenetics

7.3 Procedures During Study Treatment

7.3.1 Cycle 1 Day 1

- History and physical exam
- Vital signs, height, weight
- ECOG Performance Status assessment
- CBC w/differential, platelets *(within 24 hours prior to drug administration)*
- Serum chemistries *(within 24 hours prior to drug administration)*
- Pregnancy test *(within 24 hours prior to drug administration)*
- Correlative studies blood collection prior to study drug administration (see Protocol Addendum) (future research)
- Dispensation of study drugs

- PK sampling-pre-dose and at 0.5, 1, 1.5, 2, 4, 8, and 24 hours after dosing ixazomib (in the first 9 patients or until 3 patients have been treated at the clarithromycin MTD; Section 13.8)
- Proteasome inhibition sampling pre-dose, and at 2, 4, 8, and 24 hrs after dosing ixazomib (Section 13.8)

7.3.2 Cycle 1 Day 8

- CBC w/differential, platelets *(within 24 hours prior to drug administration)*
- Pregnancy test *(within 24 hours prior to drug administration)*

7.3.3 Cycle 1 Day 15

- CBC w/differential, platelets *(within 24 hours prior to drug administration)*
- Serum chemistries *(within 24 hours prior to drug administration)*
- Pregnancy test *(within 24 hours prior to drug administration)*
- Correlative studies blood collection prior to study drug administration (future research)
- PK sampling pre-dose, and at 0.5, 1, 1.5, 2, 4, 8, and 24 hours after dosing ixazomib (Section 13.8, phase 1)
- Proteasome inhibition sampling pre-dose, and at 2, 4, 8, and 24 hrs after dosing ixazomib (Section 13.8, phase 1)

7.3.4 Cycle 1 Day 22

- CBC w/differential, platelets *(within 24 hours prior to drug administration)*
- Pregnancy test *(within 24 hours prior to drug administration)*

7.3.5 Day 1 Cycles 2-6

- History and physical exam
- Vital signs, height, weight
- ECOG Performance Status assessment
- CBC w/differential, platelets *(within 24 hours prior to drug administration)*
- CD4 counts will also be performed on Day 1 of every odd cycle starting at Cycle 3; HIV viral load will be assessed at the same time points only for those patients with HIV.
- Serum chemistries *(within 24 hours prior to drug administration)*
- Pregnancy test *(within 24 hours prior to drug administration)*
- M-protein assessments
- Dispensation of study drugs
- Correlative studies blood collection prior to study drug administration (future research)

- PK sampling 2-6 hours after dosing ixazomib (Section 13.8, phase 2, cycles 2 and 3)
- Proteasome inhibition sampling 2-6 hours after dosing ixazomib (Section 13.8, phase 2, cycles 2 and 3)

As clinically indicated, at emergence of new symptoms, or at treating physician's discretion:

- Radiologic tumor measurement
- Bone marrow aspiration & biopsy with cytogenetics

7.3.6 Day 15 Cycles 2-6 (Phase I only)

- History and physical exam
- Vital signs, height, weight
- ECOG Performance Status assessment
- CBC w/differential, platelets *(within 24 hours prior to drug administration)*
- Serum chemistries *(within 24 hours prior to drug administration)*

7.3.7 Day 1 Maintenance Cycles

- History and physical exam
- Vital signs, height, weight
- ECOG Performance Status assessment
- CBC w/differential, platelets *(within 24 hours prior to drug administration)*
- CD4+ count (and HIV viral load for patients with HIV)
- Serum chemistries *(within 24 hours prior to drug administration)*
- Pregnancy test *(within 24 hours prior to drug administration)*
- M-protein assessments
- Dispensation of study drugs

As clinically indicated, at emergence of new symptoms, or at treating physician's discretion:

- Radiologic tumor measurement
- Bone marrow aspiration & biopsy with cytogenetics

7.4 End of Treatment Visit

An end of treatment visit should occur within 4-6 weeks of permanently discontinuing study treatment for any reason. Study procedures will include:

- History and physical exam
- Vital signs, height, weight
- ECOG Performance Status assessment
- CBC w/differential, platelets *(within 24 hours prior to drug administration)*

- CD4+ count (and HIV viral load for patients with HIV)
- Serum chemistries *(within 24 hours prior to drug administration)*
- Pregnancy test *(within 24 hours prior to drug administration)*
- M-protein assessments
- Correlative studies blood collection (future research)

As clinically indicated, at emergence of new symptoms, or at treating physician's discretion:

- Radiologic tumor measurement
- Bone marrow aspiration & biopsy with cytogenetics

7.5 Follow-up Procedures

Patients discontinuing study treatment will undergo the following procedures:

- (when applicable) Follow-up for disease progression then survival
  For those patients discontinuing study treatment prior to disease progression, follow-up visits should occur approximately every 2 months until disease progression (any additional follow-up assessments should be performed according to institutional practice).
- M-protein assessments will be performed every 2 months after completion of treatment until disease progression or for up to 3 years after the last patient has been enrolled if they have not progressed. At these follow-up assessments, patients are followed for disease status, survival, long-term toxicities, and second malignancies. Once a patient progresses, disease assessments are no longer required.
- QOL questionnaires at approximately 2 years and 3 years following registration.
- Follow-up for survival: For those patients who have disease progression and discontinue study treatment, follow-up for survival information and data regarding start of new treatment (if applicable) will occur approximately every 3 months from treatment discontinuation until 3 years following registration. Survival information may be collected by routine clinic visits or telephone.

8. DRUG INFORMATION

8.1 Ixazomib

For additional details, please see the ixazomib IB.

Other Names
MLN9708

Route of Administration
Oral

How Supplied
Ixazomib will be supplied by Millennium.

The ixazomib drug product is provided in strengths of 4.0 mg, 3.0 mg, and 2.3 mg. 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

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

Packaging and Labeling
Ixazomib capsules 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.

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

Toxicity

Adverse events observed in clinical studies are listed in Section 1.4.4.

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.

8.2 Pomalidomide

For additional details, please see the pomalidomide product label.

Other Names
CC-4047; Pomalyst®

Route of administration
Oral

How Supplied
Pomalidomide will be commercially supplied in accordance with the Pomalyst REMS™ requirements.

Pomalidomide is available in 1-mg, 2-mg, 3-mg, and 4-mg capsules for oral administration. Each capsule contains pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pregelatinized starch, and sodium stearyl fumarate. The 1-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink. The 2-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink. The 3-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink. The 4-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

Dose Strength	# in bottle	Cap Color	Body Color
1 mg	21	Dark blue opaque	Yellow opaque
1 mg	100	Dark blue opaque	Yellow opaque
2 mg	21	Dark blue opaque	Orange opaque
2 mg	100	Dark blue opaque	Orange opaque
3 mg	21	Dark blue opaque	Green opaque
3 mg	100	Dark blue opaque	Green opaque
4 mg	21	Dark blue opaque	Blue opaque
4 mg	100	Dark blue opaque	Blue opaque

Storage and stability
Pomalidomide is stored at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F).

Toxicity

Common known potential toxicities, > 10%

Blood and lymphatic system disorders:	Anemia, leukopenia, neutropenia, thrombocytopenia, lymphopenia
Gastrointestinal disorders:	Constipation, diarrhea, nausea, vomiting General disorders: Asthenia, chills, fatigue, pyrexia, pain, peripheral edema
Infections and infestations:	Bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection, nasopharyngitis
Metabolism and nutrition disorders:	Decreased appetite, hyperglycemia, hyponatremia, hypercalcaemia, hypocalcaemia, hypokalemia
Musculoskeletal and connective tissue disorders:	Musculoskeletal chest pain, back pain, muscle spasm, arthralgia, musculoskeletal pain, pain in extremity, muscular weakness, bone pain
Nervous system disorders:	Dizziness, tremor
Psychiatric disorders:	Insomnia, confusional state
Renal and urinary tract disorders:	Renal failure
Respiratory, thoracic and mediastinal disorders:	Dyspnea, cough, dyspnea exertional, epistaxis
Skin and subcutaneous tissue disorders:	Rash, hyperhidrosis, night sweats, dry skin

Less common known potential toxicities, 1% - 10%:

Blood and lymphatic system disorders:	Febrile neutropenia
Cardiac disorders:	Atrial fibrillation, cardiac failure congestive, tachycardia
Eye disorders:	Blurred vision
Gastrointestinal disorders:	Abdominal pain, dry mouth, upper abdominal pain
General disorders:	Chest pain
Infections and infestations:	Candidiasis, oral candidiasis, sinusitis, bronchopneumonia
Metabolism and nutrition disorders:	Hyperkalemia, dehydration, hypophosphatemia, hypoalbuminemia, hypomagnesemia
Nervous system disorders:	Headache, dysgeusia, peripheral neuropathy, somnolence, syncope, lethargy
Psychiatric disorders:	Anxiety, altered mood, depression
Renal and urinary tract disorders:	Acute renal failure
Respiratory, thoracic and mediastinal disorders:	Pulmonary embolism, oropharyngeal pain, productive cough, dysphonia, nasal congestion
Skin and subcutaneous tissue disorders:	Pruritus
Vascular disorders:	Deep vein thrombosis, hypotension, hypertension

Rare known potential toxicities, <1% (Limited to important or life-threatening): Secondary cancer, interstitial lung disease, respiratory distress, hyperbilirubinemia.

8.3 Clarithromycin

For additional details, please see the clarithromycin product label.

Other Names
Biaxin®

Route of administration
Oral

How Supplied
Clarithromycin will be commercially supplied in strengths of 250 mg tablets.

Storage
Clarithromycin is stored at room temperature 20° to 25°C (68° to 77°F) in a well-closed container, protected from light. Excursions permitted to 15° to 30°C (59° to 86°F).
Toxicity
Headaches diarrhea, nausea, abnormal taste, heartburn and abdominal pain are common. Irregular blood counts, shortness of breath, hypoglycemia, anxiety, hallucinations, fast heartbeat, and tremors are rare.

8.4 Dexamethasone

For additional details, please see the dexamethasone product label.
Other Names
Decadron®

Route of administration
Oral

How Supplied
Dexamethasone is commercially supplied in strengths of 0.5-, 0.75-, 1- , 1.5-, 2-, 4-, and 6 mg tablets.

Storage and stability
Dexamethasone is stored at room temperature 20° to 25°C (68° to 77°F) in tight, light resistant containers.

Toxicity

Gastrointestinal:	Nausea, vomiting, anorexia, increased appetite, weight gain; aggravation of peptic ulcers.
Dermatologic:	Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses.
Genitourinary:	Menstrual changes (amenorrhea, menstrual irregularities).
Neurologic:	Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, muscle weakness.
Cardiovascular:	Fluid retention and edema, hypertension; rarely, thrombophlebitis.
Ocular:	Cataracts, increased intraocular pressure, exophthalmos.
Metabolic:	Hyperglycemia, decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia.
Hematologic:	Leukocytosis.
Other:	Osteoporosis (and resulting back pain), appearance of serious infections including herpes zoster, varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

9. STATISTICAL AND QUANTITATIVE ANALYSES

This is a Phase I/II open label study.

9.1 Sample Size, Accrual Time and Study Duration

9.1.1 Phase I Portion

The primary endpoint for this study is toxicity as coded according to the CTCAE v4. The primary objective is to determine a recommended Phase II dose (RP2D) for the combination pomalidomide, ixazomib dexamethasone and clarithromycin.

The standard 3+3 design will be used (described below). The maximum tolerated dose (MTD) will be based on toxicities observed during the first cycle and is defined as the highest dose tested in which fewer than 33% of patients experienced dose limiting toxicity (DLT) attributable to the study drug(s), when at least six patients were treated at that dose and are evaluable for toxicity (please see table 4.2, pg 36). Based on this design there is the potential to enroll 3-6 patients per dose level. Given there are 3 dose levels, a minimum of 6 and a maximum of 12 patients can be enrolled on the phase 1 portion of the trial. The RP2D will most likely be the MTD, provided that other safety considerations are acceptable.

Toxicity will be graded according to the NCI CTCAE version 4. The dose limiting toxicity (DLT) will be defined as any treatment-related grade 3 or greater non-hematologic toxicity

(excluding alopecia, controllable nausea and vomiting), grade 4 or greater thrombocytopenia, grade 4 or greater febrile neutropenia requiring hospitalization, or treatment delay of > 4 weeks as a result of unresolved toxicity during the first cycle of therapy (section 4.2.1). Decisions to escalate or expand a dose level will be based on the first course of treatment (section 6.3). To be evaluable for toxicity, a patient must receive at least 1 complete course of treatment and be observed for at least one week after completion. All patients enrolled are to be fully followed for toxicity, but any patients who are not evaluable for toxicity will be replaced during the dose escalation phase. Within the phase I component of the study a minimum of 6 and a maximum of 12 patients will be treated.

Phase II Portion

After the MTD/RP2D has been established a total of 40 patients will be treated (including those treated on the phase I component) at dose levels previously established to be safe. Objective complete response rate (CR + sCR) will be monitored using Simon's optimal 2-stage design. This study design is optimal in the sense that it minimizes the expected sample size among competing designs. The sCR rate of patients treated on the BiPD regimen was 6 % at a mean of 12 months. A similar or greater CR rate at 6 months with the addition of MLN9708 would justify evaluation of this regimen in larger, more definitive trials. We assume a one-sided type I error rate of 5% and desire at least 80% power to conclude that this regimen elicits a sCR rate significantly greater than 6% at 6 months if the true response rate of this regimen is 6% or higher. Under these assumptions, if 1 or fewer CR's are observed in the first 20 patients, the principal investigator may conclude that regimen is insufficiently active to warrant further study. Otherwise, accrual will continue to a total of 40 patients

9.2 Safety Monitoring

We will monitor safety throughout the conduct of the trial. Safety and toxicity will be reviewed monthly at the UCDCC Data Safety Monitoring Committee (DSMC) meetings, in which all toxicities (especially Grade 3+) are assembled and reviewed. In addition, safety boundaries will be used to flag excessive, unacceptable toxicities.

All deaths on treatment or within 30 days of the last treatment will be reported to UCDCC DSMC, as well as reviewed by the Protocol Chair, and independently by the DSMC. A second occurrence of a death that is deemed at least possibly related to one of the study drugs will lead to holding of accrual for review of all safety data to date and an evaluation of whether and how to amend the regimen or terminate accrual.

9.2.1 Monitoring DLTs

Criteria for flagging an excessive number of patients with DLT are based on the sequential probability ratio test with α=0.10, β=0.10, p_o=0.20 and p_a=0.40. Every time a patient is classified as having had a DLT, the cumulative number of patients (X) who have experienced a DLT will be compared to the number of patients (N) who are at risk. If the number of patients, N, is greater than N_X, the number given in the bottom row of the Table below, then the boundary has not been crossed. If N is less than or equal to N_X, then the boundary has been crossed and a careful review of all the toxicities and tolerability will be initiated.

Table: Boundary for Monitoring DLTs						
X: # pts who experienced a DLT	4	5	6	7	8	9
N_x: Boundary crossed if # pts. at risk (N) is $\leq N_x$	≤5	≤9	≤12	≤16	≤19	≤20

These rules were selected to ensure a reasonable chance that the boundary would not be crossed if the true chance of DLT were less than 20%-25% and a reasonable chance that the boundary would be crossed if the true chance were 45%-50%. The Table below summarizes these probabilities. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval).

Table: Probability that the DLT Monitoring Boundary is Crossed Because Too Many Patients Experienced a DLT							
True Chance of a DLT	0.20	0.25	0.30	0.35	0.40	0.45	0.50
Probability of Crossing the Boundary	0.05	0.12	0.24	0.41	0.58	0.74	0.85

9.2.2 Safety Monitoring During Phase 2

During the Phase 2 component of this trial, we will also monitor toxicities.

Patients must complete at least 2 cycle of therapy and complete 80% of the planned dose to be assessed for DLTs (as defined in 4.1.2)

9.2.3 Analysis of Results

All patients who begin treatment will be accounted for; basic demographic and clinical baseline data, number of courses begun, number of courses completed, reason off treatment, reason off study, total drug(s) received, reason for discontinuing treatment, toxicities (grade, type, cycle, and attribution) experienced, best response, and time to progression will be listed for each patient and summarized using standard descriptive methods.

All patients who receive any amount of either pomalidomide, clarithromycin, dexamethasone or ixazomib will be included in the summaries of toxicity. However in the Phase 1, to be included in decisions to dose escalate/expand, patients must have received at least 1 cycle of therapy and be observed for at least 1 week after completion or have experienced a DLT. Patients who do not receive the required doses or experience a DLT will be replaced.

Similarly in the Phase 2, all patients treated at the MTD/RP2D will be included in the estimates of the complete and partial remission rates, as well as PFS. However, patients who do not receive at least one cycle of therapy AND have bloods drawn at baseline and on days 15, and day 1 of subsequent cycles, will be replaced in order to complete immune correlative studies.

9.3 Pharmacokinetic Analysis

Individual and mean plasma ixazomib concentration data will be plotted over time. Degree of proteasome inhibition will be plotted against ixazomib concentration data. A summary table will be presented for the plasma concentration data. PK parameters will be estimated using noncompartmental analysis methods. A population PK analysis will also be explored. The plasma PK parameters calculated for individual plasma ixazomib concentration-time data will include, but are not limited to: Cmax, Tmax, and AUC. Clarithromycin effects on ixazomib will be assessed by comparing drug levels on day 1 and day 15 for phase 1 subjects.

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 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).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- 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 (e.g., 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.

10.1.3 Severity (Intensity)

All adverse events will be graded for severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

10.1.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

10.1.5 Prior Experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, when either the type of event or the severity of the event is not listed in the the current Product Label.

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.

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).

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)?

10.2.1 SAE Reporting to Principal Investigator

Since this is an investigator-initiated study, the principal investigator Dr. Joseph Tuscano, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to the FDA, to the sponsor-investigator's Ethics Committee or Institutional Review Board (IRB), and to Millennium Pharmacovigilance (or designee).

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

Regardless of expectedness or causality, all SAEs must be reported to Dr. Tuscano within 24 hours of learning of any serious adverse events occurring during the study or within 30 days of the last administration of study drugs.

10.2.2 SAE Reporting to Millennium Pharmacovigilance

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 dost 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).

Regardless of expectedness or causality, all SAEs must also be reported in English to Millennium Pharmacovigilance (or designee) per the following timelines:

- **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.

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

10.2.3 SAE Reporting to FDA

The sponsor-investigator will notify the FDA according to the following timelines:

- within seven (7) calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug;
- within fifteen (15) calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study particpation.

For adverse events that are are either serious but don't meet the criteria for expedited reporting or are not serious, the FDA will be notified at the time of the IND Annual Report.

If assistance is needed with completing the MedWatch form and/filing the IND safety report, you may contact the Protocol Development Officer/IND Manager.

10.2.4 SAE Reporting to IRB

Each investigative site will following local policies for reporting to their individual IRBs.

10.3 Procedures for Reporting Non-Serious Adverse Events

- The sponsor-investigator will notify the FDA of non-serious adverse events at the time of the annual report.
- Each investigative site will following local policies for reporting to their individual IRBs.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study 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 (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). 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 Institutional Review Board (IRB) Approval

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state

regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the UC Davis Comprehensive Cancer Center coordinating site:

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the site principal investigator and any associate investigators who will be involved in the study
- Investigator's signature on the protocol signature page
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.3 Patient Registration

Registration will be done centrally at UC Davis. To register a patient, the site's data manager must complete the Eligibility Checklist and FAX a copy of this and the informed consent including the Bill of Rights to the Clinical Trials Support Unit/UC Davis Comprehensive Cancer Center at 916-734-4177. If there are any questions, contact CTSU at 916-734-3604, or PI Dr. Joseph Tuscano [redacted] After verifying the eligibility; the CTSU Coordinator will register the patient onto the study and assign a patient accession number.

Registrations for this protocol must be made between the hours of 9am and 3pm (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol by non-UC Davis institutions must be on file prior to registration of patients at these institutions.

Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

Patients may be registered up to 72 hours prior to treatment initiation. The signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays must be

faxed to UC Davis CTSU in order to register the patient. The UC Davis Protocol Coordinator will review these documents and fax a registration confirmation within 3 hours.

If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Study Coordinator must be notified by fax 24 hrs prior to proposed treatment start date that the site has a patient to register.

The Study Coordinator will verify that the patient is eligible, that pre-study tests have been completed, and that the forms are complete. The Study Coordinator will then register the patient and assign a patient accession number. The Study Coordinator will fax back a registration confirmation including the patient accession number within 3 hours.

A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the coordinating site PI or Study Coordinator.

NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.

11.4 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

11.5 Data and Safety Monitoring/Auditing

Quality assurance audits of select patients and source documents may be conducted by Quality Assurance or Data Safety Committees at participating institutions or the UC Davis Comprehensive Cancer Center as outlined in the UC Davis Comprehensive Cancer Center Data and Safety Monitoring plan.

Quality control will be maintained by research units at participating institutions and the UC Davis CTSU Quality Assurance team according to CTSU policy.

Quality assurance audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are mailed/sent by from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the sponsor/PI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, Drug Accountability Record forms, patient registration lists, response

assessment scans, x-rays, etc. available for the audit.

11.6 Protocol Deviations

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center CTSU policies and the participating site's IRB policies.

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. Protocol amendments must also be reviewed and approved by Millennium prior to implementation. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the site's IRB for approval prior to implementation.

11.8 Data Collection Forms and Submission Schedule

All data will be collected using the UCD Database System (eVELOS) forms. All data forms will be completed, submitted and processed in accordance with UCD CTSU policies. See Appendix for Data Collection Schedule.

11.9 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.10 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring activities will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator or designee and will require his/her final signature to verify the accuracy of the data.

11.11 Product Complaints for Ixazomib

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 (in this case, ixazomib). Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints:
• 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 (refer to Section 8.2).

11.12 Pharmacokinetic (PK) Sample Collection and Handling

Blood samples for PK assessment must be collected (see Section 13.8 Pharmacokinetics) in 10-mL Vacutainer tubes containing K2EDTA as the anticoagulant. Resulting blood and plasma PK samples must be stored in plastic storage tubes with caps. No blood collection tubes with separation gel should be used.

All tubes must be labeled. The printed information must include the study number, patient identification number, treatment period, and scheduled sampling day and time. No other patient identifying (PHI) information will be written on the labels.

11.12.1 Preparation of Plasma Pharmacokinetic Samples

1. Draw blood into one labeled and chilled 10 mL lavender top K2EDTA Vacutainer tube (BD Vacutainer Ref #366643).

2. Mix the blood with the anticoagulant by gently inverting the tube 8-10 times and immediately place on wet ice.

3. Note: If a refrigerated centrifuge is not available, allow samples to chill on wet ice (mixture of ice and water) for 15 minutes prior to proceeding to step 3.

4. Centrifuge the blood samples for 10 minutes at 1006g at 4° C in a refrigerated centrifuge within 10 minutes of sample collection.

   Note: No more than 60 minutes should elapse between blood collection and freezing the plasma samples.

5. Immediately following centrifugation, gently remove the plasma from the packed cells, being careful not to disturb the cells by leaving approximately 3-4 mm of plasma above the buffy coat layer. Transfer plasma to a new, sterile 15 mL conical tube. Set aside packed cells in the original K2EDTA tube for additional processing.

6. Transfer two (2) aliquots of 0.5 mL (500 µl) of the pooled plasma into two transfer vial filled with lyophilized citric acid (study provided).
   a. Vortex tubes thoroughly to fully dissolve citric acid in the plasma.
   b. Tubes should be labeled "Ixazomib PK Split 1" and "Ixazomib PK Split 2", along with the unique patient study ID, the date and time of collection, as well as the time point (pre-dose, 30 min, 1 hour, etc)
   c. Freeze tubes immediately at -70 or below and batch ship to Tandem Labs as described in Section 11.12.3.

7. Return to the packed cells in the original K2 EDTA tube. Using a 1 mL pipette tip, collect as much of the whitish buffy-coat layer between the plasma and the red blood cells.
   a. Transfer buffy coat to a cryovial that contains 1 mL of phosphate buffered saline and pipette up and down gently to resuspend cells.
   b. Aliquot into two (2) cryovials at approximately 1 mL each and freeze at -70° C or below.

8. Keep samples frozen at -70°C or lower until shipment.

Radius (cm)	G-Force	RPM
10	1006	3000
12	1006	2738
14	1006	2535
16	1006	2371
18	1006	2236
20	1006	2121
22	1006	2022
24	1006	1936
26	1006	1860
28	1006	1793
30	1006	1732

Excel formula if rotor length not listed in above table:
RPM = SQRT((1006/(0.00001118*rotor length in cm))

Questions regarding handling the plasma pharmacokinetic specimens for ixazomib should be addressed to the contact person designated by Millennium.

11.12.2 Shipment of Pharmacokinetic Samples

All pharmacokinetic samples must be sent to the bioanalytical laboratories specified below in a single shipment at the end of the study or in multiple shipments as agreed upon with the lab.

The investigator must follow the instructions below:

- Notify the bioanalytical laboratories and the designated courier at least 24 hours in advance of the planned shipment. Provide the designated courier with the appropriate account number to be used, if applicable.
- Samples should be shipped via overnight delivery only on Monday through Wednesday, excluding holidays.
- Double-bag the frozen samples for each patient in bags that can withstand dry ice conditions.
- Pack the frozen samples in sufficient quantity of dry ice in appropriate containers, to maintain a frozen state for at least 3 days.
- Avoid direct contact between sample bags and dry ice by separating them with a dry ice resistant material (e.g., newspaper).
- For all biological samples, follow the International Air Transport Association (IATA) regulations for shipment.

- Ensure that the total package weight does not exceed 27.2 kg (60 pounds).
- Label the package with the sponsor-investigator name and study number.
- Include a return address (which includes the investigator's name) on the outside of each shipping container.
- Comply with all courier regulations for the shipment of biological specimens (include all paperwork).
- Retain all documents indicating date, time, and signature(s) of person(s) making the shipment in the study files.

As soon as shipment day and air bill number(s) are available, the site must call, email, or fax the bioanalytical laboratories. The call or fax must specify the study number, number of packages shipped, the number of pharmacokinetic samples, and the time of shipment pick-up.

11.12.3 Ixazomib PK Shipping

(Ixazomib PK samples currently have 618 days of stability in lyophilized citric acid and will need to be analyzed before reaching the end of their stability). An inventory list must be included with each shipment. The inventory list must note each specimen drawn for each patient, and note any missing specimens. An email including the tracking information and an electronic version of the manifest must be sent to the Tandem Lab contacts on the day of shipment.

Ship To: Tandem Labs



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13. APPENDICES

13.1 ISS Staging Criteria and Durie-Salmon Criteria

Stage	ISS Criteria[1]	Durie-Salmon Criteria[2]
I	Serum beta-2 microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	All of the following: • Hemoglobin > 10 g/dL • Serum calcium normal or ≤ 12 mg/dL • Bone x-ray, normal bone structure or solitary bone plasmacytoma only • Low M-component production rate o IgG < 5 g/dL o IgA < 3 g/dL o Bence Jones protein < 4 g/24 h
II	Neither stage I nor stage III	Neither stage I nor stage III
III	Serum beta-2 microglobulin ≥ 5.5 mg/L	One or more of the following: • Hemoglobin < 8.5 g/dL • Serum calcium normal or > 12 mg/dL • Advanced lytic bone lesions • High M-component production rate o IgG > 7 g/dL o IgA > 5 g/dL o Bence Jones protein > 12 g/24 h

Sub-classification Criteria for Durie-Salmon
A Normal renal function (serum creatinine level < 2.0 mg/dL)
B Abnormal renal function (serum creatinine level ≥ 2.0. mg/dL)

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[2] Durie BGM, Salmon SE: A clinical staging system for multiple myeloma. Cancer 1975:36(9):842-854.

13.2 IMWG Response Criteria for Multiple Myeloma

The International Myeloma Working Group uniform response criteria will be used for determining response to therapy and disease progression [Rajkumar 2011]. Minimal response will also be assessed, as adapted from the European Group for Blood and Marrow Transplant (EBMT) [Blade 1998].

Response Category	Response Criteria
sCR, Stringent Complete Response	CR as defined below plus: Normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
CR, Complete Response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow
VGPR, Very Good Partial Response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
PR, Partial Response	• ≥ 50% reduction of serum M-protein and reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h o If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria o If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of the M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
MR, Minimal Response	• 25% - 49% decrease in the serum M-protein, AND • 50 – 89% reduction in the urine M-protein, AND • 25% – 49% reduction in the size of extramedullary plasmacytomas (if present at baseline), AND • no increase in size or number of lytic bone lesions (development of compression fracture does not exclude

	response).*
SD, Stable Disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
PD, Progressive Disease	Progressive Disease requires any one or more of the following: 1. Increase of ≥25% from lowest response value in any of the following: • Serum M-protein (absolute increase must be ≥0.5 g/dL) AND/OR: • Urine M-protein (absolute increase must be ≥200 mg/24 hours) AND/OR: • For patients without a measurable serum or urine M-protein but measurable disease by serum free light chain testing: Difference between the involved and uninvolved serum free light chain level (absolute increase must be ≥10 mg/dL) AND/OR: • For patients without a measurable serum or urine M-component or serum free light chain level: % marrow involvement with myeloma (absolute increase must be ≥10%). AND/OR: 2. Definite development of new bone lesions or extramedullary plasmacytomas or definite increase in the size of existing bone lesions or extramedullary plasmacytomas AND/OR: 3. Hypercalcemia (corrected serum calcium > 11.5 mg/dL) attributable to myeloma (e.g. not due to omitted doses of biophosphonate).

13.3 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.

13.4 Cockcroft-Gault Equation

For males:

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

For females:

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

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

13.5 Cancer Therapy Satisfaction Questionnaire

Cancer Therapy Satisfaction Questionnaire
US English

The following pages ask some questions about your cancer therapy (IV/pills). Within this questionnaire, "Cancer therapy (IV/pills)" refers to your current or most recent cancer therapy or cancer pills (including: hormonal therapy, IV therapy, and cancer pills). Please read each question and answer as honestly as you can without the help of anyone. There are no right or wrong answers; the answers should be based on your own personal experiences.

Your Thoughts about Cancer Therapy (IV/pills)

The following statements ask you to share your **thoughts about cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best represents your opinion (check only one box per question).

In general, in the last four weeks, how *often did you feel*:		**Always**	**Most of the time**	**Some-times**	**Rarely**	**Never**
1.	That cancer therapy (IV/pills) would help you to return back to a normal life?	☐	☐	☐	☐	☐
2.	That cancer therapy (IV/pills) would get rid of the cancer?	☐	☐	☐	☐	☐
3.	That cancer therapy (IV/pills) would help prevent the cancer from coming back?	☐	☐	☐	☐	☐
4.	That cancer therapy (IV/pills) would stop the cancer from spreading?	☐	☐	☐	☐	☐
5.	That your cancer therapy (IV/pills) limited your daily activities?	☐	☐	☐	☐	☐
6.	Upset about the side effects?	☐	☐	☐	☐	☐
7.	That cancer therapy (IV/pills) was worth taking even with the side effects?	☐	☐	☐	☐	☐
8	That cancer therapy (IV/pills) would help you live longer?	☐	☐	☐	☐	☐

9. In general, **in the last four weeks**, how often did you think about stopping your cancer therapy (IV/pills)?

☐ Always ☐ Most of the time ☐ Sometimes ☐ Rarely ☐ Never

Satisfaction with Cancer Therapy (IV/pills)

The following statements are about your satisfaction with your **most recent cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best describes your level of satisfaction (check only one box per question).

10. **Overall**, how worthwhile was your cancer therapy (IV/pills)?

☐ Very worthwhile	☐ Quite worthwhile	☐ Moderately worthwhile	☐ A little worthwhile	☐ Not worthwhile at all

11. **Overall,** was taking cancer therapy (IV/pills) as difficult as you expected?

☐ Much more difficult than I thought it would be	☐ Somewhat more difficult than I thought it would be	☐ As difficult as I thought it would be	☐ Somewhat easier than I thought it would be	☐ Much easier than I thought it would be

12. **Overall,** how well did the **benefits** of cancer therapy (IV/pills) meet your expectations?

☐ Much better than my expectations	☐ Somewhat better than my expectations	☐ Met my expectations	☐ Somewhat worse than my expectations	☐ Much worse than my expectations

13. **Overall,** were the **side effects** of cancer therapy (IV/pills) as you expected?

☐ Much better than I expected	☐ Somewhat better than I expected	☐ Exactly as I expected	☐ Somewhat worse than I expected	☐ Much worse than I expected

14. How satisfied were you with the **form** of your cancer therapy (IV/pills)?

☐ Very satisfied	☐ Satisfied	☐ Neither satisfied nor dissatisfied	☐ Dissatisfied	☐ Very dissatisfied

15. **Overall,** how satisfied were you with your most recent cancer therapy (IV/pills)?

☐ Very satisfied	☐ Satisfied	☐ Neither satisfied nor dissatisfied	☐ Dissatisfied	☐ Very dissatisfied

16. Taking everything into consideration, if given the choice again, would you decide to take this cancer therapy treatment?

☐ Yes, definitely	☐ Probably Yes	☐ I don't know	☐ Probably not	☐ Definitely not

Thank you.

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13.6 EORTC QLQ-MY20

EORTC Multiple Myeloma Module (QLQ-MY20)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

SCRIPT

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

Specimen

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13.7 Schedule of Events

	Screen*	Cycle 1				Cycles 2-6		Maintenance Cycles	End of Treatment[16]	Follow-Up
		D1[1]	D8	D15	D22	D1	D15	D1		
Tests & Observations										
Demographics	X									
History and physical	X	X				X	X**	X	X	
Vital signs	X	X				X	X**	X	X	
Weight, BSA	X	X				X	X**	X	X	
ECOG Performance status	X	X				X	X**	X	X	
Height	X									
Adverse event evaluation [1]		X							X	
Concurrent medications [2]	X								X	
12-lead ECG [3]	X									
QOL questionnaires [4]	X					X		X	X	X[4]
Laboratory Studies										
CBC w/diff, plts [5]	X	X	X	X	X	X	X*	X	X	
CD4+ count, HIV viral load [6]	X					X[6]		X	X	
Serum chemistries [7]	X	X		X		X	X*	X	X	
PT, PTT	X									
Serum or urine HCG [8]	X	X	X	X	X	X		X	X	
β2-microglobulin	X									
Staging										
Radiologic Tumor Measurement [9]	X					X[15]		X[15]	X[15]	
Skeletal survey [10]	X								X[11]	
Bone marrow aspiration & biopsy with cytogenetics [11]	X					X[15]		X[15]	X[11]	
M-protein assessments [12]	X					X		X	X	X[12]
Treatment										
Dispense study drugs [13]		X				X		X		
Pomalidomide		Days 1-21				Days 1-21		Days 1-21		
Ixazomib		Day 1, 8, 15				Days 1, 8, 15		Days 1, 8, 15		
Clarithromycin		Days 15-21				Days 1-21		Days 1-28		
Dexamethasone		Days 1, 8, 15, 22				Days 1, 8, 15, 22		Days 1, 8, 15, 22		
Perform drug accountability						X		X	X	
Pharmacokinetic Studies See Section 13.8										
Collection for use in future correlative studies										
Peripheral blood collection [14]		X[14]		X[14]		X[14]			X[14]	
Follow-up										
Obtain date of disease progression										X[17]
Obtain survival information										X[17]

Treatment Cycle is defined as 28 days. See Section 13.8 for Pharmacokinetics.

* Screening timelines

- To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical.
- To be completed ≤ 28 DAYS before registration: ECG and QOL.
- To be completed ≤ 42 DAYS before registration: Radiologic Tumor Measurement and Skeletal survey.
- To be completed ≤ 100 DAYS before registration: Bone marrow aspirate and biopsy

†Cycle 1, Day 1 is baseline. All baseline evaluations/procedures are to be conducted at Cycle 1, Day 1 before dosing or within 3 days before the first dose of drug unless otherwise specified. Evaluations/procedures for subsequent cycles CXD1 are to be conducted within 3 days before the drug dosing unless otherwise specified.

** To be performed during Phase I only

1. Adverse event: Adverse events to be collected once the patient signs consent form and throughout the study until at least 28 days after the last dose of study drug or until the patient starts a new treatment, whichever comes first. See Section 10 for more information.
2. Concomitant medications: Concomitant medications taken during the study are to be recorded in the patient's medical record up until 28 days after last study dose or until the start of a new treatment, whichever comes first.
3. ECG: 12-lead ECG to be performed at screening. Additional ECGs may be performed if clinically indicated.
4. QOL questionnaires: Cancer Therapy Satisfaction Questionnaire and the EORTC QLQ-MY20. During the follow-up period, the QOL questionnaires will be obtained at approximately 2 years and 3 years following registration.
5. CBC with differential and platelets must be performed within 24 hours of the scheduled study drug administration.
6. CD4+ count, HIV viral load: CD4 count and HIV viral load to be performed during screening. CD4 counts will also be performed on Day 1 of every odd cycle starting at Cycle 3; HIV viral load will be assessed at the same time points only for those patients with HIV. CD4 count and percentages will be quantified. HIV viral load studies will be performed using an assay with a limit of detection of 50 copies/mm^3 or less.
7. Serum chemistries: Complete Metabolic Panel (CMP) to include: glucose, BUN, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, and total bilirubin. Magnesium, phosphorus and LDH are also determined. Serum chemistries must be performed within 24 hours of the scheduled study drug administration.
8. Serum or urine HCG pregnancy test must be performed for all females of childbearing potential. Must be done within 10-14 days of study initiation and again within 24 hours prior to initiation of pomalidomide for each cycle. Pregnancy test must be performed weekly during the first month, then monthly thereafter in women with regular menstrual cycles (or every 2 weeks in women with irregular menstrual cycles). A new cycle of pomalidomide cannot be dispensed until a negative pregnancy test is confirmed.
9. Radiologic tumor measurements. Baseline scans can include either: 1) a CT or MRI, or 2) a whole body FDG-PET scan and diagnostic CT performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness. Baseline scans are NOT required for those patients who do not have documented or suspected measurable extramedullary plasmacytomas at the time of enrollment. Baseline scans are required ≤ 42 days prior to registration for those with known or clinically suspected measurable extramedullary disease. Measurable extramedullary disease is required prior to starting maintenance treatment and at the end of treatment if not performed within the last eight weeks, unless study treatment was stopped due to disease progression. The same imaging modality initially used to measure disease at baseline should be used over the course of the study to document response/progression.
10. Skeletal survey: A baseline skeletal survey should be completed ≤ 42 days prior to registration. A repeat skeletal survey will be obtained to confirm a CR or sCR. Otherwise, the skeletal survey should be repeated as clinically indicated.
11. Bone marrow aspiration & biopsy with cytogenetics should be completed ≤ 100 days prior to registration to determine: 1) Marrow burden of myeloma. Note: flow cytometry should NOT be used to assess marrow burden of disease. Marrow burden should be determined by aspirate differential and CD138 immunohistochemistry. 2) Fluorescent in situ hybridization testing for the following high-risk cytogenetic abnormalities: t(4;14), t(14;20), t(14;16), del(17p) and gain of 1q21. **Plasma cell purification prior to FISH testing is strongly recommended.** A repeat bone marrow aspirate and biopsy should be performed within 14 days after CR or sCR is documented.
12. M-protein assessments includes Serum protein electrophoresis (SPEP), serum immunofixation, serum free kappa and lambda light chain levels, quantitative serum IgG, IgA and IgM, urine protein electrophoresis and immunofixation. Follow-up assessments will be performed every 2 months after completion of treatment until disease progression or for up to 3 years after the last patient has been enrolled. At these follow-up assessments, patients are followed for disease status, survival, long-term toxicities, and second malignancies. Once a patient progresses, disease assessments are no longer required.
13. Only enough pomalidomide for 1 cycle of therapy may be provided to the patient each cycle. See Section 6 for study drug doses.
14. Peripheral blood for correlative studies should be collected at the same time blood is drawn for hematology and chemistries when possible, and prior to drug administration. Blood is collected prior to study drug administration on Day 1 of Cycle 1, Day 15 of Cycle 1, Day 1 of subsequent cycles, and at the end of treatment.
15. As clinically indicated, at emergence of new symptoms, or at treating physician's discretion.
16. An end of treatment visit should occur within 4-6 weeks of permanently discontinuing study treatment for any reason.
17. Follow-up visits: For those patients discontinuing study treatment prior to disease progression, follow-up visits should occur approximately every 2 months until disease progression (any additional follow-up assessments should be performed according to institutional practice); thereafter, survival information will be obtained. Patients will be followed for survival information and data regarding start of new treatment (if applicable) approximately every 3 months until 3 years following registration. Survival information may be collected by routine clinic visits or telephone.

13.8 Pharmacokinetics

	Pharmacokinetic Sampling (Phase 1)							
		Post-dose in Cycle 1 on days 1 and 15						
		Hours						
	Pre-Dose	0.5 (± .1)	1.0 (± .25)	1.5 (± .25)	2 (± .25)	4 (± .75)	8 (± 1.0)	24 (± 1.0)
PK	X	X	X	X	X	X	X	X
Proteasome Inhibition	X				X	X	X	X

	Pharmacokinetic Sampling (Phase 2)
	Cycles 2 and 3 on day 1
	2-6 hours after dose
PK	X
Proteasome Inhibition	X

Notes:

1. Proteasome inhibition samples will be obtained from the same tube of the PK blood draw.
2. On PK sampling days, cycle 1 days 1 and 15 (phase 1) and cycles 2-3 day 1 (phase 2), clarithromycin will be administered immediately prior to pomalidomide and ixazomib.

13.9 PILL DIARIES

There are three pill diaries associated with this study. Refer to:

Clarithomycin BID
Clarithomycin QD
Pomalidomide, Ixazomib and Dexamethasone (All Patients)

13.10 Data Collection Forms and Submission Schedule

All data will be collected using the UCD Database System (eVELOS) forms. Copies of the completed forms will be submitted to UC Davis data coordinating center for data entry and storage in a secure location. The original data collection forms will reside in secure location. Any and all source documentation should be maintained.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form

- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  In-House Pre-Study Evaluation Form (IH-102)

- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form

- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  Adverse Event/Drug Relationship Form

- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  In-House Treatment Cycle Form (IH-201)

- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:
  Tumor Measurement Log

- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Clinical Trials Support Unit: Notice of Protocol Deviation

- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL.