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MCCC Add 13

Mayo Clinic Cancer Center

Phase 1/2 trial of Ixazomib in combination with cyclophosphamide and dexamethasone in patients with previously untreated symptomatic multiple myeloma or light chain amyloidosis

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Drug Availability
Commercial Agents: Cyclophosphamide, Dexamethasone
Drug Company Supplied: Ixazomib

√Study contributor(s) not responsible for patient care.

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Drug administration, infusion pumps, nursing guidelines	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Adverse Events (paper AdEERS, MedWatch, Non-AER, AML/MDS)	[redacted]

*No waivers of eligibility per NCI

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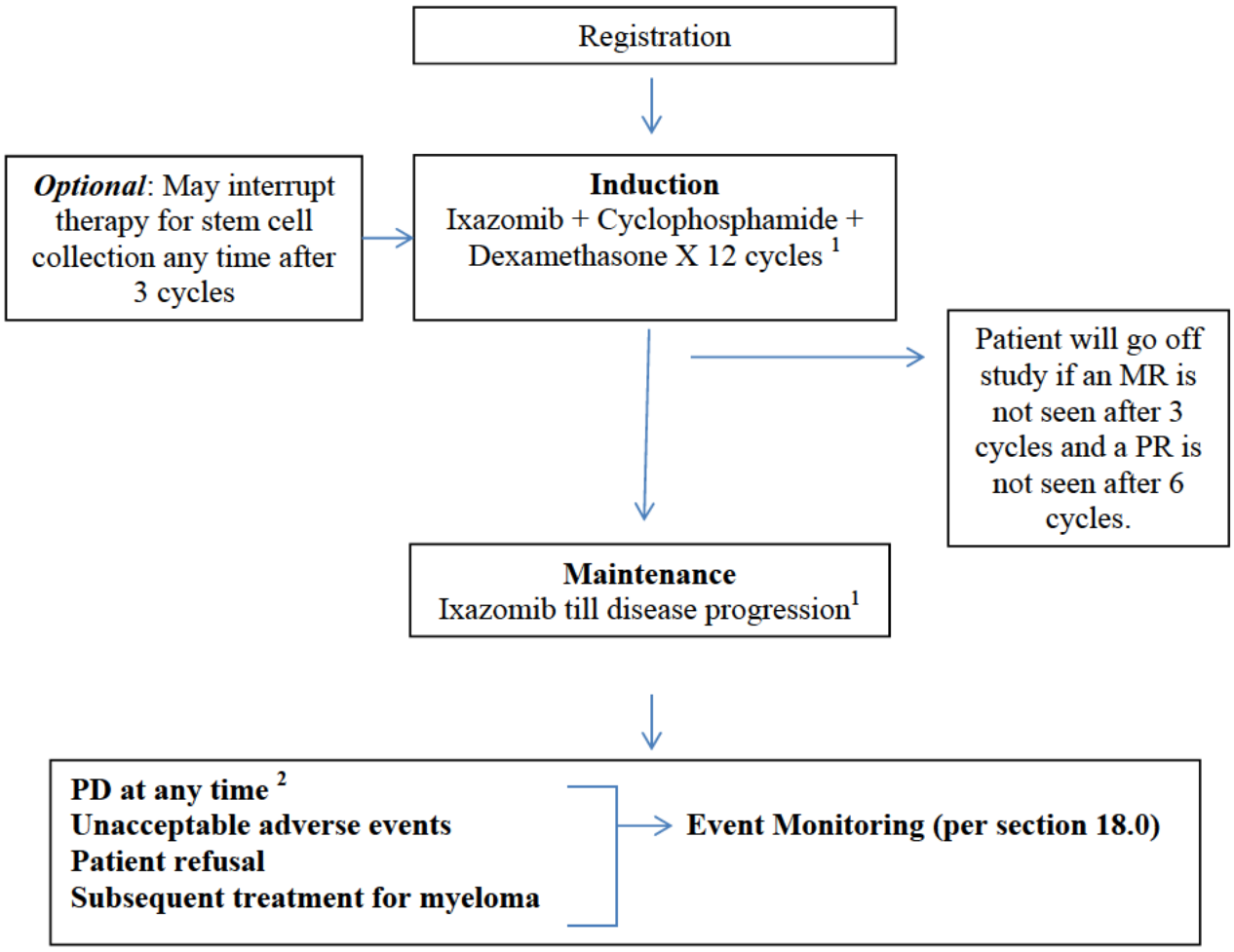
Schema (Cohort A; Multiple Myeloma)

Phase I only: Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.

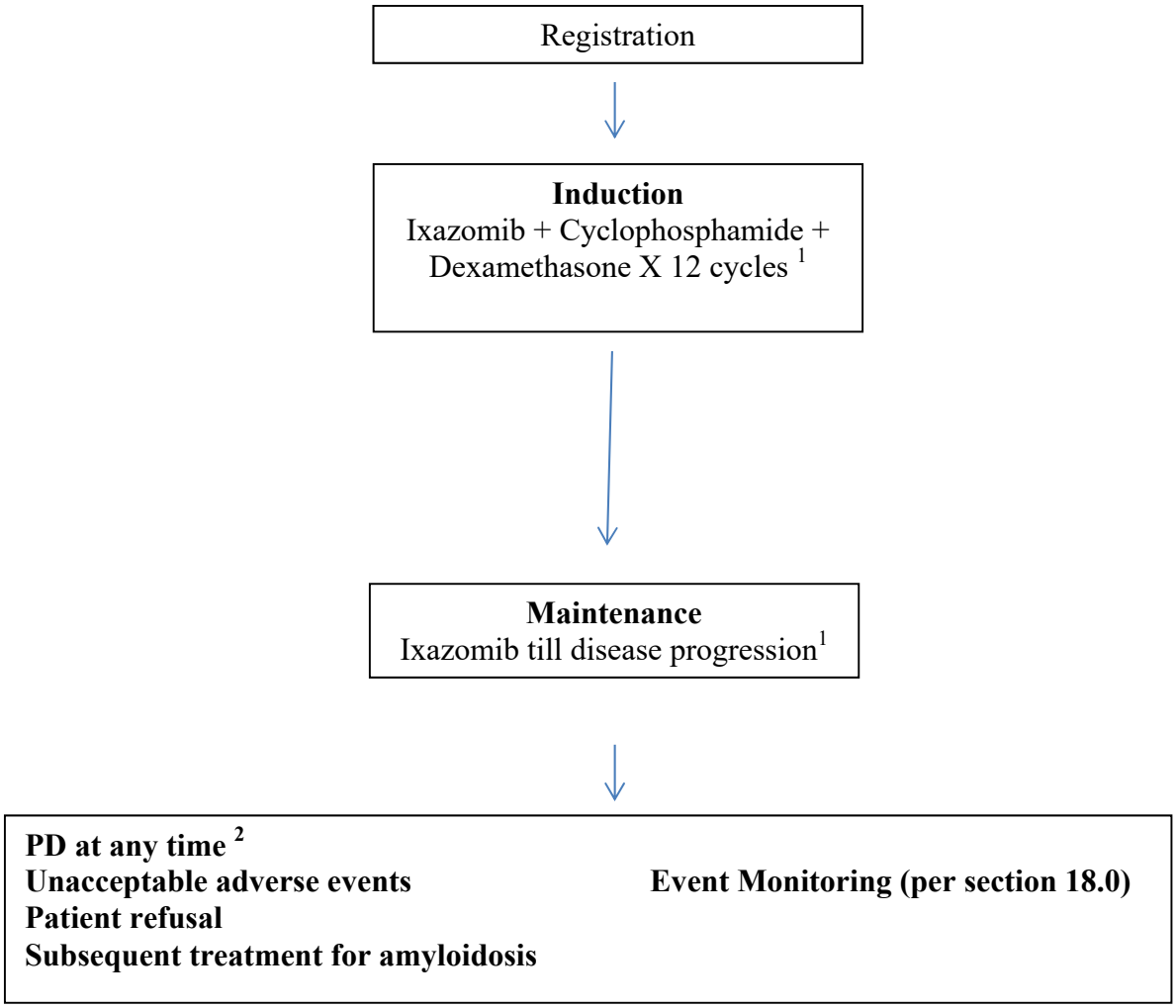


If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

[1] Cycle length = 28 days
[2] Confirmation of PD is not required

Generic name: Ixazomib Brand name(s): Mayo Abbreviation: Ixazomib Availability: Provided by Millennium Pharmaceuticals, Inc.	Generic name: Dexamethasone Brand name(s): Decadron Mayo Abbreviation: DXM Availability: Commercial	Generic name: Cyclophosphamide Brand name(s): Cytoxan Mayo Abbreviation: CTX Availability: Commercial

Schema (Cohort B; AL cohort)



If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

1 Cycle length = 28 days

1.0 Background

1.1 ***Multiple Myeloma:*** Multiple myeloma is a malignancy of the differentiated plasma cells, that affect the older patient with a median age at onset of 65-70 years and a slight male predominance. Nearly 20,000 patients with myeloma are diagnosed in the United States each year, and despite considerable improvements in therapy remains incurable and uniformly fatal with a median overall survival of around 8 years. Recent improvements in therapies have significantly improved the survival outcomes, but given the inevitable relapses seen in these patients, new approaches to therapy are clearly needed. The highly effective drug combinations currently used are beset with a degree of toxicity that precludes long-term therapy and also can affect the quality of life metrics. Finally, some of these regimens require IV or subcutaneous administration, which can require frequent clinic, visits for patients. The highly effective multi-drug regimens currently in use typically include a proteasome inhibitor, either bortezomib given IV or SQ or carfilzomib given IV.

1.2 ***The ubiquitin proteasome pathway in multiple myeloma:*** The ubiquitin-proteasome pathway is critical to cellular homeostasis, playing a major role in maintaining appropriate levels of different proteins in the cell.[1,2] The ubiquitin-proteasome system is responsible for the orderly degradation of cellular proteins involved in virtually all aspects of cell growth and proliferation. The pathway degrades proteins involved in cell cycle regulation, cell survival, and metastasis such as p53, p21, p27 and NFkB. Ubiquitin is a 9kd protein that is abundantly present in the cell and is highly evolutionary conserved. Cellular proteins that are marked for degradation gets polyubiquitinated; where C-terminal glycine residues of the ubiquitin molecules attach covalently to specific lysine residues on the protein molecule. This three step process sequentially involves the ubiquitin activating enzyme E1, an ubiquitin conjugating enzyme E2 and an ubiquitin ligase E3. The first ubiquitin molecule forms the nidus for additional ubiquitin molecules to be attached. Once, polyubiquitinated, the protein is targeted by the 26S proteasome for degradation, an active energy requiring process that maintains protein levels in the cell. The 26S proteasome in the mammalian cells consists of a core 20S catalytic complex and a 19S regulatory complex. It is a cylindrical structure with an outer ring composed of 7 alpha subunits and an inner ring that is made up of seven beta subunits. The 20S catalytic portion has chymotryptic, tryptic and peptidylglutamyl like activities, with the catalytic sites located in the inner surface of the cylinder. The ubiquitinated protein is recognized by the 19S subunit, the ubiquitin tags are cleaved, and the protein is hydrolyzed by the proteasome at six different catalytic sites present in the 20S catalytic complex. In vitro studies in a variety of cancers demonstrate the ability of proteasome inhibitors to selectively target the malignant cells supporting this strategy for cancer therapy. The mechanism of selectivity is not clear, but may be related to increased dependency of rapidly proliferating cells on the pathway. Bortezomib was the first proteasome inhibitor to enter human trials.[3]

In the setting of MM, several in vitro studies have shown the ability of proteasome inhibitors to inhibit proliferation and induce apoptosis of MM cell lines and freshly isolated patient MM cells as well as overcome adhesion mediated resistance.[4] They can inhibit the paracrine growth of human MM cells by decreasing their adherence to bone marrow stromal cells (BMSCs) and related nuclear factor κB-dependent induction of interleukin-6 secretion by BMSCs. The mechanism of anti-MM activity of proteasome inhibitors are likely multiple. Transcriptional profiling of MM cells treated with bortezomib, a proteasome inhibitor currently in the clinic, demonstrated down-regulation

of growth/survival signaling pathways, and up-regulation of molecules implicated in pro-apoptotic cascades, as well as up-regulation of heat-shock proteins and ubiquitin/proteasome pathway members. In addition, treatment decreased the levels of several anti-apoptotic proteins and triggered the release of mitochondrial cytochrome *c* and caspase-9 activation, all contributing to apoptosis of MM cells. One of the key effects is thought to be the inhibition of the NFkB pathway, which is critical to the MM cell proliferation induced by growth factors as well as adhesion to BMSC. Other purported mechanisms include (*i*) activation of classical stress response proteins such as heat shock proteins, Hsp27, Hsp70, and Hsp90; (*ii*) up regulation of c-Jun-NH2-terminal kinase (JNK); (*iii*) activation of extrinsic apoptotic signaling through Bid and caspase-8 cleavage; and (*iv*) inactivation of DNA-dependent protein kinase (DNA-PK), which is essential for the repair of DNA double-strand breaks.

1.3 ***Initial therapy of multiple myeloma***: The treatment paradigms for multiple myeloma have undergone a significant change in the past decade.[5,6] A decade ago, patients who were considered eligible for transplant underwent the procedure after a brief duration of therapy with a steroid based regimen with or without doxorubicin. Patients ineligible for transplant went on to receive melphalan and prednisone. With these treatment approaches patients had a median survival of 3-4 years, with nearly 10-20% of patients dying in the first year after diagnosis. During the last decade several new drugs were introduced such as thalidomide and its analogue lenalidomide and the proteasome inhibitor bortezomib and these along with continued use of transplant has led to improved survival in myeloma.[7] In fact, in the recent clinical trials 3-year survival has approached 90% and 1-year mortality has dropped to under 2%.[8] This progress has come through a series of investigations examining the efficacy of the new drugs used in various combinations and sequences. Initial trials in the relapsed setting confirmed significant clinical activity for all these new drugs. This was followed by several clinical trials that examined the combination of novel agents with dexamethasone in the setting of newly diagnosed disease. The studies consistently demonstrated superior response rates, deeper responses, and improved progression-free survival for patients undergoing initial therapy with novel agents.[8-11] The trials examined the role of the new drugs in the context of transplant eligible and ineligible patients. This has been followed by three drug regimens that either combined the new drugs together or incorporated an alkylator drug to the novel agent-dexamethasone combination. These have included combinations of bortezomib and dexamethasone with thalidomide (VTD), lenalidomide (VRd) or cyclophosphamide (VCD).[9,10,12,13]

Of particular interest are the VCd and VRd regimens, both of which have shown high efficacy rates and are increasingly used for initial therapy in the community.[9,13] In a phase 2 study, Reeder et al showed that initial therapy with bortezomib, cyclophosphamide and dexamethasone is associated with high rate of deep responses among patients with previously untreated myeloma, being considered for autologous stem cell transplantation. Similarly, VRd regimen has been associated with high response rates approaching 100% and deep responses with very good partial response rates and complete response rates of over 70 and 40% respectively. It has proven to be a highly effective initial therapy for patients planning stem cell transplantation with no significant effect on the ability to successfully mobilize stem cells.

In the EVOLUTION trial, patients were randomized to receive bortezomib 1.3 mg/m^2 d 1, 4, 8, 11 and dexamethasone 40 mg d 1, 8, 15, with either cyclophosphamide 500 mg/m^2 d 1, 8 and lenalidomide 15 mg d 1–14 (VDCR), lenalidomide 25 mg d1-14 (VRd),

cyclophosphamide 500 mg/m^2 d 1, 8 (VCD) or cyclophosphamide 500 mg/m^2 d 1, 8, 15 (VCD-mod) in a 21 day cycle (maximum 8 cycles).[13,14] This was followed by bortezomib 1.3 mg/m^2 (d 1, 8, 15, 22) for four 42-day maintenance cycles in all arms. VGPR or better was seen in 58, 51, 41 and 53% (CR rate of 25, 24, 22 and 47%) of patients (VDCR, VRd, VCD 8-and VCD-mod arms, respectively); the corresponding progression-free survival (PFS) at 1 year was 86, 83, 93 and 100%, respectively. Common adverse events included hematological toxicities, peripheral neuropathy, fatigue, and GI disturbances. Overall no substantial advantage was noted with the addition of cyclophosphamide to VRd, but the regimen did lead to more hematological toxicities. An important outcome of this trial was the similar results obtained with the VRd and VCd regimens, especially considering the cost differential between the two regimens.

1.4 ***Light chain amyloidosis:*** Light chain amyloidosis is characterized by light chain secreting plasma cells in the bone marrow, usually in small numbers, but leading to formation and deposition of amyloid protein in different organs including the heart, kidneys and liver. While therapeutic options have improved over time and patients with AL are living longer, it remains incurable and patients invariably need additional therapeutic options. The median survival of patients with AL amyloidosis is 18-24 months with nearly 40% dying within the first year of diagnosis. 1-4. Traditionally, therapies that have appeared to be promising for treatment of patients with myeloma have been studied in the context of amyloidosis, given the fundamental similarities in the disease.

The combination of melphalan and prednisone has been in use for decades and results in approximately 20-30% of patients achieving a measurable response 5-7. Several prospective randomized studies have demonstrated that chemotherapy-treated patients have a longer median survival than patients who do not receive chemotherapy 8-10. The median survival of the melphalan- and prednisone (MP) treated group of patients in a phase III trial conducted at Mayo Clinic was 17 months compared to 8.5 months for those not receiving MP9. Even though this represented a significant improvement, the outcome still remained dismal and patients with significant cardiac disease had a median survival of only six months. Patients in this trial who achieved a reduction in their paraprotein level had a longer survival compared to those who did not highlighting the importance of hematologic response. A similar trial conducted at the Boston University resulted in similar improvements with Melphalan and prednisone10. Majority of patients fail to demonstrate objective evidence of disease regression and ultimately succumb to their disease.

High dose therapy and melphalan with autologous peripheral blood stem cell transplantation has been used for treatment of amyloidosis, given its efficacy and survival advantage in patients with multiple myeloma 11-13. Case controlled studies have demonstrated that high dose therapy improves survival in patients with amyloidosis who are eligible to go through the procedure 14. Stem cell transplant results in improvement in the organ function in over half of the patients who survive the process13. Many of these responses also tend to be durable. However, there remains considerable selection bias as case controlled studies have shown that patients eligible for a stem cell transplant have better overall performance status and are likely to do better than the average patient even with out stem cell transplant15. Moreover, this modality is not feasible in nearly two thirds of AL patients due to poor performance status and advanced organ involvement. The risk of mortality is considerable (20-40% in different series) and increases with the

degree of individual organ involvement as well as the number of organs involved. So alternative, effective and less toxic regimens are needed for the majority of patients with this disease.

More recently, studies have highlighted the role of proteasome inhibitors in the treatment of AL amyloidosis. This agent is of particular importance given the ability to reduce immunoglobulin free light chain levels and the critical role of the free light chains in the amyloid pathophysiology. Bortezomib has been used in combination with dexamethasone alone or cyclophosphamide or melphalan along with dexamethasone. Kastritis et al reported on 94 patients from three centers treated with bortezomib and dexamethasone, with nearly 80% of the patients with relapsed disease.16 A hematologic response was achieved in 71%, including 25% complete responses. Previously untreated patients had a 47% CR rate. Hematologic responses were associated with a cardiac response and NT-proBNP reduction. Toxicity was manageable and mostly consisted of neuropathy, orthostasis, peripheral edema, and constipation or diarrhea. Reece et al studied 31 patients in a dose escalation study of bortezomib given weekly or twice weekly and observed hematologic responses in 50% of 30 evaluable patients, including 20% complete responses.17 More recently, Venner et al studied 43 patients treated with AL cyclophosphamide, bortezomib, and dexamethasone.18 The overall hematologic response rate was 81.4%, including complete response in 42% and very good partial in 51.4%. The estimated 2-year progression-free survival was 66.5% for patients treated upfront and 41.4% for relapsed patients.

Ixazomib is the first oral proteasome inhibitor introduced in the clinic, and is currently approved for use in relapsed myeloma. 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.19,20 Ixazomib has also been studied alone and in combination with dexamethasone in patients with relapsed disease not refractory to bortezomib. Thirty-three patients with relapsed multiple myeloma were treated with Ixazomib at 5.5 mg weekly for 3 of 4 weeks. Dexamethasone was added for lack of a minor response (MR) by end of cycle 2 or lack of a partial response (PR) by end of cycle 4 or for disease progression at any time. Median age was 69 years; patients had a median of two prior therapies (range 1-7). Dexamethasone was initiated in 22 (67%) patients, 17 for not reaching the desired response and 5 for progression. Response (⩾PR) to single agent was seen in five patients within four cycles of therapy including three patients with PR, one patient with complete response (CR) and one patient with stringent CR. Six additional patients with either an MR (2) or SD (4) achieved a PR after addition of dexamethasone, translating to an overall response rate of 34%. Ongoing studies continue to investigate both single-agent Ixazomib and Ixazomib in combination with standard treatments. A recently reported phase 3 trial of Ixazomib in combination with lenalidomide and dexamethasone in relapsed myeloma with 1-3 prior treatments demonstrated a significant improvement in PFS. Previously a phase 2 trial of the same combination in newly diagnosed myeloma was very effective with high rate of responses, deep responses and well tolerated with the ability to administer the drug long term.21 Ixazomib also appear to combine well with cyclophosphamide and has been shown to be effective in relapsed and newly diagnosed myeloma.

1.5 ***IXAZOMIBIxazomib:*** Ixazomib, which has been formulated for both intravenous (IV) and oral (PO) administration, is a small molecule proteasome inhibitor. It is the citrate ester of the biologically active boronic acid form, MLN2238, which is structurally similar

to bortezomib. In water or aqueous systems, Ixazomib rapidly hydrolyzes to MLN2238, therefore all doses and concentrations are expressed as MLN2238. Nonclinical studies were conducted with a solution of either MLN2238 or MLN2238 in equilibrium with Ixazomib. Similar to bortezomib, MLN2238 potently, reversibly, and selectively inhibits the 20S proteasome. However in contrast to bortezomib, it has a shorter dissociation half-life (t1/2) that may contribute to increased tissue distribution. Bortezomib has a slowly reversible dissociation rate from the red blood cell proteasome, while MLN2238 demonstrates a more rapidly reversible dissociation rate from the blood but sustained effects on bone marrow and tumor proteasomes suggesting better tissue distribution. The pharmacologic implications of this difference in binding kinetics and tissue distribution may in turn result in differences in safety and efficacy profiles in a broader range of tumors. In xenograft-bearing mice, the more rapid dissociation rate correlates with an increased ratio of tumor proteasome inhibition to blood proteasome inhibition, and Ixazomib shows greater antitumor activity in several xenograft models, both solid tumor and bortezomib-resistant xenografts, than bortezomib.

Nonclinical Pharmacology: MLN2238 refers to the biologically active, boronic acid form of the drug substance, Ixazomib. Ixazomib refers to the citrate ester of MLN2238. In water or aqueous systems, the equilibrium shifts from Ixazomib to the biologically active boronic acid form MLN2238. All doses and concentrations are expressed as the boronic acid, MLN2238.

In Vitro Pharmacology: MLN2238 preferentially binds the β5 site of the 20S proteasome; at higher concentrations, it also inhibits the activity of the β1 and β2 sites. MLN2238 inhibits ß5 site 20S proteasome activity in vitro, with a half-maximal inhibitory concentration (IC50) of 3.4 nM. Potency is reduced roughly 10-fold versus ß1 (IC50 31 nM) and 1,000-fold versus ß2 (IC50 =3500 nM). MLN2238 was also tested for inhibition against a panel of 103 kinases, 18 receptors (neurotransmitter, ion channel, brain and gut receptors), and 9 serine proteases. In all cases, the IC50 values were > 10 μM. MLN2238 and bortezomib have different β5 proteasome dissociation half-lives (t1/2), reflecting differences in their on-off binding kinetics (the β5 proteasome dissociation t1/2 for MLN2238 and bortezomib are 18 and 110 minutes, respectively). Based on these favorable characteristics, Ixazomib is anticipated to be effective against multiple myeloma. (Ixazomib Investigator's Brochure (IB). Proteasome inhibition results in the accumulation of poly-ubiquitinated substrates within the cell and leads to cell cycle disruption, with concomitant activation of apoptotic pathways and cell death. Consistent with inhibition of ß5 20S activity, MLN2238 demonstrated potent activity against cultured MDA-MB 231 human breast cancer cells in the WST cell viability assay. In nonclinical models MLN2238 has activity against both solid tumor and bortezomib-resistant xenografts

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

inhibition and in changes in GADD34 and ATF-3 expression. In WSU-DLCL2 xenografts, greater tumor proteasome inhibition was observed with MLN2238 compared to bortezomib and resulted in increased expression of GADD34 and ATF-3. MLN2238 efficacy experiments demonstrated strong antitumor activity in 4 xenograft models: CWR22 (a human prostate cancer cell line) and 3 human lymphoma cell lines (WSU-DLCL2, OCI-Ly7-7D1-luc, and PHTX-22L). In the case of the CWR22 xenograft model, significant antitumor activity was seen with both IV and PO dosing, demonstrating that this molecule has antitumor activity when administered via different dosing routes. In all 3 lymphoma lines, MLN2238 demonstrated stronger antitumor activity than did bortezomib. In summary, MLN2238, similar to bortezomib, is a dipeptide boronic acid proteasome inhibitor that potently, reversibly, and selectively inhibits the proteasome. There are several features, such as sustained pharmacodynamic effects and activity in a bortezomib-refractory lymphoma xenograft model, that suggest that it may have activity that extends beyond that seen with bortezomib.

Nonclinical Pharmacokinetics and Pharmacodynamics: Nonclinical Pharmacokinetics: The pharmacokinetic (PK) properties of MLN2238 were studied in severe combined immunodeficient (SCID) mice bearing human CWR22 tumor xenografts, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Because of the extensive red blood cell (RBC) partitioning of MLN2238, both blood and plasma PK parameters were determined in these studies. MLN2238 had a very low blood clearance (CLb) and a moderate blood volume of distribution at steady-state (Vss,b) after IV administration. The concentration-versus-time curve of MLN2238 displayed a distinct bi-exponential profile with a steep initial distribution phase and a long terminal $t_{1/2}$ (> 24 hr) in all species tested. MLN2238 had higher plasma clearance (CLp) and a larger plasma volume of distribution at steady-state (Vss,p) than in blood, largely because of the extensive RBC partitioning. The PK properties of MLN2238 after oral administration were studied in rats and dogs. The plasma oral bioavailability (F) was 41% in rats and nearly 100% in dogs. A clinical prototype formulation of the Ixazomib capsule demonstrated that MLN2238 had excellent oral F and an excellent absorption profile in dogs. In addition, interindividual variability, as measured by %CV, in Cmax and $AUC_{0\text{-}24hr}$ after oral administration was low to moderate, similar to that after IV administration. The terminal $t_{1/2}$ after oral administration was also similar to that after IV administration. Comparison of the PK profiles after IV or PO administration in the dog is reported in further detail in the IB. MLN2238 is predicted to have very low CLb (0.0045 L/hr/kg) and a moderate Vss,b (0.79 L/kg) with a long terminal $t_{1/2}$ (> 24 hours) in humans. The human efficacious IV dose of MLN2238 is predicted to be 2.0 mg/m^2 (0.054 mg/kg) twice weekly. The human efficacious oral dose is predicted to be between 2 and 5 mg/m^2 twice weekly, based on a predicted oral F of between 41% (as seen in rats) and 100% (as seen in dogs). The efficacious dose projection for once weekly oral would be higher than twice weekly oral (data not provided).

Metabolism appears to be a major route of elimination for MLN2238 and urinary excretion of the parent drug was negligible (< 5% of dose). In vitro in liver microsomes, the metabolism of MLN2238 was high in mice and low to moderate in all other species studied. MLN2238 is metabolized by multiple cytochrome P450 (CYP) isozymes and non-CYP enzymes and proteins. The rank order of relative biotransformation activity of each of the 5 major human CYP isozymes in the in vivo studies was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (negligible).

MLN2238 is neither an inhibitor of CYP isozymes 1A2, 2C9, 2C19, 2D6, or 3A4 (IC50 > 30 μM, with an estimated inhibition dissociation constant [Ki] > 15 μM) nor a time dependent inhibitor of CYP3A4/5 (up to 30 μM). The potential for Ixazomib treatment to produce DDIs via CYP inhibition is inferred to be low.

In a Caco-2 cell assay, MLN2238 showed medium permeability with a B-to-A/A-to-B permeability ratio of 2.9. MLN2238 may be a low-affinity substrate of para-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) efflux pump transporters. MLN2238 is not an inhibitor of P-gp, BCRP, and MRP2 (IC50 > 100 μM). Consequently, the potential for MLN2238 to cause DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is low.

See the IB for further details.

1.4 ***Safety Pharmacology***: In exploratory safety pharmacology studies, MLN2238 was a weak inhibitor of the cloned cardiac potassium (K+) human ether à-go-g o related gene (hERG) channel, with an IC50 of 59.6 μM, which exceeds, by approximately 200-fold, the plasma Cmax (111 ng/mL [0.3 μM]) predicted to occur in humans at the optimally efficacious dose after IV administration.

In the GLP-compliant, 1-cycle, repeat-dose, PO toxicology study in beagle dogs, an increase in QTc was seen in male dogs at non-tolerated doses, and a potential increase in QTc was seen in male dogs at tolerated doses. However, increased QTc was not seen in female dogs at any dose, despite the fact that female dogs had plasma Cmax values similar to those of male dogs. Additionally, in a GLP-compliant, 2-cycle, repeat-dose, IV toxicology study in beagle dogs, no increase in QTc was seen in either male or female dogs at any dose, even though dogs in the IV study had higher MLN2238 plasma Cmax values than did the male dogs in the PO study. These data suggest that MLN2238 has a low potential for prolonging the QT interval in vivo.

Toxicology: All studies discussed in this section were conducted with a solution of either MLN2238 or MLN2238 in equilibrium with Ixazomib. Because Ixazomib was shown to dissociate immediately to MLN2238 upon exposure to plasma in vitro and therefore could not be detected in plasma samples in vitro all doses, concentrations, and PK parameters noted, here and in the IB, are expressed as the boronic acid, MLN2238.

The toxicology studies of MLN2238 were studied in SCID mice bearing human CWR22 tumor xenografts, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Details of these studies are included in the IB.

In Vitro Toxicology: MLN2238 was not mutagenic in a Good Laboratory Practice (GLP)-compliant bacterial reverse mutation assay (Ames assay).

In Vivo Toxicology: Details of the in vivo toxicology IV dosing and oral dosing studies are provided in the IB. To summarize, the toxicologic effects seen in the IV and PO studies are qualitatively similar to what was previously observed in rodents dosed with bortezomib, for which Ixazomib is the next-generation molecule. MLN2238 did not cause significant toxicities that have not been previously observed after dosing with bortezomib. Therefore, on the basis of the similarity in the toxicity profile in rats between MLN22338 and bortezomib, MLN2238 is not known to present any additional safety risks beyond those that occur after treatment with bortezomib. In addition, there

were no significant findings at tolerated exposures in dogs observed after PO administration that were not seen after IV administration, and similar exposures were tolerated regardless of the route of administration.

The potential risks identified from nonclinical studies in dogs and rats include:

- GI toxicity that could result in nausea, vomiting, diarrhea, dehydration, electrolyte imbalance, bleeding, bowel obstruction including ileus and intussusception, and sepsis.
- Reduced blood counts manifest as thrombocytopenia, neutropenia, and anemia. Reticulocytopenia was described in animals and may be associated with anemia. Reductions in blood counts may predispose to an increased susceptibility to infection, bleeding, and anemia.
- Peripheral nerve ganglia effects that may be associated with peripheral neuropathy that includes pain, burning sensation, and numbness. Autonomic and motor neuropathy may be observed, as both have been reported for bortezomib.
- Lymphoid cell depletion that may be associated with increased risk of infection, including re-activation of herpes zoster.
- Acute phase response that may result in fever and metabolic changes.

All of the effects seen in the GLP-compliant PO toxicology studies in both dogs and rats at tolerated doses were reversible/reversing and can be monitored in the clinic with routine clinical observations (GI disturbances and infections secondary to lymphoid compromise), clinical pathology assessments (inhibition of erythropoiesis, thrombocytopenia, and inflammatory leukogram), and neurologic assessment, as are commonly done for patients treated with bortezomib. The neurologic lesions in these studies are similar to what has been described after treatment with bortezomib and are believed to be the cause of the peripheral neuropathy observed in patients treated with bortezomib.

Further details are presented in the IB.

Clinical Experience with Ixazomib

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

Pharmacokinetics and Drug Metabolism: Clinical IV and PO pharmacokinetic (PK) data show that Ixazomib (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 is rapidly absorbed with a median time to first maximum plasma concentration (T_{max}) of approximately 0.5 to 2.0 hours and terminal $t_{1/2}$ after

multiple dosing of approximately 5 to 7 days.[15] 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.[16] 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. See the IB for information on the PK for IV doses of Ixazomib.

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

Clinical Trial Experience Using the Oral Formulation of Ixazomib:

In the 7 studies actively enrolling patients to investigate oral Ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with different doses of Ixazomib, either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-1.

Table 1-1 Ongoing Studies of Oral IXAZOMIB

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

Table 1-1 Ongoing Studies of Oral IXAZOMIB

N=11			W MTD: 4 mg DLT:
Solid tumors, Lymphomas N = 22	C16009	PO, W, single agent	5.5 mg fixed dose* W
RRMM N = 1	C16010	PO, W, combination with LenDex	4.0 mg fixed dose* W
RRMM N = 5	TB-MC010034	PO, W, single agent in 1s part of study then in combination with LenDex in 2nd part	3.0 mg fixed dose* W DLT: thrombocytopenia, nausea, hypertension, diarrhea

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

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

Overview of the Oral Formulation of Ixazomib

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

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral Ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 146 patients have been treated as of 30 April 2012. These patients have been treated with different doses of 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 Summary of Most Common (At Least 10% of Total) All Grade Treatment-Emergent Adverse Events (Oral Ixazomib Single-Agent [C16003/4/7/9] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N=146 n (%)**

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

Source: Ixazomib Investigator's Brochure Edition 6

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

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

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

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

Primary System Organ Class	**Preferred Term and Incidence N= 96 n (%)**
Subjects with at Least One Adverse Event 135 (92)	

Gastrointestinal disorders 70 (73)	Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26) Diarrhoea 22 (23)
General disorders and administration site conditions 64 (67)	Fatigue 37 (39); Oedema peripheral 20 (21); Pyrexia 19 (20)
Skin and subcutaneous tissue disorders 57 (59)	Rash 13 (14)
Nervous system disorders 46 (48)	Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11)
Musculoskeletal and connective tissue disorders 45 (47)	Back pain 18 (19); Muscle spasms 10 (10)
Blood and lymphatic system disorders 42 (44)	Thrombocytopenia 28 (29); Anaemia 22 (23); Neutropenia 19 (20)
Infections and infestations 40 (42)	Upper respiratory tract infection 17 (18);
Metabolism and nutrition disorders 38 (40)	Decreased appetite 11 (11)
Respiratory, thoracic and mediastinal disorders 34 (35)	Dyspnoea 13 (14); Cough 11 (11)
Psychiatric disorders 23 (24)	Insomnia 15 (16)

Source: Ixazomib Investigator's Brochure Edition 6.

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.
Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

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

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

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

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

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

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];
2. Carfilzomib expansion cohort
3. Proteasome Inhibitor-Naïve expansion cohort
4. VELCADE-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest Ixazomib has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated.[11,12]

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

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

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

Most Common (> 20%) Any Grade and Irrespective of Cause	Thrombocytopenia (54%) Fatigue (48%) Nausea (44%), diarrhea (44%)

	Vomiting (37%) Decreased appetite (33%) Rash* (31%) Anemia (25%) Neutropenia (23%)
Drug-Related Grade ≥ 3 in > 5% of patients	Thrombocytopenia (38%) Diarrhea and neutropenia 17% (each), fatigue and lymphopenia 10% (each), nausea and decreased appetite 8% (each) and vomiting 6%

Source: Ixazomib Investigator's Brochure Edition 6

* Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic,
pruritus,, rash erythematous, exfoliative rash, and rash popular

Dose reductions required were due to AEs that included rash, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, hypotension, increase in serum creatinine, abdominal pain, ileus, fatigue, and pneumonia. The AEs reported for the 5 patients who were required to discontinue treatment included Grade 2 Ixazomib-related nausea/vomiting in 1 patient treated above the MTD, Grade 3 Ixazomib-related diarrhea in a second patient, related Grade 3 thrombocytopenia, related Grade 2 dyspnea, and notrelated Grade 4 elevation in creatinine(1 patient each). There were no on-study deaths.

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

Clinical data as of 30 April 2012 is available. The MTD in Study C16005 was determined to be 2.97 mg/m^2 given weekly in a 28-day cycle with LenDex. The DLTs were urticarial rash, dizziness, nausea, orthostatic hypotension, vomiting, diarrhoea, and syncope. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to, analyses of efficacy results and adverse events (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Given that the dose of Ixazomib at 2.97 mg/m^2 compromised the maximal dosing of lenalidomide and that the dose of 2.23 mg/m^2 is very tolerable and clinically active, Millennium designated 2.23 mg/m^2 as the RP2D after evaluation of the data and discussion with investigators. The RP2D of 2.23 mg/m^2 has been translated into a fixed dose of 4.0 mg based on the results from the population PK analysis. Enrollment in this study has been completed; final study results are not available, but preliminary data suggests oral Ixazomib given weekly plus lenalidomide and dexamethasone in a 28-day cycle appears well tolerated with manageable toxicity and encouraging antitumor activity.

In Study C16005, 15 of 15 (100%) patients in the dose escalation portion of the study experienced at least 1 TEAE irrespective of grade or causality. At the MTD across all dose expansion cohorts 49 of 53 patients (including 3 patients from the dose escalation

cohort [92%]) reported at least 1 TEAE irrespective of grade or causality. In the MTD cohorts, fatigue was the most common AE reported (38%). Other common AEs reported include nausea (32%), constipation (30%), upper respiratory infection (23%), and peripheral oedema (21%). Skin toxicity, primarily erythematous rash, occurred in 62% of patients (of note, rash is an overlapping toxicity with Ixazomib and lenalidomide). Peripheral neuropathy was reported in 13% of patients; Grade 3 in 1 patient.

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

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

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

Source: Ixazomib Investigator's Brochure Edition 6

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

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

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

Most Common (> 20%) Any Grade and	Fatigue (37%)

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

Source: Ixazomib Investigator's Brochure Edition 6.
a Related means to ANY drug in the study drug combination.

The most common drug-related SAEs reported in Study C16005 as of 30 April 2012 include pneumonia, infection, diverticulitis, localised infection, gastrointestinal haemorrhage, respiratory syncytial virus (RSV) pneumonia faecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral oedma, asthenia, hyponatraemia vomiting, diarrhoea, nausea, chest pain, dehydration, anemia, dizziness, peripheral sensory neuropathy, orthostatic hypotension, embolism, muscular weakness, acute renal failure, blood creatinine increased, maculopapular rash, atrial fibrillation, syncope, hypotension, and deep vein thrombosis, and back pain.

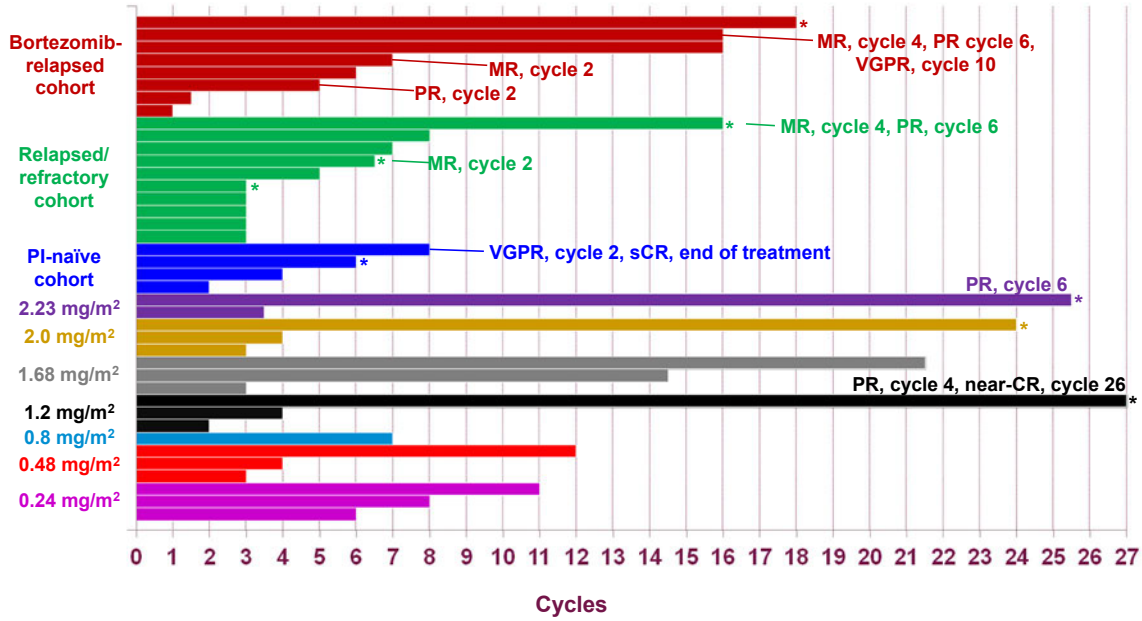
As of the clinical data cutoff, 4 patients have discontinued treatment due to TEAEs including gastrointestinal haemorrhage, angioedema, syncope, and RSV pneumonia.

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

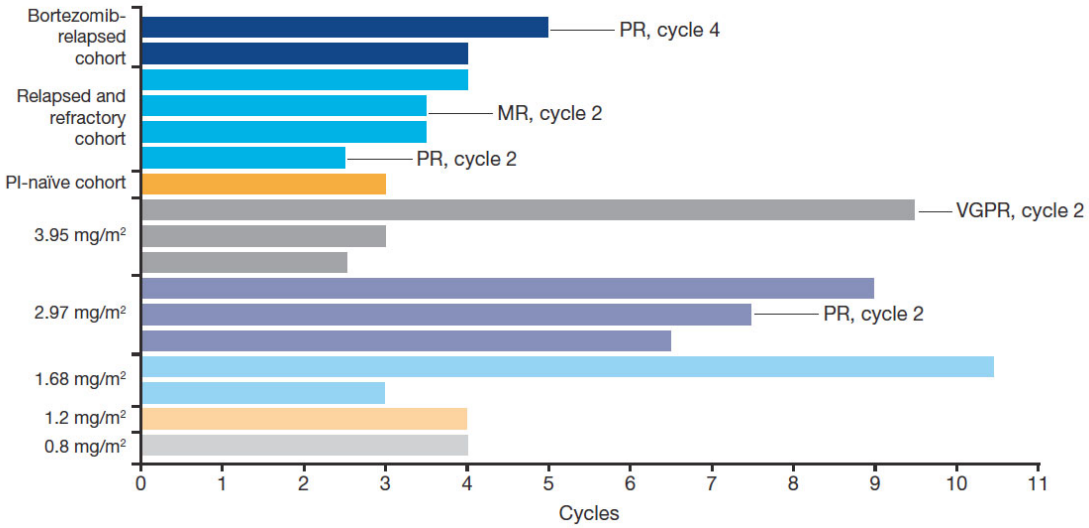
1.6 Anti-myeloma activity of Ixazomib:

Several clinical trials have been conducted with Ixazomib in patients with relapsed myeloma as well as newly diagnosed myeloma. These have included trials of Ixazomib as a single agent, in combination with dexamethasone, as well as in combination with lenalidomide. As mentined before, two different dose schedules have been explored as well; once weekly for 3 out of four weeks and twice weekly for 2 out of 3 weeks.

Ixazomib was studied as a single agent in patients with relapsed and or refractory MM (NCT00932698).[17] The trial was designed to assess safety, MTD, and response rate with twice-weekly oral Ixazomib. Patients with ≥2 prior therapies (including bortezomib, thalidomide/lenalidomide, and corticosteroids) were enrolled and treated with Ixazomib on d 1, 4, 8, and 11 of 21-d cycles. At the MTD (2.0 mg/m^2), patients were enrolled to relapsed and refractory [RR], bortezomib-relapsed [VR], proteasome-inhibitor [PI] naïve, and carfilzomib [CZ] expansion cohorts. Fifty-eight patients were enrolled, 38 to the expansion cohorts (19 RR, 11 VR, 6 PI naïve, 2 CZ). Patients have received a median of 3 cycles (range 1-24) to date (data cut-off Dec 1, 2011); 7 (12%) have received ≥13 cycles. Of 53 response-evaluable patients, 6 have achieved ≥PR, with 1 sCR (PI naïve cohort) and 5 PRs (2 in dose-escalation, 1 in RR, 2 in VR cohorts), and 1 VR patient has achieved MR, with duration of disease control of up to 18.6 months (Figure 1 below).

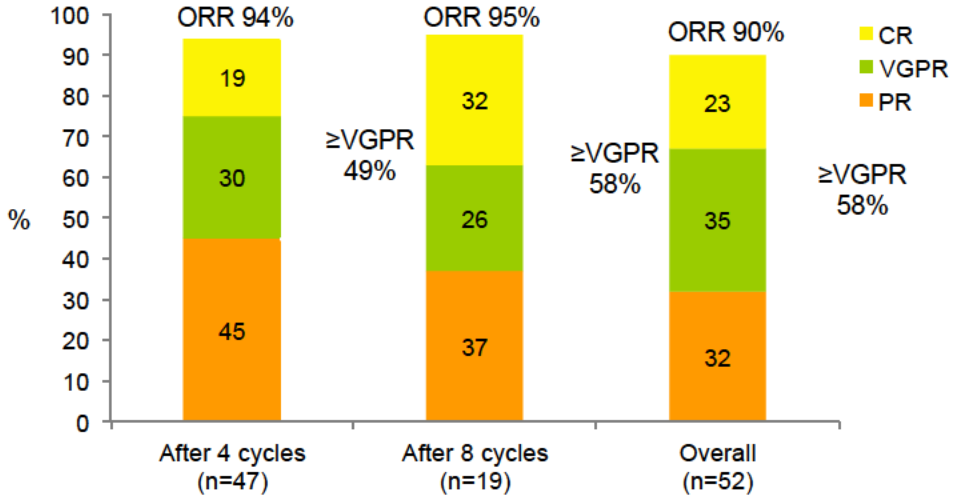


In a very similar trial Ixazomib was administered once weekly for 3 weeks in 4 week cycles. (NCT00963820).[18] Patients with relapsed/refractory MM who had ≥2 prior therapies (including bortezomib, thalidomide/lenalidomide, and corticosteroids) were treated with Ixazomib on d 1, 8, and 15 of 28-d cycles. At the MTD, patients were to be enrolled to relapsed and refractory (RR), bortezomib-relapsed (VR), proteasome inhibitor (PI) naïve, and carfilzomib (CZ) expansion cohorts. Overall, 52 patients have been enrolled, 32 in the dose-escalation phase (0.24–3.95 mg/m2) and 23 to expansion cohorts (12 RR, 5 VR, 5 PI naïve, 1 CZ). Patients have received a median of 2 cycles (range 1–11); 15 patients remain on treatment at last follow up. In 18 response-evaluable patients, 1 had a VGPR at 3.95 mg/m2, 1 had a PR at 2.97 mg/m2, 2 had a PR in the expansion cohorts and 12 have achieved SD durable for up to 9.5 months (Figure 2 below).



We recently enrolled 32 patients on a phase 2 trial of single agent Ixazomib with dexamethasone added for lack of response (NCT01415882). This study recently completed accrual and preliminary results show 11 patients with a confirmed partial response or better (35%, including two stringent complete responses (sCR) (Unpublished data).

More recently, a phase 1/2 trial of Ixazomib in combination with lenalidomide and dexamethasone in patients with newly diagnosed MM completed accrual (NCT01217957).[19] Patients with newly diagnosed MM were enrolled and treated with oral Ixazomib (days 1, 8, and 15) plus lenalidomide 25 mg (days 1-21) and dexamethasone 40 mg (days 1, 8, 15, 22) for up to twelve 28-day cycles, then maintenance therapy with Ixazomib (same schedule) every 28 days until progression. Patients were allowed to undergo stem cell collection after 3 cycles and discontinue for autologous stem cell transplant (ASCT) after 6 cycles. Overall, 65 patients were enrolled, 15 in Phase 1 and 50 in Phase 2. Patients received a median of 6 cycles (range 1-19) with 27 (42%) remaining on treatment as of November 2012. Of those who have undergone stem cell mobilization, a median yield was 11.3 x 10^6 CD34+ cells/Kg (range 5-28). Ixazomib MTD was established as 2.97 mg/m2 and RP2D was selected as 2.23 mg/m2; RP2D translates to a 4.0 mg fixed dose based on population PK results. Among the 64 evaluable patients, the overall response rate was 92%, including 55% VGPR and 23% CR (Figure 3 below). Median time to first response was 0.92 months (range 0.89-6.44).



1.7 Potential Risks and Benefits of Ixazomib:

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

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

Ixazomib 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 [3,4,5,6,8,9,10].

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

1.8 **Role of maintenance therapy in myeloma**: The concept of maintenance therapy has been tested mostly in the setting of high dose therapy and autologous stem cell transplantation. Patients invariably relapse after initial treatment strategies including SCT and various trials have attempted to maintain the SCT response through maintenance approaches. Initial trials prior to the availability of the new drugs have examined steroids or interferon, and a small randomized clinical trial of interferon- (3×10^6 units/m^2) subcutaneously 3 times weekly, following initial ASCT, suggested a modest improvement in EFS.[20] The IFM99-02 trial randomized patients with standard-risk MM ($Beta_2$-microglobulin [B2M] <3, no deletion 13), were: to receive no maintenance, pamidronate, or pamidronate plus thalidomide after tandem SCT.[21] Thalidomide was associated with higher response rates, improved EFS (52% vs. 36% with no maintenance) and improved overall survival (4-year estimated survival from diagnosis with thalidomide (87%) compared with no maintenance (77%). At least 5 different randomized trials have examined the role of thalidomide as a maintenance therapy post-SCT.[22-24] A meta-analysis of these trials support the improved progression-free survival, but remains equivocal in terms of overall survival improvement. In addition, high discontinuation rate has been noted in all these studies due to toxicity. In particular the Canadian study showed worsening of QoL parameters among patients getting thalidomide maintenance.[24]

A phase 3 study from the IFM enrolled 614 patients < 65 years, with non-progressive disease, within 6 months after upfront ASCT.[25] Patients received 2 cycles of consolidation with lenalidomide 25 mg daily for 3 of 4 weeks followed by a randomization to lenalidomide 10-15 mg/d until relapse or to placebo (n=307 in each arm). Patients were stratified according to Beta-2M, del13, and VGPR to initial therapy. There was an improvement in the PFS with maintenance therapy, with a median PFS of 42 months for lenalidomide vs. 24 months for the placebo. The improvement in the PFS was seen in all the subgroups based on stratification. With the current follow up, overall survival (OS) remains identical in the two groups. In a very similar trial, McCarthy and colleagues randomized patients 70 years or younger, who attained a stable disease or better with their induction therapy and underwent ASCT within one year of diagnosis, to lenalidomide (5-15 mg/day) or placebo until relapse.[26] Patients were stratified based on Beta-2M and use of thalidomide or lenalidomide therapy during induction. Patients were enrolled prior to the ASCT, with 19% of the 568 enrolled dropping out before randomization. As expected, grade 3 and 4 adverse events were significantly higher in the maintenance arm, with hematological toxicities being the common events. The median time to progression was 42 months with lenalidomide compared to 21.8 months with the placebo, results very similar to the French study. More recent updates suggest an improvement in the overall survival for the lenalidomide arm in the CALGB study. There are differences, however, between the two trials in terms of the design as well as duration of therapy. Patients in the IFM trial received uniform induction therapy unlike the CALGB trial. Patients in the IFM study received 2 cycles of consolidation with lenalidomide before starting maintenance. In addition, the IFM trial limited maintenance to approximately 24 months based on concerns regarding second malignancies and did

not allow cross over. However, the CALGB trial allowed cross over from placebo arm to lenalidomide maintenance based on interim analysis and also allowed maintenance until progression.

Very few trials have explored the role of maintenance therapy outside of the context of SCT prior to the advent of the new drugs. Three large recent trials have explored the role of maintenance therapy in the older patient population following a defined period of initial therapy with 3 or 4 drug combinations. In a recent multicenter phase 3 study (MM-015), Palumbo et al have evaluated the safety and efficacy of continuous lenalidomide treatment after MPR (MPR-R; n=152) versus MP (n=154) or MPR (n=153) in 459 newly diagnosed transplant ineligible MM patients who were >= 65 years of age.[27] The treatment schema consisted of melphalan 0.18 mg/kg on days 1-4, prednisone 2 mg/kg on days 1-4, with (MPR or MPR-R) or without (MP) lenalidomide 10 mg/day on days 1-21 for nine 28-day cycles. Following 9 cycles of MPR, patients received maintenance lenalidomide (10 mg/day on days 1-21) (MPR-R) or placebo (MPR) until progression; MP patients also received placebo until progression. After a median follow-up of 21 months, MPR-R compared with MP resulted in a higher overall RR (77% vs. 50%, $p <$ .001) and higher rates of CR (16% vs. 4%, $p <$ .001). In addition, MPR-R reduced the risk of disease progression by 58% compared with MP (HR =0.423, $p <$ .001) and resulted in a higher 2-year PFS rate (55% vs. 16%). Adverse events associated with MPR-R and MP resulted in treatment discontinuation in 20% and 8% patients, respectively. In another trial, patients receiving initial therapy with bortezomib, thalidomide, melphalan and prednisone were continued on maintenance with bortezomib and thalidomide, resulting in superior PFS compared to the control group of patients receiving VMP.[28] Finally, a Spanish trial randomized patients to initial therapy with VMP or VTP and then randomized all patients at the end of therapy to maintenance with VT or VP and showed an improved PFS in patients getting VT maintenance. In all these trials patients assigned to receive maintenance therapy with an IMiD or bortezomib + IMiD combination appeared to have improvements in the depth of response and better progression-free survival.[29]

However, significant questions remain as to the duration of maintenance therapy with different trials sporting different designs in terms of duration of therapy. Given the data showing that the rate of second malignancies may be higher after 24 months of maintenance, and the cost and side effects of maintenance, it has been suggested that two years of lenalidomide maintenance is sufficient, and the current IFM/DFCI trial has been amended to limit maintenance duration to two years.[25] But the major improvement in OS seen with lenalidomide maintenance was with therapy until progression. Hence, the issue of optimal duration of maintenance is pressing.

1.9 **Rationale for the current trial:** Ixazomib is a second-generation proteasome inhibitor, with excellent oral bioavailability, that is currently in phase 1 and 2 clinical trials.[30] The preliminary data from the phase 1 trials and the expansion cohorts at MTD, using single agent MLN 9708, demonstrates excellent tolerability and early evidence of efficacy.[31,32] In combination with lenalidomide in the setting of newly diagnosed myeloma, the combination has shown very high response rates and deep responses. Given these results, it is only logical to evaluate the efficacy of cyclophosphamide and Ixazomib with dexamethasone in the context of newly diagnosed disease. The results of this phase 2 can be compared with the historical controls form similar studies that have looked at Rd, VRd, and VCd, to give us an estimate of the comparative efficacy. We hypothesize that this fully oral regimen will have significant activity in this setting and will provide for a

convenient schedule. In addition, given the clinical efficacy seen with bortezomib, cyclophosphamide and dexamethasone, we hypothesize that the combination of Ixazomib, cyclophosphamide and dexamethasone, will be active in light chain amyloidosis.

2.0 Goals

2.1 Primary

2.11 Phase 1 Cohort A: To determine the maximum tolerated dose of cyclophosphamide that can be combined with Ixazomib and dexamethasone in patient with previously untreated symptomatic MM.

2.12 Phase 2 Cohort A: To determine the complete plus very good partial response rate (>=VGPR) of Ixazomib, used in combination with cyclophosphamide and dexamethasone in patients with previously untreated symptomatic MM.

2.13 Phase 2 Cohort B: To determine the hematologic response rate of Ixazomib, used in combination with cyclophosphamide and dexamethasone in patients with previously untreated light chain amyloidosis

2.2 Secondary

2.21 Cohort A: To determine the progression free survival and overall survival among patients with previously untreated symptomatic MM following treatment with Ixazomib in combination with cyclophosphamide and dexamethasone followed by Ixazomib maintenance till progression.

2.22 Cohort A: To determine the toxicities associated with Ixazomib in combination with cyclophosphamide and dexamethasone in patients with previously untreated symptomatic MM.

2.23 Cohort B: To determine the organ response rate of Ixazomib, used in combination with cyclophosphamide and dexamethasone in patients with previously untreated light chain amyloidosis

2.24 Cohort B: To determine the progression free survival and overall survival among patients with previously untreated light chain amyloidosis following treatment with Ixazomib in combination with cyclophosphamide and dexamethasone followed by Ixazomib maintenance till progression.

2.25 Cohort B: To determine the toxicities associated with Ixazomib in combination with cyclophosphamide and dexamethasone in patients with previously untreated light chain amyloidosis.

2.3 Correlative Research

2.31 Cohort A: To examine the pharmacokinetics of Ixazomib when used in combination with cyclophosphamide and dexamethasone.

2.32 Cohort A: To assess the incidence of neurotoxicity using patient completed questionnaires.

3.0 Patient Eligibility

Phase I only: Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.

3.1 Inclusion Criteria

3.11 **Cohort A**: Multiple myeloma or

Cohort B: Biopsy proven light chain amyloidosis with organ involvement requiring therapy

3.12 Age ≥18 years.

3.13 The following laboratory values obtained ≤14 days prior to registration.

- Calculated creatinine clearance (using Cockcroft-Gault equation below)* >=30 mL/min
- Absolute neutrophil count (ANC) ≥1000/mm^3
- Platelet count ≥75000/mm^3
- Hemoglobin ≥8.0 g/dL
- Total bilirubin ≤ 1.5 x ULN
- ALT and AST ≤ 3 x ULN

Cohort B only:

- Alkaline phosphatase ≤750 U/L
- NT-ProBNP < 7500 ng/dL

*Cockcroft-Gault Equation:

Creatinine clearance for males = (140 - age)(actual body weight in kg)
(72)(serum creatinine in mg/dL)

Creatinine clearance for females = (140 - age)(actual body weight in kg)(0.85)
(72)(serum creatinine in mg/dL)

3.14 Prior therapy for the treatment of solitary plasmacytoma is permitted, but >14 days should have elapsed from the last day of radiation. NOTE: Prior therapy with clarithromycin, DHEA, anakinra, pamidronate or zoledronic acid is permitted. Any additional agents not listed must be approved by the Principal Investigator.

3.15 Measurable disease of multiple myeloma as defined by at least ONE of the following:

- Serum monoclonal protein ≥1.0 g/dL (see Section 11.1 for definition)
- >200 mg of monoclonal protein in the urine on 24 hour electrophoresis
- Serum immunoglobulin free light chain ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.

Cohort B only:

- Serum immunoglobulin free light chain ≥5 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.

3.16 ECOG performance status (PS) 0, 1 or 2 (Appendix VII)

3.17 Previously untreated.

3.18 Provide informed written consent.

3.19a Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.19b Willing to follow strict birth control measures as suggested by the study.
Female patients: If they are of childbearing potential, agree to one of the following:

- Practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, AND must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

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

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

3.19c Willing to return to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.2 Exclusion Criteria

3.21 MGUS or smoldering myeloma only.

3.22 Prior cytotoxic chemotherapy or corticosteroids for the treatment of multiple myeloma. NOTE: Prior corticosteroid use for the treatment of non-malignant disorders is permitted

3.23 Diagnosed or treated for another malignancy ≤ 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. NOTE: Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

3.24 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.25 Other co-morbidity which would interfere with patient's ability to participate in trial, e.g. uncontrolled infection, uncompensated heart or lung disease.

3.26 Other concurrent chemotherapy, or any ancillary therapy considered investigational. **NOTE:** Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.

3.27 Peripheral neuropathy ≥ Grade 3 on clinical examination or grade 2 with pain during the screening period.

3.28 Major surgery ≤14 days prior to study registration.

3.29a Systemic treatment with strong CYP3A4 inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, Gingko biloba, St. John's wort) ≤14 days prior to registration.

3.29b Evidence of current uncontrolled cardiovascular conditions (NYHA Class III or IV), including hypertension, cardiac arrhythmias, congestive heart failure, unstable angina, or myocardial infarction within the past 6 months. Note: Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.

3.29c Radiotherapy ≤ 14 days prior to registration. NOTE: If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the Ixazomib.

3.29d Known human immunodeficiency virus (HIV) positive.

3.29e Known hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection.

3.29f Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

3.29g Known allergy to any of the study medications, their analogues or excipients in the various formulations.

3.29h Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of Ixazomib including difficulty swallowing.

3.29i Diarrhea > Grade 1, based on the NCI CTCAE grading, in the absence of antidiarrheals.

3.29j Participation in any other clinical trials with other investigational agents not included in this trial, ≤30 days prior to registration.

4.0 Test Schedule

4.1 Cohort A

Cohort A	*Days Prior to Registration*		*Every 14 days (3 cycles)*[1]	*Every cycle, pre-treatment*[1,11,]	*Maintenance Phase:*
	≤30 days	*≤14 days*			*(every cycle)*[1, 11]
Complete medical history	X				
Adverse Event monitoring		X	X[7]	X[13]	X
Physical exam, including weight and vital signs		X		X[13]	X
Height		X			
Performance status (ECOG scale)		X	X	X[13]	X
CBC with diff.		X	X	X[13]	X
Prothrombin time (PT)	X				
Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; Total and Direct bilirubin; SGOT (AST);ALT serum creatinine, calcium		X	X	X[13]	X
LDH, $Beta_2$-microglobulin, C-reactive protein, Plasma cell assessment	X				
Electrophoresis of serum and urine		X		X[12]	X[12]
Affected Immunoglobulin		X		X[9]	X[9]
Immunofixation serum and urine	X			X[2]	X[2]
Immunoglobulin free light chain		X		X[5]	X[5]
X-ray skeletal survey	X			X[4]	X[4]

Bone marrow aspirate and biopsy, myeloma FISH, metaphase cytogenetics, plasma cell proliferation, and flow cytometry.	X			X[6]	X[6]
Research bone marrow and blood sample as per 521-93, optional[R]	X			X[6]	X[6]
Chest x-ray	X				
Pharmacokinetics (see schedule below)					
Serum pregnancy test		X[3]			
Patient Medication Diary (Appendix IV)[8]				X	X
FACT/GOG neurotoxicity questionnaire (Appendix V)		X		X[10]	X[10]

1) All scheduled visits will have a window of ± 4 days unless otherwise stated
2) Immunofixation (IF) needed only in the absence of M-spike to document CR or sCR.
3) For women of childbearing potential only. Must be done ≤7 days prior to registration.
4) Every 6 cycles.
5) FLC is required only if used to assess disease response during active phase
6) At the end of 4 and 12 cycles and only required to document CR after that. If a bone marrow was done to confirm CR prior to end of 12 cycles, no further bone marrow examination is required.
7) Every 14 days times 3 cycles then monthly thereafter during induction treatment;
8) The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution.
9) Affected immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient "non-secretory" or if patient has no heavy chain, i.e. light chain myeloma. . Affected immunoglobulin is required after baseline only if it used for disease monitoring instead of SPEP (for e.g. IgA myeloma)
10) The FACT/GOG neurotoxicity questionnaire will be filled out by the patient at baseline, every cycle for the first 4 cycles, and then every 3 cycles (+/- 1 cycle).
11) During the induction phase, patients should return every cycle for the first 4 cycles, and then can return every two cycles provided the required laboratory evaluations can be obtained and toxicity assessments can be performed over the phone. During maintenance phase patients can return every three cycles provided the required laboratory evaluations can be obtained and toxicity assessments can be performed over the phone.
12) Urine Electrophoresis required only if used to assess disease response
13) Does not need to be repeated at Cycle 1 Day 1. Baseline values can be used for cycle 1.

R Research funded (see Section 19.0). Will be charged to study and not to patient's account.

4.2 Cohort B

Cohort B	*Days Prior to Registration*		*Every 14 days (3 cycles)*[1]	*Every cycle, pre-treatment*[1,9]	*Maintenance Phase:*
	≤30 days	*≤14 days*			*(every cycle)*[1,9]
Complete medical history	X				
Adverse Event monitoring		X	X[6]	X[11]	X[13]
Physical exam, including weight and vital signs		X		X[11]	X[13]
Height		X			
Performance status (ECOG scale) and NY Heart Association Class		X	X	X[11]	X[13]
CBC with diff.		X	X	X[11]	X[13]
Prothrombin time (PT)/INR, APTT	X				
Factor X chromogenic activity assay	X				
Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; Total and Direct bilirubin; AST; ALT; uric acid; serum creatinine, calcium		X	X	X[11]	X[13]
Cardiac troponin-T, NTProBNP,	X			X[12]	X[12,13]
ECHO with strain; Ejection fraction (obtain using echocardiogram)	X			X[12]	X[12,13]
Electrophoresis of serum and urine (24 hour)		X		X[10]	X[10,13]
Affected Immunoglobulin		X		X[8]	X[8,13]
Immunofixation serum and urine	X			X[2]	X[2,13]
Immunoglobulin free light chain		X		X	X[13]
Bone marrow aspirate and biopsy, plasma cell proliferation	X			X[5]	X[5]
Research bone marrow and blood sample as per 521-93, optional[R]	X			X[5]	X[5]
Chest x-ray	X				
Serum pregnancy test		X[3]			
24-hour creatinine clearance	X			X[12]	X[12]
Abdominal non-contrast CT	X			X[12]	X[12]

Nerve conduction studies (only nerve involvement that will be followed by response), including compound muscle action potential (CMAP)	X			X[12]	X[12]
Neurology consult for Nerve Impairment Score (only nerve involvement that will be followed for response)	X			X[12]	X[12]
Patient Medication Diary (Appendix IV)[7]	X			X	X
FACT/GOG neurotoxicity questionnaire (Appendix V)		X		X[14]	X[14]

1) All scheduled visits will have a window of ± 4 days unless otherwise stated.
2) Immunofixation (IF) needed only in the absence of M-spike to document CR or sCR.
3) For women of childbearing potential only. Must be done ≤7 days prior to registration.
4) Every 6 cycles.
5) At the end of 4 and 12 cycles and only required to document CR after that. If a bone marrow was done to confirm CR prior to end of 12 cycles, no further bone marrow examination is required.
6) Every 14 days times 3 cycles then monthly thereafter during induction treatment.
7) The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution.
8) Affected immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient "non-secretory" or if patient has no heavy chain, i.e. light chain myeloma. Affected immunoglobulin is required after baseline only if it used for disease monitoring instead of SPEP (for e.g. IgA myeloma).
9) During the induction phase, patients should return every cycle for the first 4 cycles, and then can return every two cycles provided the required laboratory evaluations can be obtained and toxicity assessments can be performed over the phone. During maintenance phase patients can return every three cycles provided the required laboratory evaluations can be obtained and toxicity assessments can be performed over the phone.
10) Urine Electrophoresis required only if used to assess disease response.
11) Does not need to be repeated at Cycle 1 Day 1. Baseline values can be used for cycle 1.
12) Do only to follow organ involvement and response (e.g. EMG for peripheral nerve, CT or US for liver). Not needed in all patients.
13) Required evaluations can be done through local facility, phone contact, or by local lab as applicable
14) The FACT/GOG neurotoxicity questionnaire will be filled out by the patient at baseline, every cycle for the first 4 cycles, and then every 3 cycles (+/- 1 cycle).

R Research funded (see Section 19.0). Will be charged to study and not to patient's account.

Table 4.2 Cohort A only: Pharmacokinetic sampling					
Cycle 1					Cycle2
Day 1		Day 8	Day 15	Day 22	Day1
(Post-dose) Hours					
1 (+/-0.25)	4 (+0.75)	Predose (within 1 hour of dosing)	Predose (within 1 hour of dosing)	No dose given, PK can be drawn at anytime	Predose (within 1 hour of dosing)
X	X	X	X	X	X

5.0 Grouping Factor:

5.1 Phase: I vs. II

5.2 Cohort: A (multiple myeloma) vs. B (light chain amyloidosis)

6.0 Registration/Randomization Procedures

6.1 Phase I

Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] for dose level and to insure that a place on the protocol is open to the patient.

6.11 Registration Procedures

6.111 To register a patient, fax [redacted] a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Phase II

6.21 Registration Procedures

To register a patient, access the Research Registration Application at [redacted]. The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the application, call the Mayo Clinic Site Management Team at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday) or email them at [redacted] Quick Reference Guides (QRGs) for the application are available to study staff on the Mayo Clinic Office of Clinical Trials, Site Management Team website.

Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC patient ID number must be provided The patient ID will begin with an 'R' and will be followed by 8 digits. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the Research Registration Application can be confirmed in any of the following ways:

- Contact the Mayo Clinic Site Management Team. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.

- View your list of registered patients via the Accruals Tile on the Patient Landing page of the Research Registration Application.

6.211 Documentation of IRB approval must be on file with the Site Management team before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Site Management Team is no longer necessary.

6.212 Verification

Prior to accepting the registration, the Registration Application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Phase I and II

6.31 Correlative Research: (See section 14)

6.32

6.33 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of Multiple Myeloma at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.34 **Cohort A:** Treatment on this protocol must commence at Mayo Clinic Rochester or Mayo Clinic Arizona, under the supervision of a hematologist.

As of amendment 12

Cohort B: Treatment on this protocol must commence under the supervision of a hematologist from the enrolling institution.

6.35 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.36 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.37 All required baseline symptoms (see Section 10.51) must be documented and graded.

6.38 Study drug is available on site.

6.4 The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

PHASE 1 INDUCTION (Cycles 1-12)				
Agent	**Dose Level**	**Route**	**Day**	**Retreatment**
Ixazomib*	As assigned by MCCC Registration Office	PO	1, 8, 15	Every 28 days
Cyclophosphamide		PO	1, 8, 15, 22	Every 28 days
Dexamethasone		PO	1, 8, 15, 22	Every 28 days

Cohort A: PHASE 2 INDUCTION (Cycles 1-12)				
Agent	**Dose Level**	**Route**	**Day**	**Retreatment**
Ixazomib*	Based on phase I results	PO	1, 8, 15	Every 28 days
Cyclophosphamide		PO	1, 8, 15, 22	Every 28 days
Dexamethasone		PO	1, 8, 15, 22	Every 28 days

Cohort B: PHASE 2 INDUCTION (Cycles 1-12)				
Agent	**Dose Level**	**Route**	**Day**	**Retreatment**
Ixazomib*	4 mg	PO	1, 8, 15	Every 28 days
Cyclophosphamide	500 mg	PO	1, 8, 15, 22	Every 28 days
Dexamethasone	40 mg	PO	1, 8, 15, 22	Every 28 days

MAINTENANCE (All patients)				
Ixazomib*	Phase 2 dose (continue with same dose as cycle 12)	PO	1, 8, 15	Every 28 days**

*The study drug should be taken on an empty stomach, at least 1 hour before or at least 2 hours food. Each capsule should be swallowed separately with a sip of water. A total of approximately 240 mL of water should be taken with the capsules

** Treatment will continue till disease progression, unacceptable toxicity, withdrawal of consent, or if patient and/or physician prefer to discontinue therapy.

7.2 The doses of Ixazomib used in this study are based on data from Millennium's ongoing phase 1 trials. In these trials the dose of Ixazomib was based on BSA. A population PK

analysis was performed for Ixazomib to assess the feasibility of switching from BSA-based dosing to flat dosing. A population PK model was built using nonlinear mixed effects modeling in NONMEM VII software compiled with the Intel Fortran 9.2 compiler. Data from both the twice-weekly and once-weekly IV dosing regimens were used in the analysis (N = 42). Population PK analysis showed that Ixazomib PK can be well described by a 3- compartment model with linear elimination. Race, sex, BSA, and/or body weight do not appear to significantly affect clearance (CL) and volume of distribution (V1) in the central compartment. Clearance and volume of distribution in the central compartment are the PK parameters that will affect AUC and C_{max}, respectively. CL and V1 are primary parameters that are independent of the route of administration of drug. Therefore, BSA is not expected to affect C_{max} or AUC after oral dosing, and thus flat dosing is appropriate for both oral and IV routes of administration.

7.3 Patients should be instructed to swallow Ixazomib capsules whole, with water, and not to break, chew, or open the capsules. The study drug should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food. 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.

The prescribed administration of Ixazomib doses in this study is the MTD of Millennium study C16004 weekly in a 28-day cycle. Missed doses can be taken as soon as the patient remembers as long as 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.

Drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients may be treated on an outpatient basis, if possible.

The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel.

7.4 **Cohort A:**
For cohort A the patient must be evaluated at the consenting institution (Mayo Clinic) as described in the Test Schedule (Section 4). Treatment by a local medical doctor (LMD) is not allowed.

Cohort B (as of amendment 12)
For cohort B, the patient must return to the consenting institution for evaluation at least every third cycle, provided the drug can be sent to the patient and necessary interval evaluations as required by the protocol can be completed remotely or through local healthcare facilities

7.5 Patients are allowed to collect stem cells any time after 3 cycles of initial therapy. Therapy may be interrupted for up to 4 weeks for the purpose of stem cell collection. Stem cells can be collected using standard institutional protocols. Once stem cell

collection is completed, patients will initiate next cycle of therapy and continue as per protocol. Any delay beyond 4 weeks should be discussed with the study PI prior to reinitiating protocol therapy. Patients can go off study treatment for stem cell transplantation any time after 6 cycles of therapy. Patients who discontinue therapy for stem cell transplantation will go to event monitoring phase of the study and will not get any additional therapy with Ixazomib.

7.6 Phase I – determination of Maximum Tolerated Dose (MTD)

7.51 Dose Escalation for individual drugs

Dose level	**Ixazomib (Days 1, 8, 15)**	**Cyclophosphamide (Days 1, 8, 15, 22)**	**Dexamethasone (Days 1, 8, 15, 22)**
-2	3 mg	200 mg/m^2	12 mg
-1	4 mg	200 mg/m^2	20 mg
0*	4 mg	300 mg/m^2	40 mg
+1	4 mg	400 mg/m^2	40 mg

***starting dose level**

7.611 Treatment by a local medical doctor is not allowed.

7.612 Three patients will be treated at each dose level and observed for a minimum of 28 days, to assess toxicities, before new patients are treated. The study will temporarily close. Doses will not be escalated in any individual patient.

7.613 Investigators are to contact the Study Chair as soon as any dose-limiting toxicity (DLT) occurs.

7.62 Definitions of DLT

7.621 For this protocol, dose-limiting toxicity (DLT) will be defined as an adverse event attributed (definitely, probably, or possibly) in the first cycle to the study treatment and meeting the following criteria:

Toxicity*	***DLT Definition***
Investigations	Grade 4 neutropenia (ANC < 500/mm$^{3)}$ for ≥7 days or Grade 4 thrombocytopenia (<25,000/mm$^{3)}$ for ≥7 days
Infection and infestations	Grade 4
Blood and lymphatic system disorders	Defined as fever ≥ 38.5^{o}C (38 > 1 hour) with grade ≥ 3 neutropenia
Other Non-hematologic	≥ Grade 3 as per NCI Common Terminology

	Criteria for Adverse Events v 4.0**.
Dose Delay	Any toxicity that causes a dose delay of > 2 weeks of the next intended dose
Dose Reduction	Any dose reduction within cycle 1

* Adverse event at least possibly related to the study medication.

**Grade 3 nausea, vomiting, or diarrhea with maximal supportive treatment(s) will be considered dose limiting. Fatigue and mouth sores that are considered Grade 3 with an attribution of definitely, probably, or possibly related to treatment will be reviewed by the study team to determine if they were due to other causes (i.e. disease progression or infection) or treatment. If it is determined that the fatigue or mouth sores were due to other causes they would not be considered a DLT and if they were due to treatment they would be considered a DLT.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Individual drugs can be dose reduced as per the table below depending on the adverse event attribution. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels for each drug in the combination. The same dose modification schema will be used for Ixazomib in the maintenance phase (Based on Adverse Events in Tables 8.*2* and 8.*3*)

Cohorts A and B Ixazomib (Days 1, 8, 15)	
Starting dose	4 mg
-1	3 mg
-2	2.3 mg
-3	2.3 mg days 1, 15

Cohorts A and B Ixazomib (Days 1, 8, 15)	
-4	Discontinue

If patients cannot tolerate dose level – 3 of Ixazomib they will go to event monitoring.

Cohort A Cyclophosphamide (Days 1, 8, 15, 22)				
Starting dose	400 mg/m^2	300 mg/m^2	200 mg/m^2	100 mg/m^2
-1	300 mg/m^2	200 mg/m^2	100 mg/m^2	Discontinue
-2	200 mg/m^2	100 mg/m^2	Discontinue	
-3	100 mg/m^2	Discontinue		
-4	Discontinue			

Cohort B Cyclophosphamide (Days 1, 8, 15, 22)	
Starting dose	500 mg
-1	400 mg
-2	200 mg
-3	Discontinue

Cohorts A and B Dexamethasone (Days 1, 8, 15, 22)		
Starting dose	40 mg	20 mg
-1	20 mg	12 mg
-2	12 mg	4 mg
-3	4 mg	Discontinue
-4	Discontinue	

Note: If Ixazomib is discontinued, the patient will go to event monitoring per Section 18.0. If cyclophosphamide and/or dexamethasone are discontinued, the patient may continue treatment.

8.11 Instruction for initiation of a new cycle of therapy

A new cycle of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1000/μL
- The platelet count is ≥ 75,000/μL
- Any other non-hematologic Ixazomib-related adverse event that may have occurred has resolved to ≤ Grade 1 or baseline severity.

If these conditions are not met on Day 1 of a new cycle, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate.

If any drug dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.

If any drug dosing was omitted for the remainder of the previous cycle or if the new cycle is held due to known hematologic toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction. If a new cycle of therapy cannot be restarted within 4 weeks of the scheduled Day 1 due to non-resolution of drug related toxicities, the patient will be removed from protocol therapy and will go to event monitoring.

8.2 Dose modifications based on adverse events during a cycle

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT[#]**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT (Days 2-28 of each cycle)			
Investigations	If platelet count < 30×10^9/L or ANC <1.0×10^9/L or ANC > 1.0×10^9/L (up to LLN) with fever (temperature > 38.5°C)	Ixazomib	Days 2-15: Ixazomib dose should be omitted. Complete blood count (CBC) with differential should be followed weekly. If ANC is ≥ 1.0×10^9/L and/or platelet counts > 30×10^9/L, Ixazomib may be reinitiated with 1 dose level reduction (see table 8.1). The subsequent cycle will use the reduced dose. If a patient is already at the lowest drug level, go to event monitoring.
Skin and subcutaneous tissue disorders	Rash, maculopapular, ≥Grade 2	Ixazomib	Omit IxazomiB till rash resolves to ≤ Grade 1 (See Section 9.9b). Restart at same dose. If the rash recurs, reduce dose by one dose level. If a patient is already at the lowest drug level, go to event monitoring.
	Any skin, Grade 4	Ixazomib	Discontinue Ixazomib and go to event monitoring
Nervous System Disorders	New or worsening Grade 1 peripheral neuropathy with pain, ≥ Grade 2 peripheral neuropathy,	Ixazomib	Omit Ixazomib until resolution to Grade ≤ 1 or baseline
	Grade 2 neuropathy with pain or Grade 3 peripheral neuropathy	Ixazomib	Omit Ixazomib until toxicity resolves to ≤ Grade 1 or returns to baseline. When toxicity resolves, re-initiate Ixazomib at the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring.
	Grade 4 peripheral neuropathy	Ixazomib	Permanently discontinue Ixazomib.
Genitourinary	Cystitis > grade 2	Cyclophosphamide	Omit cyclophosphamide until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate cyclophosphamide at the next lower dose level.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT#**	**ACTION****
Other	Any other non-hematological Grade 3 attributable toxicity except: > Grade 3 nausea and/or emesis in the absence of optimal anti-emetic prophylaxis > Grade 3 diarrhea that occurs in the absence of optimal supportive therapy ≥ Grade 3 fatigue	Ixazomib Cyclophosphamide	Omit Ixazomib or cyclophosphamide or both depending on the attribution to either or both drugs, until resolution to Grade < 1 or baseline. , hold both drugs. Restart at next lower dose. If a patient is already at the lowest drug level, go to event monitoring. If the toxicity can be attributed to either of the drugs, cyclophosphamide should be discontinued at first instance followed by Ixazomib for recurrence of the same toxicity necessitating dose modification.
	Grade 4 Nonhematologic Toxicities	Ixazomib	Permanently discontinue cyclophosphamide. Consider permanently discontinuing Ixazomib. Exception, in the case where the investigator determines the patient is obtaining a clinical benefit.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

NOTE: For toxicities attributable to both Ixazomib and cyclophosphamide, only one of the drugs should be reduced for each incidence of toxicity severe enough to necessitate dose reduction. The drug reduced should alternate starting with cyclophosphamide for the first dose reduction.

8.3 Dose modifications for dexamethasone based on adverse events during a cycle

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
BASED ON INTERVAL ADVERSE EVENT (Days 2-28 of each cycle)			
Gastrointestinal disorders	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL)	Dexamethasone	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥Grade 3 (Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self-care ADL; disabling)	Dexamethasone	Omit dexamethasone until symptoms adequately controlled. Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume. Ixazomib should be continued.
	Pancreatitis ≥ Grade 3 (Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support))	Dexamethasone	Discontinue dexamethasone and do not Resume. Ixazomib should be continued
General disorders and administration site conditions	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Dexamethasone	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction. Ixazomib should be continued.
Psychiatric disorders	Confusion or Mood alteration ≥ Grade 2 (Severe disorientation; limiting self-care ADL)	Dexamethasone	Omit dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume. Ixazomib should be continued.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Musculoskeletal and connective tissue disorders	Muscle weakness ≥ Grade 2 Weakness limiting self care ADL; disabling	Dexamethasone	Decrease dexamethasone dose by one dose level; if weakness persists despite above measures decrease dose by one additional dose level. Discontinue dexamethasone and do not resume if symptoms continue to persist. Ixazomib should be continued.
Metabolism and nutrition disorders	Hyperglycemia Grade 3 or higher, (>250 - 500 mg/dL; >13.9 - 27.8 mmol/L); hospitalization indicated	Dexamethasone	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level at a time until levels are satisfactory.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the three dose-reduction steps (levels -1, -2 and -3) will be at the discretion of the Principal Investigator, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

9.0 Ancillary Treatment/Supportive Care

9.1 Patients may receive concurrent treatment with a bisphosphonate.

9.2 Patients may continue on low level/stable steroid doses for replacement or inhalation therapy.

9.3 The following medications are not permitted during the trial:

- Any other investigational treatment
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Any external beam radiotherapy

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

9.4 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.

9.5 Granisetron should be given prior to Ixazomib for prophylaxis. Additional antiemetics may be used at the discretion of the attending physician. Dexamethasone should not be administered as an anti-emetic. Volume depletion should be corrected before initiation of study drug.

9.6 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2932-2947

9.7 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.8 Diarrhea: This can be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.9a Two cases of acute renal failure have been reported in patients treated at or above the MTD for intravenous Ixazomib (see Section 1.4.3). Volume depletion should be corrected before initiation of study drug. Until further information is available, intake of nonsteroidal anti-inflammatory drugs immediately prior to the administration of Ixazomib should be discouraged and requires consultation with the principle investigator.

All necessary supportive care consistent with optimal patient care shall be available to patients as necessary.

9.9b Herpes Zoster prophylaxis with acyclovir 400 mg PO BID should be used while on study therapy and for 1 month beyond the end of therapy

9.9c Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: If there were to be a drug-drug interaction with an inducer, Ixazomib exposure would be decreased. -

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba.

The following procedures are prohibited during the study.

- Participation in clinical trials with other investigational agents, not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
- Any antineoplastic treatment with activity against MM except for drugs in this treatment regimen.
- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study drug dosing.
- Adjuvant hormone therapy for breast or prostate cancer.

9.9d Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with Ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of Ixazomib (and/or other causative

agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). 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.

9.9e Thrombocytopenia

Thrombocytopenia has been reported to date primarily at the higher doses tested. 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. Thrombocytopenia nadirs commonly recover without intervention by the beginning of the next scheduled cycle. Ixazomib administration should be modified as noted as per dose modification recommendations in Table 6-2 when thrombocytopenia occurs. 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.

9.9f Neutropenia

Neutropenia has been reported with Ixazomib. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable with G-CSF according to standard clinical practice. Neutropenic nadirs commonly recover without intervention by the beginning of the next scheduled cycle or with a short delay in treatment. Ixazomib administration should be modified when neutropenia occurs, as noted in the dose modification recommendations in Table 6-2. Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

9.9g Fluid Deficits

Dehydration should be avoided because Ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported with Ixazomib. Fluid deficits should be corrected before initiation of study drug and during treatment and as needed during therapy. Until further information is available, intake of NSAIDs while on this protocol should be avoided.

9.9h Hypotension

Symptomatic hypotension and orthostatic hypotension 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.

9.9i Posterior Reversible Encephalopathy Syndrome

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

9.9j 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.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting 10 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56	Will automatically be sent to [redacted]
Mayo Clinic Sites	11 Mayo Clinic Cancer Center SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to [redacted]

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.5). With this information, determine whether the event must be reported as an expedited report (see Section 10.). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same

as serious AE which is defined in the table in Section 10.4.

10.2 **Expected vs. Unexpected Events**

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 **Assessment of Attribution**

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the <u>SAME</u> Arm**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

<u>Routine Reporting</u>

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.

- Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators. See Section 10.6.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.

- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A.

- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.4 Expedited Reporting Requirements for IND/IDE Agents

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent

one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.41 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional instructions:

1. Special reporting requirements for **Takedea/Millennium**

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

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

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

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

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

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

Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event

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

See below for contact information for the reporting of SAEs to Takeda 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 Takeda.

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

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Takeda Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Takeda Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?
Sponsor-investigator must also provide Takeda 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: [redacted]
Suggested Reporting Form:

- MedWatch 3500A
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
AND
- Takeda SAE Report Form

Product Complaints
A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

For Product Complaints
- Phone: [redacted]
- E-mail: [redacted]

- FAX: 1-800-881-6092
- Hours: Mon-Fri, 9 a.m. – 7 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 Takeda Pharmacovigilance

10.41 **Special Situations for Expedited Reporting**

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events[1]

An expedited report may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will **supercede** the standard Expedited Adverse Event Reporting Requirements (see footnote 1):

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
General disorders and administrations site conditions	Fatigue	≤ Grade 3
Gastrointestinal	Vomiting	≤ Grade 3
	Nausea	≤ Grade 3
	Diarrhea	≤ Grade 3
Investigations	Neutrophil count decreased	≤ Grade 4
	Platelet count decreased	≤ Grade 4
	Lymphocyte count decreased	≤ Grade 4
	White blood cell decreased	≤ Grade 4
Blood and lymphatic system disorders	Anemia	≤ Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring **within 30 days** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring **greater than 30 days** after the last does of the investigational agent/intervention requires expedited reporting within 24

hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.55 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). 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 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:
Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

The Mayo SAE coordinator and/or Regulatory Affairs Until will notifiy Takeda at the address below (if applicable):

SAE and Pregnancy Reporting Contact Information

US & Canada

Fax Number: [redacted]
Email [redacted]

Rest of World

Fax #: [redacted]

10.6 Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	Baseline # of Stools	X	
	Diarrhea		X
	Constipation		X

Infections and infestations	Sepsis	X	X
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Skin and subcutaneous tissue disorders	Rash, maculopapular	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.62 The MCCC Routine AE Data Submission Policy does not apply, as this study does not collect AE attribution. Submit Grade 2 or greater AEs via the Nadir/AE Log when AEs experienced by the patient are not specified in Section 10.5.

10.63 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.64 Distribution of Millennium Safety Updates
Millennium Pharmaceuticals will send to the sponsor-investigator Ixazomib safety letters (real-time safety letters and/or the quarterly safety updates). All safety letters pertaining to the Ixazomib program will be sent to the Investigator-Sponsor via an electronic distribution using Mercury, the Millennium Secure File Transfer (MFT) system. For each

safety letter distributed, Sponsor-Investigator will receive an e-mail inviting to download the Adobe/PDF document from Mercury.

10.65 To meet GCP requirements, Millennium is required to send Sponsor-Investigators the safety letters within 15 days after the world-wide receipt date of the safety event. Sponsor-Investigators responsibility is to read the safety letter, and provide the safety letter to the Institutional Review Board or Ethics Committee per institution's policy. Sponsor-investigator will be responsible for forwarding such reports to any sub-investigator(s).

11.0 Treatment Evaluation

Cohort A (Multiple Myeloma): The International Myeloma Working Group (IMWG) uniform response criteria (Rajkumar et al, 2011) will be used to assess response to therapy

11.1 Terms and definitions

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

  Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.
  - M-proteins migrating in the β-region (usually IgA M-proteins)
  - Cases in which the M-protein is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
  - Cases in which there are multiple peaks of same M-protein (aggregates or dimers)

  If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-protein values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

  Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

  FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a

monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

  In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.

  - Serum M-protein ≥1 g/dl
  - Urine M-protein ≥ 200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
  - Bone marrow plasma cells ≥ 30%

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine M-protein) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results*** with the exception of defining stringent complete response.

- **Evaluable disease**: Patients who do not have a "measurable" serum M-protein, serum free light chain, or urine M-protein.

- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-protein or urine M-protein, but has had a detectable M-protein in his/her serum and/or urine and/or measurable serum free light chain.

- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable M-protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

Table 11.2

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])

On Study Baseline Value	SPEP[4]	24 hr UPEP[2]	Ig FLC	BM Bx
Serum M-protein ≥1 g/dl, and urine M-protein≥ 200 mg/24 hrs	X	X		
Serum M-protein ≥ 1 g/dl, but urine M-protein < 200 mg/24 hrs	X			
Serum M-protein <1 g/dl, and urine M-protein≥ 200 mg/24 hrs		X		
Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X	
Serum M-protein < 1 g/dl, urine M-protein< 200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells				X[3]

[1] ***SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy*** *are required to document CR regardless of registration values, and in addition* ***FLC*** *measurement and* ***bone marrow immunophenotyping*** *is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.*

[2] *For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category*

[3] *At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.*

[4] *If serum M-protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.*

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum M- protein, serum immunoglobulin free light chain (when primary determinant of response) and urine M- protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.
- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2

11.4 Bone progression

Caution must be exercised to avoid rating progression on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.5. Progressive disease for all patients as defined in Table 11.5.

Table 11.5

CATEGORY	RESPONSE CATEGORY [a]
Stringent Complete Response (sCR) [b]	• CR as defined *plus* • Normal FLC ratio *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry [i]
Complete Response (CR) [b]	• Negative immunofixation of serum and urine [c] *and* • Disappearance of any soft tissue plasmacytoma *and* • <5% PCs in Bone Marrow *and* • If the only measurable disease is FLC, a normal FLC ratio [d]
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis [c] *or* • ≥90% reduction in serum M-protein and urine M-protein <100 mg/24 h [c] • If the only measurable disease is FLC, a >90% reduction in the difference between involved and uninvolved FLC levels
Partial Response (PR)	• If present at baseline, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24hrs [c] • If the only measurable disease is FLC, a ≥50% reduction in the difference between involved and uninvolved FLC levels

	• If the only measurable disease is BM, a ≥ 50% reduction in BM PCs (provided the baseline PCs was ≥ 30%) • If present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas
Minor Response (MR)	• If present at baseline, ≥25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours [c] *and* • If present at baseline, 25-49% reduction in the size of soft tissue plasmacytoma *and* • No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive Disease (PD) [b, h]	Increase of 25% from lowest value in any of the following [f, g]: • Serum M-protein (absolute increase must be ≥ 0.5 g/dL) *and/or* • Urine M-protein (absolute increase must be ≥ 200 mg/24 hrs) *and/or* • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) *and/or* • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be ≥ 10%) [e] Or any one or more of the following: • Development of new bone lesion or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue plasmacytoma • Development of hypercalcemia (corrected serum calcium > 11.5mg/dL) that can be attributed solely to the PC proliferative disorder
Stable Disease (SD)	Not meeting criteria for sCR, CR, VGPR, PR, MR or PD

[a] All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy; sCR, CR, VGPR, PR, MR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed.

[b] CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

[c] If more than one M protein spike meets the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

[d] In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

[e] Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC;

[f] A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-protein is ≥ 5 g/dL, an increase in serum M-protein of ≥ 1 g/dL is sufficient to define disease progression.

[g] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

[h] Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

[i] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

Cohort B (light chain amyloidosis) – The Amyloidosis Consensus Criteria response criteria will be used to assess response to therapy

11.6 Hematologic Response Considerations

11.61 **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, monoclonal paraprotein, M-component.

Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.

- M-proteins migrating in the β-region (usually IgA M-proteins)
- Cases in which the M-spike is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.

If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-spike values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable

and are not recommended.

FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

11.62 **Response terms:** The following response terms will be used: stringent Complete Response (sCR), amyloid complete response (ACR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease or no response (SD), and progression or relapse (PD) and relapse from CR (RFCR). See Tables for definitions.

In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uACR, uVGPR, uPR, uMR, uPD.

11.63 **Measurable disease:** Patients who have a measurable serum or urine monoclonal protein by any of these means.

- serum M-protein is ≥ 1 g/dL
- urine M-spike is ≥ 200 mg/24 hours
- **dFLC 5 mg/dL provided the kappa to lambda free light chain ratio is abnormal (primary criteria for response)**

The serum free light chain (FLC) assay is the most important parameter of response assessment. When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response.

11.64 **Confirmed response:**

11.641 ***Confirmed hematologic response.*** In order to be classified as a confirmed hematologic response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations. Listed below are the minimal required tests required to assess response and confirm hematologic response based on the characteristics of their disease at on study.

Table 11.641

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])				
On Study Baseline Value	**SPEP**	**24 hr UPEP[2,3]**	**Ig FLC**	**BM Bx[1,4]**
Serum M-spike ≥1 g/dl, and urine M-spike≥ 200 mg/24 hrs, and involved serum FLC ≥ 7.5 mg/dL	X	X	X	
Serum M-spike ≥ 1 g/dl, but urine M-spike < 200 mg/24 hrs and involved serum FLC ≥ 7.5 mg/dL	X	X	X	
Serum M-spike<1 g/dl, and urine M-spike≥ 200 mg/24 hrs and involved serum FLC ≥ 7.5 mg/dL		X	X	
Serum M-spike < 1 g/dl, urine M-spike < 200 mg/24 hrs, but and involved serum FLC ≥ 7.5 mg/dL			X	
Serum M-spike < 1 g/dl, urine M-spike < 200 mg/24 hrs, involved serum FLC is <7.5 mg/dL, bone marrow ≥30% plasma cells				X[4]

1 **Bone marrow biopsy and immunofixation studies of both serum and urine** are required to document ACR regardless of registration values, and in addition **FLC** measurement and **bone marrow immunophenotyping** is required to document sCR. Bone marrow biopsy results do not need to be confirmed (i.e. repeated after documented response)

2 For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category unless they have renal amyloid. In this group, the 24 hour urine is required to document organ response as well.

3 For those patients with renal amyloidosis, the 24 hour urine protein electrophoresis should be done at every measurement

4 For all disease categories, bone marrow biopsy is required to document sCR and ACR, but not PR, MR, or progression unless unmeasurable disease.

11.642 **Confirmed organ response.** In order to be classified as a confirmed organ response, the repeat testing listed in Table 11.642 is required. For organ progression, 2 observations beyond first suspected progression are allowed due to variability of results (see table below).

Table 11.642

Organ response	Response test	Confirmation required?
Cardiac	• NT-ProBNP • cTnT • NYHA stage	Yes Yes Yes
Renal	• Creatinine • 24 hour urine protein • Creatinine clearance (optional)	Yes Yes Optional
Hepatic	• Alkaline phosphatase • Liver image	Yes Yes
Neuropathy	• Nerve conduction studies • Neurologic impairment score	Yes Yes

11.643 **Response and Progression:** Criteria for hematologic response and progression are listed in Table 11.643 and for organ response in Table 11.644.

Table 11.643

CATEGORY	RESPONSE CRITERIA[a]
Stringent complete response (sCR)	• ACR as defined below plus all of the following • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence[b]
Amyloid Complete response (ACR). For the purpose of response assessment this is hematologic complete remission.	• Negative immunofixation of the serum and urine • <5% plasma cells in bone marrow • Normal serum FLC ratio • If at on study, the only measurable non-bone marrow parameter was FLC, normalization of FLC ratio
Very good partial response (VGPR)	• dFLC (difference between the involved and uninvolved serum free light chain) <4 mg/dL
Partial Response (PR)	• dFLC >50% decrease
No Response (NR)	• ≥25% but < 49% reduction of serum M-protein and reduction in 24h urine M-protein by 50-89%, which still exceeds 200 mg per 24 h
Progressive disease (PD)	Any one or more of the following: • Increase of 25% from lowest confirmed response in: ▪ Serum M-component (absolute increase must be ≥0.5 g/dl)[c] ▪ Serum M-component increase ≥1 g/dl, if lowest M component was ≥5 g/dl ▪ Urine M-component (absolute increase must be ≥ 200 mg/24 h)[c] ▪ If at on study, the only measurable non-bone marrow parameter was FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl) ▪ Bone marrow plasma cell percentage (absolute % must be ≥10%)[c]

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy.

[b] Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1:2.

[c] Positive immunofixation alone in a patient previously classified as ACR will not be considered progression.

Table 11.644

ORGAN	CRITERIA	
	Response	Progression
Heart • NT-ProBNP response	>30% and >300 ng/L decrease if baseline NT-proBNP ≥ 650 ng/L	>30% and >300 ng/L increase
• cTnT	Only for progression	≥ 33% increase
• EF	Only for progression	≥ 10% decrease
Renal	50% reduction in 24-hour urine protein excretion (at least 0.5 g/day). Creatinine and creatinine clearance must not worsen by 25% (minimum change of creatinine 0.5 mg/dL and of creatinine clearance 15 ml/min).	50% increase in urinary protein loss (at least 1 g/24 hours), or 25% worsening of creatinine or creatinine clearance, (minimum change of 0.5 mg/dL and 15 ml/min, respectively).
Liver (any of following):	Type A. ≥50% decrease in an initially elevated alkaline phosphatase level, or Type B. Decrease in liver size by at least 2 cm (radiographic determination).	Type A. ≥50% increase of alkaline phosphatase above lowest level Type B. Increase in liver size by at least 2 cm (radiographic determination).
Neuropathy (any of the following):	Type A. Reduction in the Neuropathy Impairment Score (NIS) by 10 points. The NIS is based on the neurologic examination, and the items provide a measure of severity of muscle weakness (scored as 0= normal, 1= 25%, 2= 50%, 3= 75% weak, 4= paralyzed); loss of deep tendon reflexes scored as normal (0), decreased (1), or absent (2) and sensory loss graded as normal (0), diminished (1), or absent (2). Type B. Improvement in the	Type A. Increase in the Neuropathy Impairment Score (NIS) by 10 points. Type B. Worsening in the summated compound muscle action potential (CMAP) amplitude by 2 mv. This value is derived from summated value of compound muscle action potential amplitudes of the tibial, peroneal and ulnar nerves from the nerve conduction studies.

ORGAN	CRITERIA	
	Response	Progression
	summated compound muscle action potential (CMAP) amplitude by 2 mv. This value is derived from summated value of compound muscle action potential amplitudes of the tibial, peroneal and ulnar nerves from the nerve conduction studies.	

12.0 Descriptive Factors

12.1 Cohort A only: Parameters followed for hematologic response (pick one):.serum monoclonal protein ≥ 1 g/dL and urine M-spike ≥200 mg/24 hours vs. serum monoclonal protein ≥1g/dL only vs. urine M-spike ≥200 mg/24 hours only vs. serum immunoglobulin free light chain ≥10 mg/dL. Distinguish between SPEP measurement versus quantitative IgA measurement for serum monoclonal protein.

12.2 Autologous stem cell transplant: eligible vs. not eligible

12.3 Dose level: -2 vs. -1 vs. 0 vs. 1

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are sCR, CR, VGPR, PR, MR, or SD (or usCR, uCR, uVGPR, uPR, uMR) will continue treatment per protocol.

13.2 Patients who develop progressive disease or start alternate therapy while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD, including stem cell transplantation, will go to the event-monitoring phase per Section 18.0.

13.4 Patients who are discontinued from therapy for an unacceptable adverse event(s) will be followed until resolution or stabilization of the AE(s).

13.5 Criteria for Patient Withdrawal from Study Treatment

Patients may be withdrawn from the study for the following reasons:

- Progressive multiple myeloma
- Patient refuses further treatment on the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions)
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation

All attempts should be made to complete the End of Study procedures if a patient withdraws from the trial early.

13.6 Criteria for Study Discontinuation

The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice guidances or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB.

13.7 Phase I only: If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

13.8 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.9a A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.9b A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens: Cohort A ONLY

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol: Pharmacokinetic sampling is included in this study. The sampling schedule is as shown below.

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Cycle 1				Cycle 2	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
					Day 1 (post-dose, hours 1 & 4)	Day8 (pre-dose)	Day 15 (pre-dose)	Day 22 Anytime	Day 1 (pre-dose)		
Pharmacokinetics	Mandatory	Blood	EDTA (lavender)	4 mL (1)	X	X	X	X	X	Yes	Store -70, ship on cry ice

14.2 Collection and Processing:

Collect 3ml of blood into chilled 4ml K2 EDTA tube (lavender top tube) per time point. Gently invert tube 8-10 times to mix the additive with the collection blood prior to centrifugation. Place immediately on wet ice. Centrifuge the container for 30 minutes at approximately 3000 rpm at approximately 4ºC in a refrigerated Centrifuge. Immediately following centrifugation, gently remove the plasma from the packed cells and aliquot into two transfer vials filled with lyophilized citric acid. Each aliquot should contain exactly 0.500ml of plasma. Vortex split tubes well. Any remaining plasma can be discarded. Replace cap on tube and freeze the samples immediately at -70ºC. No more than 60 minutes will elapse between blood collection and freezing the plasma samples. Keep samples frozen at -70ºC or lower until shipment

Pharmacokinetic (PK) Sample Collection and Handling

Blood samples for PK assessment must be collected in 3-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 information will be written on the labels.

Preparation of Plasma Pharmacokinetic Samples

1. Draw blood into labeled and chilled 3 mL lavender top K2EDTA Vacutainer tube.

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

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

4. Immediately following centrifugation, gently remove the plasma from the packed cells and aliquot into two transfer vial filled with lyophilized citric acid. Each aliquot should contain 0.5 mL of plasma.

5. Vortex split tubes thoroughly. Any remaining plasma post split1/split 2 sample aliquots should be discarded following appropriate biohazard disposal procedures.

NOTE: If < 0.5 mL plasma is obtained post centrifugation, do not process or store split1 or split2, record split1: ISV (Insufficient Sample Volume), split2: ISV. If < 1.0 mL plasma is obtained post centrifugation, process and store split1 according to procedure; do not process or store split2, record split 2: ISV. Discard remaining plasma using appropriate biohazard waste disposal procedures.

6. Replace cap on tube and freeze the samples immediately at -70°C

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

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

Note: Wet ice is defined as a mixture of ice and water

Radius of rotation (rotor arm length) (cm)	**RPM speed needed to achieve 1000g**
4	4743
5	4242
6	3873
7	3585
8	3354
9	3162
10	3000
11	2860
12	2738
13	2631
14	2535
15	2449

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 should be addressed to the contact person designated by Millennium.

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14.3 Shipping and Handling

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 (Ixazomib PK samples currently have 618 days of stability 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.

The investigator must follow the instructions below:

- For all international shipments, a courier will be designated.

- 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 (eg, 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 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.

Ship the samples for each patient after the final C2D1 predose samples are obtained. Ship the samples on dry ice.

Samples should be shipped to:
Ship To:

Tandem Labs

[redacted]

14.4 Background and Methodology

14.41 Pharmacokinetics:

Blood samples (3 mL) for the determination of plasma concentrations of MLN2238 will be collected during Cycles 1 and 2. Blood samples are to be collected in Cycle 1 at post dose (1 hour and 4 hours) on Day 1, predose on Days 8, 15 and anytime on day 22. In Cycle 2, blood samples will be collected at predose on Day 1, .

15.0 Drug Information

15.1 Ixazomib

15.11 **Background**: Ixazomib is a second-generation small molecule inhibitor of the 20S proteasome that is under development for the treatment of non-hematologic malignancies, lymphoma, and multiple myeloma.

Ixazomib (MLN2238) refers to the biologically active, boronic acid form of the drug substance, Ixazomib citrate (MLN9708). The transition to MLN2238 occurs in any aqueous system.

15.12 **Formulation**: The Ixazomib capsule drug product formulation consists of drug substance, microcrystalline cellulose, talc, and magnesium stearate. Seven difference capsule strengths are manufactured: 0.2, 0.5, 2.0, 3.2, 3.0, 4.0, and 5.5 mg; each capsule strength has a unique color. Dosage strength is stated as Ixazomib (the active boronic acid). Ixazomib capsules are individually packaged in blisters.

Matching placebo capsules have been manufactured for the 2.3, 3.0, 4.0, and 5.5 mg ixazomab (Ixazomib) capsules. The placebo capsules contain microcrystalline cellulose, talc, and magnesium stearate and are identical in color and size to the corresponding active dose.

15.13 **Preparation and storage**: Ixazomib capsules (0.2 mg, 0.5 mg, 2.0 mg), individually packaged in blisters, can be stored at 2ºC to 8ºC or "Do not store above 25°C. Do not freeze." Ixazomib capsules (2.3 mg, 3.0 mg, 4.0 mg, and 5.5 mg), individually packaged in blisters can be stored at "2°C - 8°C" or "Do not store above 30°C. Do not freeze."

Ixazomib that is dispensed to the patient for take-home dosing should remain in the blister packaging until the point of use. The investigative site is responsible for providing the medication to the patient in units that comprise the correct daily dose configurations. Capsules should remain in the blisters until the point of use. Ixazomib capsules must be administered as intact capsules and must not be opened or manipulated in any way. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients will be instructed to store the medication in the refrigerator until the time of use. Reconciliation will occur accordingly when the patient returns for their next cycle of therapy. Any extremes in temperature should be reported as an excursion and will be managed on a case by case basis. Returned unused capsules should be discarded in a proper biohazard container.

Ixazomib is an anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling Ixazomib. It is recommended to wear gloves and protective garments during preparation when dispensed in clinic. Please refer to published guidelines regarding the proper handling and disposal of anticancer agents.

15.14 **Administration:** Ixazomib capsules must be administered as intact capsules and are not intended to be opened or manipulated in any way. Capsules should be taken on an empty stomach with approximately 8 oz (1 cup) of water (no food for 2 hours before and for 1 hour after dosing).

Ixazomib should not be taken if the patient has had a serious allergic reaction to boron or boron containing products

15.15 **Pharmacokinetic information**: a) Absorption: After oral dosing, ixazomib is rapidly absorbed with a median T_{max} of 1 hour. The lack of a discernible relationship between BSA and ixazomib clearance over a relatively wide BSA range (1.4-2.6 m^2) indicates that total systemic exposure (AUC) following fixed dosing should be independent of the individual patient's BSA. A high-fat meal decreased both the rate and extent of absorption. Therefore, ixazomib should be administered on an empty stomach.
b) Distribution: The steady state volume of distribution is large and is estimated to be 543 L. Ixazomib is 88-94% protein bound.
c) Metabolism: Metabolism is the primary route for elimination of ixazomib by both CYP and non-CYP enzymes. CYP3A4 and 1A2 comprise the major CYP isozymes that contribute to ixazomib metabolism.
d) Excretion: The mean terminal half-life is 9.5 days. Renal elimination is a minor clearance pathway for ixazomib. Dosing adjustment is not required in patients with mild and moderate renal impairment in studies. However, in a dedicated renal impairment study (C16015), unbound AUC0-last was 38% higher in patients with severe renal impairment or
end-stage renal disease (ESRD) requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is recommended in patients with severe renal impairment and ESRD requiring dialysis. Unbound systemic exposures of ixazomib are 27% higher in patients

with moderate or severe hepatic impairment as compared to patients with normal hepatic function. A reduced starting dose of ixazomib is recommended for patients with moderate or severe hepatic impairment.

15.16 **Potential Drug Interactions**: The PK of Ixazomib was similar with and without coadministration of clarithromycin, a strong CYP3A inhibitor, and therefore no dose adjustment is necessary when Ixazomib is administered with CYP3A inhibitors. In the population PK analysis, coadministration of strong CYP1A2 inhibitors did not affect Ixazomib clearance. Thus, no dose adjustment is required for patients receiving strong CYP1A2 inhibitors. In a clinical rifampin DDI study, Ixazomib Cmax and AUC0-last were reduced in the presence of rifampin by approximately 54% and 74%, respectively. As a result, the coadministration of strong CYP3A inducers with Ixazomib should be avoided. Ixazomib is neither a time-dependent nor reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, therefore the potential for Ixazomib to produce DDIs via CYP isozyme inhibition is low. Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity. The potential for Ixazomib to cause DDIs with substrates or inhibitors of P-gp, BCRP, MRP2, MATE-1, MATE2-K, OCT2, OAT1, OAT3, and OATPs is low.

Pharmacokinetic parameters for Ixazomib coadministered with lenalidomide and dexamethasone (LenDex) are similar to those observed when Ixazomib is administered as a single agent. This suggests that there is no readily apparent effect of coadministration of LenDex on the clinical PK of Ixazomib.

Ixazomib should not be taken if the patient has had a serious allergic reaction to boron or boron containing products.

15.17 **Known potential toxicities**: See the current version of the Investigator's Brochure for more complete information including potential risks, as well as recommendations for clinical monitoring and medical management of toxicity.

Very common (≥10%): anemia, neutropenia, thrombocytopenia, constipation, diarrhea, nausea, vomiting, fatigue, decreased appetite, , peripheral neuropathy
Common (≥1% to <10%): Herpes zoster, peripheral sensory neuropathy, erythema, rash, erythematous rash, pruritic rash, macular rash, peripheral edema, upper respiratory tract infection, back pain, maculo-papular rash, papular rash

Uncommon (≥0.1% to <1%): generalized pruritis, generalized rash

Herpes zoster – antiviral prophylaxis should be considered in patients being treated with Ixazomib to decrease the risk of herpes zoster reactivation.

Rare but serious risks – intestinal obstruction, pneumonia, life-threatening severe skin rash (Steven Johnson syndrome, TEN, DRESS syndrome), thrombotic thrombocytopenic purpura, tumor lysis syndrome, renal failure, posterior reversible encephalopathy syndrome, transverse myelitis, progressive multifocal leukoencephalopathy.
Overdose – There is no known specific antidote for Ixazomib overdose. In the event of an overdose in blinded studies, study medication assignment should be unblinded immediately. The clinician should consider admitting the patient to the hospital for IV hydration, monitoring for adverse drug reactions, monitoring of vital signs, and appropriate supportive care. Gavage may be considered, but it should be kept in mind that Ixazomib absorption is rapid. Ixazomib is not readily dialyzable.

15.18 **Drug procurement and accountability:** Investigational product will be supplied free of charge to trial participants by Millennium Pharmaceuticals, Inc.

15.19 Nursing Guidelines

15.191 Capsules must be administered intact and should not be opened or manipulated in any way. Additionally, capsules should remain in the blister packs until they are ready to be taken. It is recommended to wear gloves and protective garments during preparation when dispensed in clinic.

15.192 Capsules should be taken on an empty stomach (either 1 hour before or 2 hours after meals) with 8 oz of water.

15.193 Cytopenias have been observed. Monitor CBC w/diff. Instruct patient to report any signs or symptoms of infection or bleeding to the study team.

15.194 GI side effects have been seen (nausea, diarrhea, vomiting), treat symptomatically and monitor for effectiveness of intervention.

15.195 Rash has been seen. Rarely Steven Johnson syndrome (SJS) has been seen with this agent. Instruct patients to report any rash to study team.

15.196 Assess patients concomitant medications, including over the counter and supplements. Ixazomib is metabolized through both CYP and non-CYP enzymes, and drug to drug interactions exist. Instruct patients not to start any new medications or supplements without checking with the study team first.

15.197 Fatigue has been seen. Instruct patient in energy conserving lifestyle.

15.198 Insomnia can be seen. Treat symptomatically and monitor for effectiveness.

15.199a Patients who have had an allergic reaction to boron or boron containing products should not take MLN9708.

15.199b The following rare but life threatening conditions have been seen with agent: CHF, liver failure, TTP, TLS, renal failure, bowel obstruction, and RPLS, transverse myelitis, progressive multifocal leukoencephalopathy. Monitor labs closely, instruct patient to report any new or worsening symptoms to the study team and provide further assessment based on symptoms.

15.2 **Dexamethasone for Oral Administration (DXM)**

15.21 **Background**: Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

15.22 **Formulation**: Commercially available for oral administration as:
Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg
Solution, oral: 0.5 mg/mL (500 mL)
Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL)

15.23 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (60ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.

15.25 **Pharmacokinetic information**:
Onset of action: Prompt
Duration of metabolic effect: 72 hours
Metabolism: Hepatic
Half-life elimination: Normal renal function: 1.8-3.5 hours; **Biological half-life:** 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine and feces

15.26 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP3A4 (major); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong)
Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.

Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
Ethanol/Nutrition/Herb Interactions:
Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
Herb/Nutraceutical: Avoid cat's claw (*Uncaria tomentosa)*, echinacea (have immunostimulant properties)

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 Nursing Guidelines:

15.291 Monitor patient regularly for hypertension, CHF and other evidence of fluid retention.

15.292 Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.

15.293 Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.

15.294 Evaluate signs of infection, particularly local candidal infections and treat appropriately**.**

15.295 Monitor blood glucose frequently.

15.296 Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

15.297 Advise patient that easy bruising is a side effect.

15.3 Cyclophosphamide for Oral Administration (Cytoxan®, Neosar®, CTX)

15.31 **Background**: Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

15.32 **Formulation**: Commercially available for oral administration as:
Tablets: 25 mg, 50 mg

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature preferably below 25ºC (77ºF). This product will withstand brief exposure to temperatures up to 30ºC (86ºF), but should be protected from temperatures above 30ºC (86ºF). Dispense in a tight container as defined in the USP/NF. Refer to labeling on the bottle for expiration date of the commercial tablets.

15.34 **Administration:** Refer to the treatment section for specific administration instructions. Tablets are not scored and should not be cut or crushed. To minimize the risk of bladder irritation, do not administer tablets at bedtime.

15.35 **Pharmacokinetic information**:
Distribution: V_d: 0.48-0.71 L/kg; crosses placenta; crosses into CSF (not in high enough concentrations to treat meningeal leukemia)
Protein binding: 10% to 60%
Bioavailability: >75%
Time to peak, serum: Oral: ~1 hour
Metabolism: Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard
Half-life elimination: 3-12 hours
Excretion: Urine (<30% as unchanged drug, 85% to 90% as metabolites)

15.36 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP2A6 (minor), 2B6 (major), 2C9 (minor), 2C19 (minor), 3A4 (major); **Inhibits** CYP3A4 (weak); **Induces** CYP2B6 (weak), 2C8 (weak), 2C9 (weak)
Increased Effect/Toxicity: Allopurinol may cause an increase in bone marrow depression and may result in significant elevations of cyclophosphamide cytotoxic metabolites. CYP2B6 and CYP3A4 inducers may increase the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inducers. Etanercept

may enhance the adverse effects of cyclophosphamide. Cyclophosphamide reduces serum pseudocholinesterase concentrations and may prolong the neuromuscular blocking activity of succinylcholine and mivacurium.
Decreased Effect: Cyclophosphamide may decrease the absorption of digoxin tablets. CYP2B6 and CYP3A4 inhibitors may decrease the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inhibitors.
Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Dermatologic: Alopecia but hair will usually regrow although it may be a different color and/or texture. Hair loss usually begins 3-6 weeks after the start of therapy.
Endocrine & metabolic: Fertility: May cause sterility; interferes with oogenesis and spermatogenesis; may be irreversible in some patients; gonadal suppression (amenorrhea)
Gastrointestinal: Nausea and vomiting, usually beginning 6-10 hours after administration; anorexia, diarrhea, mucositis, and stomatitis are also seen
Hematologic: Thrombocytopenia and anemia are less common than leukopenia

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Facial flushing
Central nervous system: Headache
Dermatologic: Skin rash

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Cyclophosphamide may potentiate the cardiac toxicity of anthracyclines. Other adverse reactions include anaphylactic reactions, darkening of skin/fingernails, dizziness, hemorrhagic colitis, hemorrhagic ureteritis, hepatotoxicity, hyperuricemia, hypokalemia, jaundice, malaise, neutrophilic eccrine hidradenitis, radiation recall, renal tubular necrosis, secondary malignancy (e.g., bladder carcinoma), SAIDH, Stevens-Johnson syndrome, toxic epidermal necrolysis, weakness.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 **Nursing Guidelines:**

15.391 Myelosuppression is common. Monitor CBC including platelets. Instruct patient on signs/symptoms of infection and to inform health care team of any unusual bruising, or signs of bleeding.

15.392 Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate keeping the bladder clear of drug.

15.393 Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria. Administer mesna with high dose cytoxan to prevent hemorrhagic cystitis. It may be necessary to catheterize and provide constant bladder irrigation.

15.394 Advise patient in possible strong metallic taste associated with Cytoxan and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.

15.395 Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration.

15.396 Report and record any complaint of lightheadedness, facial "heat sensation," diaphoresis during administration.

15.397 Use of an ice cap may be helpful in preventing or limiting alopecia.

15.398 Corticosteroids, phenothiazine, imipramine, vitamin A succinylcholine, digoxin, thiazide diuretics, warfarin and allopurinol may inhibit Cytoxan metabolism and modify its' effect. They may also increase bone marrow suppression.

15.399a Advise female patients of possible menstrual changes or amenorrhea.

15.399b Patients on anticoagulant therapy should have INR levels carefully monitored as cytoxan increases their effect.

15.399c Monitor electrolytes and for signs/symptoms of SIADH and tumor lysis syndrome.

15.399d Monitor digoxin levels closely as cytoxan may decrease these levels.

15.399e Cytoxan may potentiate doxorubicin-induced cardiomyopathy. Instruct patient to report any chest pain.

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a phase I/II study of a novel regimen of Ixazomib with cyclophosphamide and dexamethasone for treatment in two cohorts of patients: initial treatment of newly diagnosed multiple myeloma patients requiring therapy (cohort A) and treatment of light chain amyloidosis (cohort B). The phase I study is designed to determine the maximally tolerated dose (MTD) and toxicity profile of Ixazomib in combination with cyclophosphamide and dexamethasone in patients with previously

untreated multiple myeloma using the standard cohort 3+3 design. The phase II portion is designed to assess the complete plus very good partial response rate associated with therapy with Ixazomib in combination with cyclophosphamide and dexamethasone, in patients with previously untreated multiple myeloma using a single stage phase II study design (cohort A). As of Addendum 9, a second single stage phase II study design is being added to assess the hematologic response rate of this regimen in patients with light chain amyloidosis (cohort B).

16.11 Endpoint: The primary endpoint of the phase I portion of this trial is to assess the maximum tolerated dose (MTD). For cohort A of the phase II portion of this trial, the primary endpoint is the rate of complete or very good partial response. A success will be defined as a an sCR,a, CR or VGPR noted as the objective status on two consecutive evaluations. For cohort B of the phase II portion, the primary endpoint is the rate of hematologic response. A success will be defined as an sCR, ACR, VGPR, or PR noted as the objective status on two consecutive evaluations. Response will be evaluated using the first 12 cycles (induction therapy). Throughout Section 16.0, sCR, CR, or VGPR (cohort A) or sCR, ACR, VGPR, or PR (cohort B) will be considered synonymous with "success" in the phase II portion, unless specified otherwise.

16.12 Sample Size: The phase I portion of this study is expected to require a minimum of 6 and a maximum of 12 evaluable patients. The 6 patients treated at the MTD in the phase I portion will also be included in the phase II portion. A maximum of 35 additional evaluable patients will be accrued at the MTD dose level for a maximum of 41 evaluable patients in the phase II portion of this study. We anticipate accruing up to 4 additional patients (1 phase I, 3 phase II) to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, a maximum of 13 patients will be accrued in the phase I portion and a maximum of 38 patients will be accrued to the phase II portion for an overall maximum of 51 patients for the entire study.

As of Addendum 9, 51 patients have been accrued to cohort A and cohort B is being added to the phase II portion of this study. A maximum of 33 evaluable patients will be accrued to cohort B. We anticipate accruing up to 3 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons in cohort B. Therefore, a maximum of 36 patients will be accrued to cohort B for an overall maximum of 87 patients for the entire study.

16.13 Accrual Rate and Study Duration: The anticipated accrual rate is 3-4 evaluable multiple myeloma patients per month. At this rate, it will likely take about 2.5 months to enroll, treat, and evaluate each cohort in the phase I portion of this study. The phase I portion is expected to take between 5 and 10 months. The phase II portion of this study will accrue in the subsequent 1 year. The maximum total study duration is expected to be approximately 3 years, or until the last patient accrued has been observed for at least 12 months.

As of Addendum 9, it is anticipated that the accrual rate in cohort B is 3-4 evaluable light chain amyloidosis patients per month. It is anticipated that cohort B will accrue in approximately 12 months. The maximum total study duration is

expected to be approximately 2 years after Addendum 8 is activated, or until the last patient accrued has been observed for at least 12 months.

Phase I Portion

16.2 Study Design: The phase I study is designed to determine the maximally tolerated dose (MTD) and toxicity profile of Ixazomib in combination with cyclophosphamide and dexamethasone in patients with previously untreated multiple myeloma using the standard cohort 3+3 design. Three patients will be treated at each dose level and observed for a minimum of four weeks (i.e. one full cycle) before new patients are treated. Doses will not be escalated in any individual patient.

16.21 MTD Definition: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% ($1-(1-0.25)^6$).

Refer to Section 7.52 for definition of dose-limiting toxicity (DLT).

16.22 MTD Determination:

Dose Escalation: The phase I portion of this study will utilize a standard cohort of three design. The dose levels to which patients will be assigned in sequential cohorts are described in Section 7.51. The first cohort of three patients will be treated at dose level 0. Decisions on when and how to dose escalate are described below.

16.221 Three patients will be treated at a given dose level combination and observed for 1 cycle to assess toxicity.

16.222 If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

16.223 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded and further accrual will cease to this cohort. If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

16.224 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and

defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

16.225 Dose de-escalation: If dose-limiting toxicity meets the stopping boundaries set by the above dose escalation algorithm at dose level 0 (for example, more than 1 out of 3 patients or more than 1 out of 6 patients), the next cohort of three patients will be entered at a dose level of -1. If dose level -1 meets the stopping boundaries, the next cohort of three patients will be entered at dose level -2. Further dose re-escalation will depend on the toxicity profile observed at these dose levels, and re-evaluation of the regimen by the study team may be done.

16.226 If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

16.227 Operating Characteristics for standard cohort of 3 design: The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the cohorts of 3 design described above.

True Rate of DLT (%)	**Probability of Dose Escalation**
10	0.91
20	0.71
30	0.49
40	0.31
50	0.17

16.23 Analysis Plans: All the relevant results pertaining to toxicity, MTD, response, timed endpoints and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion. The small sample size and the heterogeneous patient population associated with phase I studies restricts the generalizability of the results. Any notable statistical result should only be viewed as preliminary evidence for further study in Phase II trials rather than a definitive finding in and of itself.

16.231 Adverse Events Profile

The number and severity of all adverse events (overall and by dose-level) will be tabulated and summarized in this patient population. The Grade 3+ adverse events will also be described and summarized in a

similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

16.232 Toxicity Profile

The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading.

Overall toxicity incidence as well as toxicity profiles by dose level, patient and tumor site will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

16.233 Response Profile

A response is defined to be a CR, VGPR, or PR noted as the objective status. Response will be evaluated using all cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

Responses will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease in this patient population.

Phase II Portion

16.3 Statistical Design:

Cohort A (multiple myeloma):

16.31 Decision Rule:

A combination of lenalidomide plus dexamethasone, an oral regimen, is the mainstay therapy for newly diagnosed multiple myeloma. In a large multi-center study, 208 patients were evaluated for response to treatment with lenalidomide plus low dose dexamethasone.[8] Eighty-four patients (40%) achieved a complete or very good partial response. Ixazomib in combination with cyclophosphamide and dexamethasone is another fully oral regimen. An increase in the rate of complete plus very good partial response compared to lenalidomide plus dexamethasone would be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 40%, and the smallest success

proportion that would warrant subsequent studies with the proposed regimen in this patient population is 60%. The following one-stage binomial design requires 41 evaluable patients (35 from phase II and 6 from the MTD portion of phase I) to test the null hypothesis that the true success proportion in this patient population is at most 40%.

16.311 Final Decision Rule: If 20 or fewer successes are observed in the first 41 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 21, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.312 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.44.

16.32 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e. there is a 10% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.40	0.45	0.50	0.55	0.60
Then the probability of declaring that the regimen warrants further study is…	0.10	0.26	0.50	0.74	0.90

16.33 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

Cohort B (light chain amyloidosis):

16.34 Decision Rule:

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 30%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 50%. The following one-stage binomial design requires 33 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 30%.

16.341 Final Decision Rule: If 13 or fewer successes are observed in the first 33 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 14,

this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.342 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.44.

16.35 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .09, i.e. there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.30	0.35	0.40	0.45	0.50
Then the probability of declaring that the regimen warrants further study is…	0.09	0.24	0.45	0.68	0.85

16.36 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.4 Analysis Plan

16.41 Primary Outcome Analyses:

16.411 Definition: For cohort A, the primary endpoint in the phase II portion of this trial is the proportion of complete plus very good partial responses. A success is defined as a sCR, CR or VGPR noted as the objective status on two consecutive evaluations. For cohort B of the phase II portion, the primary endpoint is the rate of hematologic response. A success will be defined as an sCR, ACR, VGPR, or PR noted as the objective status on two consecutive evaluations. Response will be evaluated using the first 12 cycles (induction therapy). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.412 Estimation: In each cohort independently, the proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportions will be calculated.

16.42 Secondary Outcome Analyses (to be evaluated in each cohort independently)

16.421 Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier[33].

16.422 Progression-free survival is defined as the time from registration to the earliest date of documentation of disease progression or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier

16.423 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.424 Cohort B only: For each disease site (heart, renal, liver, neuropathy), the organ response rate will be estimated by the total number of patients who have an organ response divided by the total number of evaluable patients who had involvement in that organ at baseline. Exact binomial 95% confidence intervals for the true organ response rates will be calculated.

16.43 Correlative Analyses

16.431 Cohort A only: Individual and mean plasma concentration data will be plotted over time. A summary table will be presented for the plasma concentration data. PK parameters will be estimated using noncompartmental analysis methods. The plasma PK parameters calculated for individual plasma Ixazomib concentration-time data will include, but are not limited to: Cmax, Tmax, and AUC. PK parameters will be summarized using descriptive statistics.

16.432 The FACT/GOG neurotoxicity questionnaire will be completed by patients at baseline, after each cycle for the first 4 cycles, and then every three cycles. Patients will be evaluated by overall score at each time point and changes over time will be calculated. These measures will be correlated with outcome using Fisher's exact test and Kaplan-Meier methods where appropriate.

16.44 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final endpoint estimates and confidence intervals.

16.5 Data & Safety Monitoring:

16.51 The principle investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety

Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules (includes all phase II patients, including phase I patients treated at the MTD to be evaluated in each phase II cohort separately): The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- if 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

- if after the first 15 patients have been treated, 40% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2 years after the study opens to accrual to cohort B. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 12 months.

16.7 Inclusion of Women and Minorities

16.71 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender

groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	29	57	0	86
Ethnic Category: Total of all subjects*	29	58	0	**87**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	1	1	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	28	57	0	85
Racial Category: Total of all subjects*	29	58	0	**87**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study Form: Multiple Myeloma	≤2 weeks after registration
On-Study Form: Amyloidosis	
Baseline Adverse Event Form	
Pretreatment Measurement Form: Multiple Myeloma	
Pretreatment Measurement Form: Amyloidosis	
Patient Questionnaire Booklet Compliance Form[1]	
SPEP, UPEP, FLC , Serum and Urine Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey, Plasma Cell Proliferation and Assessment, Cytogenetic, FISH on study reports	
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet[2]	≤2 weeks after registration Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.

1. This form must be completed **only** if the Quality of Life Patient Questionnaire contains absolutely **NO** patient provided assessment information.
2. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)

	At each evaluation during treatment	At end of treatment
Evaluation/Treatment Form: Cohort A (Multiple Myeloma)	X	X
Evaluation/Treatment Form: Cohort B (Amyloidosis)	X	X
Stem Cell Harvest Form (optional)	X[3]	
Nadir/Adverse Event Form	X	X
Measurement Form: Multiple Myeloma	X	X
Measurement Form: Amyloidosis	X	X
SPEP, UPEP, FLC , Serum and Urine Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey	X[4]	X[4]
Research Blood Submission Form	X (see Section 14.0)[5]	
Patient Questionnaire Booklet	X[1, 5]	
Patient Questionnaire Booklet Compliance Form	X[2]	
End of Active Treatment/Cancel Notification Form		X
ADR/AER	At each occurrence (see Section 10.0)	

1. Patient questionnaire booklet must be used; copies are not acceptable for this submission. (see Section 4.0).
2. This form must be completed only if the Quality of Life Patient Questionnaire contains absolutely NO patient provided assessment information. (see Section 4.0).
3. May interrupt therapy for stem cell collection at any time after 3 cycles of Induction treatment (see Schema). Submit the Stem Cell Harvest Form after stem cell collection has been completed.
4. Submission of these reports is only required for documentation of CR or progression. For documentation of CR, submit all of these reports at the first confirmation of CR. For documentation of progression, submit one report for one of the measures where progression was seen. Attention: [redacted].
5. Only when required by the Test Schedule (see Section 4.0).

Follow-up Material(s)

CRF	**Event Monitoring Phase[1]**				
	q. 3 months until PD or subsequent treatment for myeloma	At PD or subsequent treatment for myeloma	After PD or subsequent treatment for myeloma q. 6 mos.	Death	New Primary
Event Monitoring Form	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.

19.0 Budget

19.1 Costs charged to patient: routine clinical care, study drugs cyclophosphamide and dexamethasone

19.2 Tests to be research funded: Study drug Ixazomib, **Pharmacokinetic sampling (cohort A only)**

19.3 Other budget concerns: None

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Mayo Risk Stratification

High Risk

FISH deletion 17p

FISH t(14; 16)

FISH t(14; 20)

GEP (if done) High risk signature

NYHA Classification

Class I: NO Symptoms with ordinary activity

Class II: Symptoms with ordinary activity

Class III: Symptoms with minimal activity

Class IV: Symptoms at rest

Multiple Myeloma Diagnostic Criteria

Standard criteria for a diagnosis of multiple myeloma are as follows (Kyle et al *British Journal of Haematology. 121(5):749-57, 2003)*

Multiple Myeloma
Monoclonal protein present in serum ≥ 3 g/dl
and/or
Bone marrow clonal plasma cells ≥ 10%

Myeloma-related organ or tissue impairment (ROTI)
Calcium 1 mg/dL (0.25 mmol/L) above the upper limit of normal
Creatinine > 2 mg/dL (173 mmol/L)
Lytic bone lesions or osteoporosis

Asymptomatic myeloma
Multiple myeloma and absence of ROTI

Symptomatic myeloma
Multiple myeloma and presence of any ROTI that can be attributed to myeloma.

Name _____

Mayo Clinic No. _____

PATIENT MEDICATION DIARY

Please complete this diary on a daily basis. Write in the amount of the dose of Ixazomib, Cyclophosphamide and dexamethasone that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

Please swallow the Ixazomib capsules whole, with water, and not to break, chew, or open the capsules. It should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food. 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.

If you experience any health/medical complaints or take any medication other than Ixazomib, Cyclophosphamide or dexamethasone, please record this information.

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Ixazomib							
Cyclophosphamide							
Dexamethasone							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Ixazomib							
Cyclophosphamide							
Dexamethasone							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Ixazomib							
Cyclophosphamide							
Dexamethasone							

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Ixazomib							
Cyclophosphamide							
Dexamethasone							

Patient Signature_____

Date:_____

My next scheduled visit is: _____
If you have any questions, please call: _____

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. You answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains one set of questions:
   a. (11 questions) FACT-GOG Neurotoxicity questionnaire

2. Directions on how to complete the set of questions is written on the top of the set.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse or your physician

Thank you for taking the time to help us.

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands	0	1	2	3	4
I have numbness or tingling in my feet	0	1	2	3	4
I feel discomfort in my hands	0	1	2	3	4
I feel discomfort in my feet	0	1	2	3	4
I have joint pain or muscle cramps	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I have trouble hearing	0	1	2	3	4
I get a ringing or buzzing in my ears	0	1	2	3	4
I have trouble buttoning buttons	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
I have trouble walking	0	1	2	3	4

Millennium Pregnancy Reporting Form

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS) Page 1 of 4

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

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

Reporter name: _____	Title: _____	
Address: _____	Telephone No.: _____	Fax No. _____
City, State/Province: _____	Postal Code: _____	Country: _____

FATHER'S INFORMATION ❒ Father Unknown

Initials: _____ Date of Birth: ___/___/_____ or Age: _____years
DD MM Yr

Participating in an MPI clinical study? ❒ No ❒ Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

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

_____
_____

Race: _____
Occupation: _____
Number of children: _____

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

MOTHER'S INFORMATION:

Initials: _____ Date of Birth: ___/___/_____ or Age: _____years
DD MM Yr

Participating in an MPI clinical study? ❒ No ❒ Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

Race: _____
Occupation: _____

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

_____

_____

_____

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

Outcomes of previous pregnancies:
(Please indicate number of occurrences)

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

MOTHER'S DRUG EXPOSURE INFORMATION

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

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

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

CURRENT PREGNANCY INFORMATION

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

Pregnancy Status

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

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

Fetal/Neonatal Status

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

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

Additional Details:

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

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

❒Ultrasound ❒Amniocentesis ❒Maternal Serum-Alpha-Fetoprotein
❒Chorionic Villi Sampling ❒Human Chorionic Gonadotropin ❒Other:_____

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

_____

What are the defect(s) attributed to:_____

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

Infant Information:

Gestational weeks at birth or at termination: _____weeks

Date of birth or termination: ____/____/_____
DD MM Yr

If multiple births (e.g. twins), indicate number: _____
(Please complete separate form for each child)

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

Breast-fed: ❒Yes ❒ No ❒ Unk

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

Sex: ❒ Male ❒ Female ❒ Unk

Length: _____ ❒ cm ❒ in

Weight: _____ ❒ g ❒ lbs

Head circumference: _____ ❒ cm ❒ in

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

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

Resuscitation required: ❒ Yes ❒ No ❒ Unk

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

Additional Notes:

_____

_____

_____

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

Investigator signature: _____ Date: ____/____/_____
DD MM Yr

Investigator Name: _____

ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.