Mayo Clinic Cancer Center

Phase 2 Trial of Ixazomib Combinations in Patients with Relapsed Multiple Myeloma

Study Chair: [redacted]

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Statistician: [redacted]

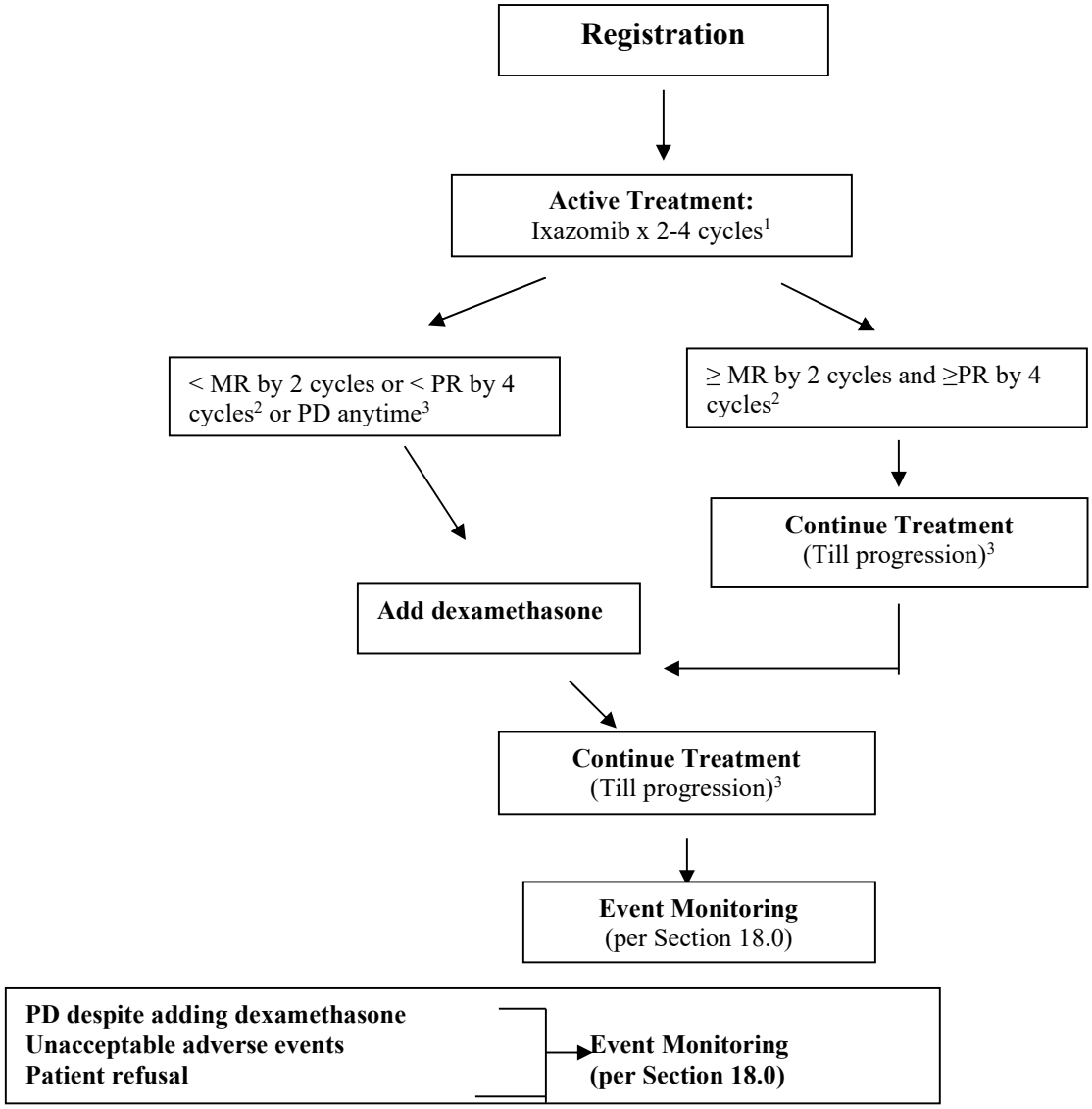
Drug Availability
Commercial Agents: Dexamethasone, Cyclophosphamide
Drug Company Supplied: Ixazomib, Daratumumab

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

Document History	Effective Date	Document History	Effective Date	Document History	Effective Date
Activation	January 31, 2011	**Addendum 10**	April 2, 2014	**Addendum 20**	May 22, 2017
Addendum 1	March 22, 2012	**Addendum 11**	May 1, 2014	**Addendum 21**	December 18, 2017
Addendum 2	June 12, 2012	**Addendum 12**	July 23, 2014	**Addendum 22**	March 20, 2018
Addendum 3	August 10, 2012	**Addendum 13**	January 19, 2015	**Addendum 23**	September 13, 2018
Addendum 4	November 8, 2012	**Addendum 14**	April 23, 2015	**Addendum 24**	January 28, 2019
Addendum 5	February 27, 2013	**Addendum 15**	November 23, 2015	**Addendum 25**	July 23, 2019
Addendum 6	June 7, 2013	**Addendum 16**	January 5, 2016	**Addendum 26**	February 26, 2020
Addendum 7	August 26, 2013	**Addendum 17**	February 4, 2016	**Addendum 27**	May 11, 2020
Addendum 8	October 1, 2013	**Addendum 18**	February 11, 2016	**Addendum 28**	April 29, 2021
Addendum 9	December 10, 2013	**Addendum 19**	June 9, 2016	**Addendum 29**	August 31, 2021
				Addendum 30	September 29, 2023

Index

Schema – Arm A (permanently closed to accrual per Addendum 5)

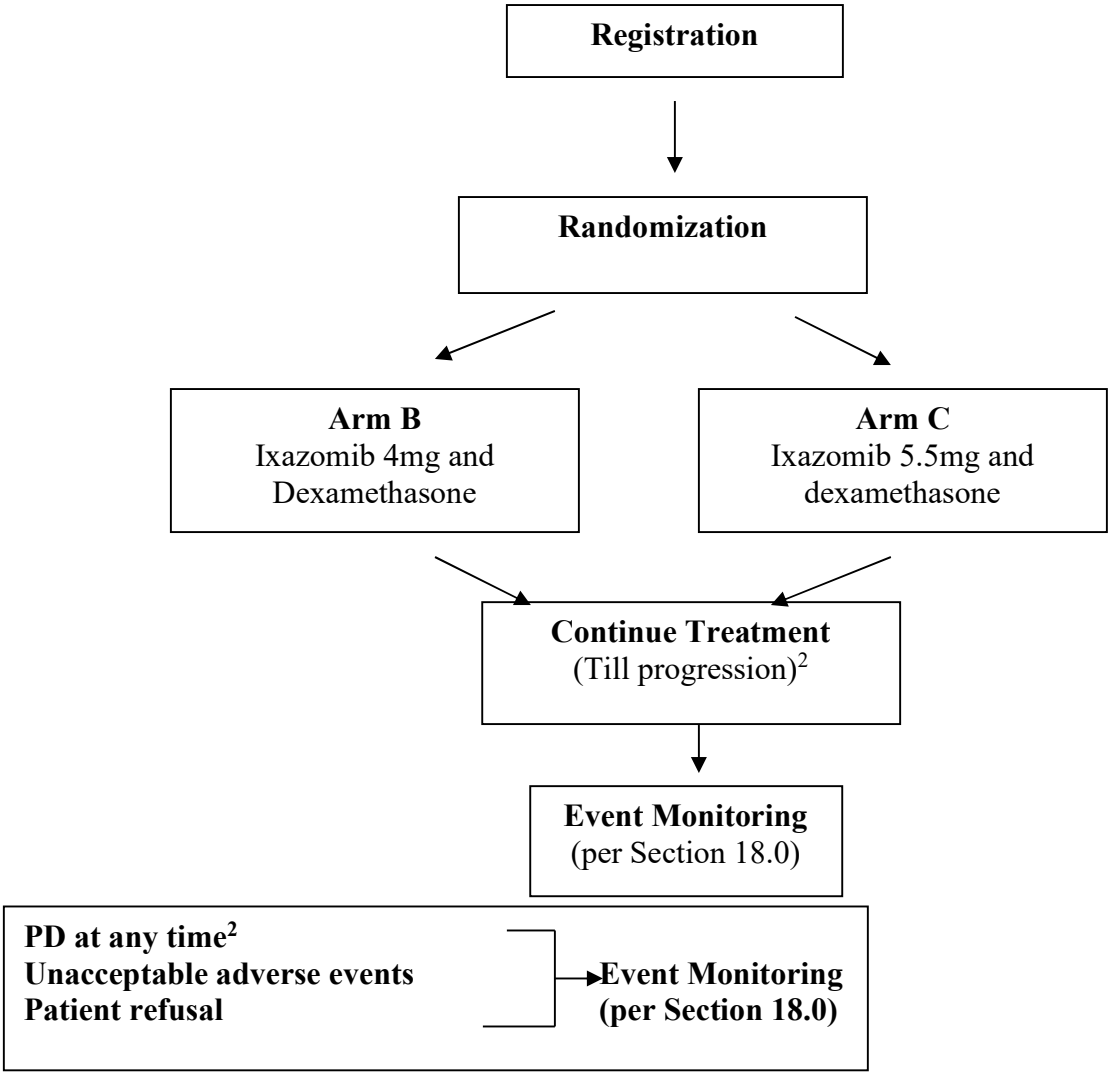


If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

[1] Cycle length = 28 days
[2] MR by 2 cycles and PR by 4 cycles can be unconfirmed responses
[3] Confirmation of PD is not required

Generic name: Ixazomib Brand name(s): Ninlaro® Mayo Abbreviation: MLN9708 Availability: Provided by Millennium Pharmaceutica	Generic name: Dexamethasone Brand name(s): Decadron Mayo Abbreviation: DXM Availability: Commercial

Schema – Arm B and C (closed)



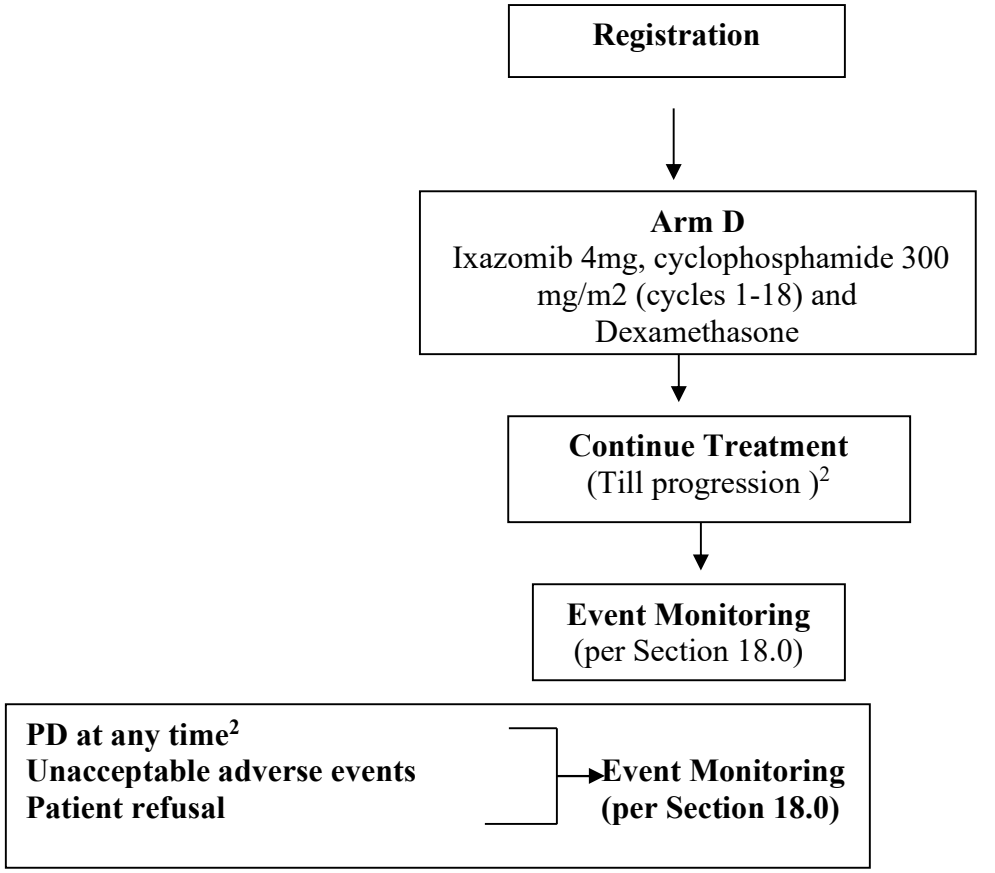
If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

[1] Cycle length = 28 days

[2] Confirmation of PD is not required

Generic name: Ixazomib Brand name(s): Ninlaro® Mayo Abbreviation: MLN9708 Availability: Provided by Takeda/Millennium Pharmaceuticals, Inc.	Generic name: Dexamethasone Brand name(s): Decadron Mayo Abbreviation: DXM Availability: Commercial

Schema – Arm D



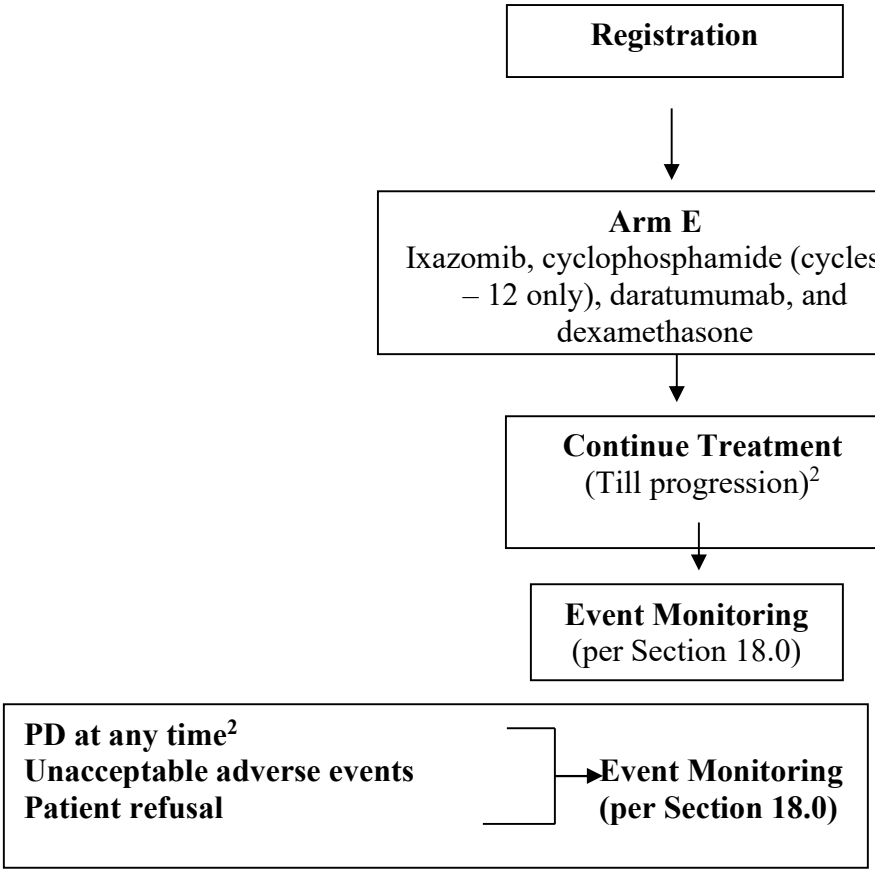
If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

[1] Cycle length = 28 days

[2] Confirmation of PD is not required

Generic name: Ixazomib Brand name(s): Ninlaro® Mayo Abbreviation: MLN9708 Availability: Provided by Takeda/ Millennium Pharmaceuticals, Inc.	Generic name: cyclophosphamide Brand name(s): Cytoxan Mayo Abbreviation: CTX Availability: Commercial	Generic name: Dexamethasone Brand name(s): Decadron Mayo Abbreviation: DXM Availability: Commercial

Schema – Arm E (added as of Addendum 23)



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

Note: Patients are allowed to be re-registered to a different arm due to progression.

Generic name: Ixazomib Brand name(s): Ninlaro® Mayo Abbreviation: MLN9708 Availability: Provided by Takeda/Millennium, Inc.	Generic name: cyclophosphamide Brand name(s): Cytoxan Mayo Abbreviation: CTX Availability: Commercial
Generic name: Dexamethasone Brand name(s): Decadron Mayo Abbreviation: DXM Availability: Commercial	Generic name: Daratumumab Brand name(s): Darzalex Mayo Abbreviation: DARA Availability: Provided by Janssen

1.0 Background

1.1 Treatment

1.11 ***Relapsed multiple myeloma***: Multiple Myeloma (MM) is a plasma cell proliferative disorder characterized pathologically by accumulation of clonal plasma cells predominantly in the bone marrow, with circulating tumor cells seen usually in the late stages of the disease (Kyle*, et al* 2003). Clinically, myeloma is manifested by destructive bone lesions that can result in pathological fractures, anemia and or thrombocytopenia, hypercalcemia, and renal insufficiency, which can be multifactorial in origin. In this country, the estimated annual diagnosed incidence is 19,200, with approximately 50,000 prevalent cases. In Europe, the estimated annual diagnosed incidence is 21,611 with approximately 54,536 prevalent cases. Multiple myeloma accounts for 10% of all hematologic malignancies and 1% of all malignancies. The median survival of patients with symptomatic MM treated with melphalan and prednisone or other combination chemotherapy medications was 3 to 4 years (Kyle*, et al* 2003). Advances in high-dose chemotherapy and stem cell transplantation have improved overall survival and event-free disease periods in patients with MM, but relapses are inevitable.(Kumar*, et al* 2008) New therapeutic agents, such as bortezomib and thalidomide analogues, have shown promising clinical benefit in patients with relapsed or refractory disease. Despite these therapeutic advances, MM remains essentially incurable and is associated with high morbidity and mortality.

1.12 ***The ubiquitin proteasome pathway:*** The ubiquitin-proteasome pathway is critical to cellular homeostasis, playing a major role in maintaining appropriate levels of different proteins in the cell.(Adams*, et al* 1998, Adams*, et al* 1999) 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.(Adams 2002a)

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.(Richardson*, et al* 2003b) 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.

1.13 ***Clinical experience with bortezomib and combinations in Relapsed/ Refractory MM***: Bortezomib (N-pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid; Velcade; Millennium Pharmaceuticals) is a small, cell permeable molecule that specifically and selectively inhibits the proteasome by binding in a reversible manner.(Adams 2001, An*, et al* 2000, Dai*, et al* 2003, Hideshima*, et al* 2001, Ling*, et al* 2002, Shah*, et al* 2001, Sunwoo*, et al* 2001, Teicher*, et al* 1999) Chemically, bortezomib is a modified dipeptidyl boronic acid derived from leucine and phenylalanine. Bortezomib inhibits the 20S proteasome with a K_i of 0.6 nM and has a short plasma half-life following iv administration indicating rapid clearance.(Adams 2002b) Bortezomib is metabolized by cytochrome P450 system into several inactive deboronated metabolites. Bortezomib is extensively bound to plasma proteins (83% in man). Tissue distribution of bortezomib, following IV infusion in rats, indicates that the highest levels are found in the adrenal glands, renal cortex, liver,

prostate and spleen. When used at the recommended dosing schedule, nearly 60% proteasome inhibition is achieved.

In a phase II multicenter trial of bortezomib in MM, 202 patients with progressive disease on treatment or disease progression within 60 days of completing therapy were treated with bortezomib alone, with addition of dexamethasone after 2 cycles in the absence of response.(Richardson*, et al* 2003a) Of the 193 assessable patients, 53 (27%) achieved a partial response to therapy including 4% of patients with a CR. The median survival for all patients was 16 months, and the median time to progression was 7 months. Responses were durable, with median response duration of 12 months in patients who achieved a CR, partial response, or minor response to therapy. Another randomized phase II trial in patients who failed to respond or relapsed after front-line therapy examined the two doses of bortezomib: 1.0 mg/m^2 vs. 1.3 mg/m^2 on days 1, 4, 8, and 11 every 21 days. Responses (CR, partial response, or minor response) were seen in 33% of patients at the dose level of 1.0 mg/m^2 and 50% of patients at the dose level of 1.3 mg/m$^{2.}$ In a phase III trial comparing bortezomib with dexamethasone, the overall response rates were 38 percent for bortezomib and 18 percent for dexamethasone, and the complete response rates were 6 percent and less than 1 percent, respectively (Richardson*, et al* 2005). Median times to progression in the bortezomib and dexamethasone groups were 6.2 months and 3.5 months respectively. There was improvement in the overall survival in patients receiving bortezomib as well. Correlative studies from the initial studies suggest that bortezomib is able to overcome the adverse prognostic effect of the genetic abnormalities seen in MM such as deletion 13.(Jagannath*, et al* 2007).

1.14 ***Ixazomib***: Ixazomib, which has been formulated for both intravenous (IV) and oral (PO) administration, is a small molecule proteasome inhibitor. The proteasome is a large protein complex that degrades ubiquitinated proteins via the ubiquitin-proteasome pathway (UPP), which is responsible for the degradation of the majority of intracellular proteins. Due to the accumulation of many different proteasome substrates, proteasome inhibition affects multiple signaling cascades within cells, resulting in downstream effects including antitumor activity, promotion of apoptosis, and antiangiogenic and antiproliferative activities. These consequences of proteasome inhibition are of particular importance in plasma cells and multiple myeloma cells, which produce high levels of secreted Ig proteins. Ixazomib is a small molecule proteasome inhibitor.

Ixazomib is the citrate ester of the biologically active boronic acid form, MLN2238, which is structurally similar to borezomib. 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.

1.15 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.

1.16 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.

1.17 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.

1.18 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.

1.19a Clinical Experience: Like bortezomib, ixazomib is a small molecule peptide boronic acid analog. Clinical studies with bortezomib have yielded detailed understanding of its safety profile. For details, refer to the package insert for bortezomib. Ixazomib is in the early stages of clinical investigations, with 5 ongoing phase 1 trials and 3 planned phase 1/2 trials in humans with safety, tolerability, PK, pharmacodynamics, electrocardiogram (ECG) parameters, and disease response assessed in each study. Ixazomib is the first investigational proteasome inhibitor with substantial oral bioavailability in patients with multiple myeloma.

As of 24 September 2010, 112 patients have been treated with single-agent ixazomib in the 4 ongoing phase 1 studies (C16001, IV administration twice weekly in adult patients with advanced non-hematologic malignancies, n = 67; C16002, IV administration weekly in adult patients with advanced lymphoma, n = 11; C16003 and C16004, PO administration twice weekly and weekly, respectively, in adult patients with relapse or refractory multiple myeloma, n = 19 and 15, respectively). 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, and in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. The emerging safety profile as presented in the IB and updated here, demonstrates that ixazomib is generally well tolerated with manageable and reversible adverse reactions and treatment emergent adverse events (TEAEs), irrespective of ixazomib causality. In the non-hematologic malignancies study (C16001), the MTD for twice-weekly IV dosing in a 21-day treatment cycle is 1.76 mg/m^2 based on transient Grade 4 thrombocytopenia in 2 patients and reversible Grade 3 acute renal failure in 1 patient at 2.34 mg/m^2. The MTD is yet to be determined in the other studies.

Across the 4 ongoing clinical studies, 106/112 patients (95%) have experienced at least 1 TEAE, irrespective of causality and of grade of severity. This frequency is similar in both the IV and oral formulations. However, TEAEs Grade 3 or higher irrespective of cause, drug-related

adverse events both all grades and Grade 3 or higher are more frequent with the IV than oral formulation (56% vs 26%; 78% vs 68%; and 36% vs 18% respectively).

Using the IV formulation, the TEAEs (any grade irrespective of causal relationship) observed most frequently (> 10% of patients) include: fatigue (56%), rash (45%), nausea (37%), thrombocytopenia (35%), vomiting (32%), anorexia (28%), diarrhea (27%), pyrexia (23%), constipation (22%), headache (21%), anemia (19%), abdominal pain, chill, and dyspnea (14% each) and cough and back pain (13% each). Using the oral formulation, the TEAEs (any grade irrespective of causal relationship) observed most frequently (> 10%) include fatigue (47%), rash 37%), nausea (26%), diarrhea (24%), anemia (21%), cough, dyspnea, and vomiting (15% each) and headache (12%).

As of 24 September 2010, a total of 41/112 patients experienced serious adverse events (SAEs) while participating in ixazomib clinical studies. Sixteen of these 41 patients experienced SAEs considered by their investigator as related to ixazomib. The most common (in ≥ 2 patients) treatment-emergent drug-related SAEs include thrombocytopenia (2 patients, 1 each Grades 3 and 4), nausea (2 patients, Grade 3), dehydration (2 patients, Grade 3), transient renal toxicity (2 patients: Grade 4 elevated creatinine; Grade 3 acute renal failure), fatigue (2 patients, Grade 3), pneumonia or pneumonitis (1 patient each, Grade 3). Both patients with acute renal insufficiency experienced vomiting and/or profuse diarrhea with poor oral intake immediately prior to the reported renal events as well as acute intake of nonsteroidal anti-inflammatory drugs (NSAIDs; NSAIDs acute intake). These factors could be considered as potential precipitating factors of ischemic acute renal failure. Both patients recovered from the renal toxicity and ultimately discontinued from study treatment. The first occurrence of renal toxicity was a dose limiting toxicity (DLT) at the 2.34 mg/m^2 dose in Study C16001. The second renal event occurred in the MTD (1.76 mg/m2) expansion phase of Study C16001. As a precautionary measure until more data are available, all ixazomib studies have been amended to include an adjustment of the relevant eligibility criterion, supplementary measures to monitor kidney function, as well as advice under Precautions and Restrictions (Section 3.7) regarding correction of volume depletion and concomitant medications. There have been no reports of renal failure and/or elevated creatinine related to ixazomib in the 2 studies investigating the oral formulation in patients with MM or in the study investigating the IV formulation in patients with advanced lymphoma. Seven patients discontinued study drug for TEAEs (6 in Study C16001 [IV formulation] due to progressive disease [2] and 1 each ileus, peripheral neuropathy, acute renal failure, and pneumonitis) and one in C16004 [weekly, oral formulation] due to progressive disease. Five on-study deaths were reported, all attributable to disease progression, none of which were considered by the investigator to be related to treatment with ixazomib.

To mitigate the inherent risks in clinical studies of ixazomib, patients will be monitored closely for anticipated potential toxicities, as well as for unanticipated toxicities when they receive ixazomib and for at least 30 days after their last dose. Patients are evaluated by routine outpatient procedures and tests every 1 to 3 weeks as outlined in each protocol while they are receiving treatment. Additional evaluations can be conducted according to physician discretion. Guidance for reducing doses is provided in the protocols, and drug dosage can be reduced by either reducing the planned dose administered or by interruption of the scheduled treatment within a cycle. Each protocol, in addition to the IB, contains information regarding toxicity management.

Based on observations from nonclinical toxicology studies of ixazomib and preliminary clinical observations from the 4 ongoing phase 1 clinical studies, the potential safety risks of ixazomib are generally consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with bortezomib. The emerging safety profile demonstrates that ixazomib is generally well tolerated with manageable and reversible adverse reactions and treatment-emergent adverse events, irrespective of ixazomib causality. Thrombocytopenia and erythematous rash with or without pruritus have been listed as adverse drug reactions in the ixazomib IB. Based on evidence from preliminary ixazomib clinical studies, potential risks could include: transient and manageable anemia, diarrhea, nausea, vomiting, anorexia, constipation, abdominal pain, fatigue, elevated creatinine, and peripheral neuropathy. Additional safety risks may include fever, cough, dyspnea, peripheral edema, and headache. Based on clinical evidence from bortezomib studies, lymphopenia and lymphoid cell depletion (increased risk of infection, re-activation of herpes zoster and herpes simplex viruses); acute phase response (fever and metabolic change), and tumor lysis syndrome may be reported in the future though these have not been seen to date.

Like bortezomib, ixazomib is a small molecule peptide boronic acid analog. Clinical studies with bortezomib have yielded detailed understanding of its safety profile. For details, refer to the package insert for bortezomib. Ixazomib is in the early stages of clinical investigations in humans with safety, tolerability, PK, pharmacodynamics, electrocardiogram (ECG) parameters and disease response assessed in each study. Ixazomib is the first investigational proteasome inhibitor with substantial oral bioavailability in patients with multiple myelomas.

As of 12 January 2011, 143 patients have been treated with ixazomib across 5 phase 1 studies with a twice weekly and a weekly dosing schedule being evaluated. 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 and, in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle:

- C16001, single agent IV administration twice-weekly in adult patients with advanced non-hematologic malignancies, n = 78;

- C16002, single agent IV administration weekly in adult patients with advanced lymphoma, n = 15;
- C16003 and C16004, single agent PO administration twice-weekly and weekly, respectively, in adult patients with relapsed or refractory multiple myeloma [previous exposure to bortezomib, IMiD, and corticosteroid required], n = 26 and 22, respectively;
- C16005, PO administration in combination with lenalidomide and low-dose dexamethasone q28 days, n=2).

Currently, in addition to the trials noted above and this trial, there are 2 additional planned trials (C16006, Phase 1/ 2, oral administration of ixazomib added to melphalan and prednisone in patients with NDMM; C16007, Phase 1, single-agent ixazomib oral administration weekly in patients with relapsed or refractory light chain amyloidosis). None of these have begun to enroll patients.

In the 3 enrolling studies investigating oral ixazomib in multiple myeloma, a total of 50 patients have been treated thus far at single agent doses of 0.24 to 2.23 mg/m^2 twice-weekly (C16003) , 0.24 to 2.97 mg/m^2 weekly (C16004) and at the first dose level of 1.68mg/m^2 in combination with lenalidomide and low-dose dexamethasone (C16005). The most frequent (> 10%) TEAEs of any grade irrespective of causality to oral ixazomib [pooled oral data], include fatigue (40%), diarrhea (36%), nausea (30%), vomiting and anemia (20% each), upper respiratory infection (18%), thrombocytopenia (16%), cough (14%), and rash, headache and abdominal pain (12% each). Two of the 3 studies are still in the dose escalation phase (C16004 and C16005), while the MTD has been determined in study C16003.

As of 12 January 2011 in study 16003 (n=26), patients have received a median of 4 cycles of therapy (range 1-12); 7 patients are currently receiving therapy. One patient at the 1.2mg/m^2 dose level achieved PR; 17 patients achieved disease stabilization. The most common treatment emergent adverse events of any grade irrespective of causality (>20%) in this specific study are fatigue and diarrhea (42%), nausea (31%), thrombocytopenia, vomiting, anemia, cough, and upper respiratory infection (27% each), and rash (23%). Nine patients had treatment-related AEs ≥ Grade 3; only thrombocytopenia (n=4) and neutropenia (n=2) were seen in > 1 patient. Three patients have experienced drug related serious adverse events (SAEs) involving the following events thrombocytopenia, pancytopenia, nausea, vomiting, abdominal pain, chest pain [non-cardiac], or pneumonia. There has been one on-study death reported as not related to study drug.

In Study C16003, 1 of 3 patients experienced a protocol-defined DLT (Grade 3 rash) at a dose of 2.23mg/m^2. An additional patient at this dose experienced Grade 4 thrombocytopenia (platelet count of 10,000/mm^3). Per protocol, a DLT related to platelets required either a platelet count < 10,000/mm^3 or Grade 4 thrombocytopenia lasting more than 7 consecutive days; therefore a platelet count equal to 10,000/ mm^3 did not

formally meet the protocol definition for DLT. Thrombocytopenia and rash are identified as adverse drug reactions in the Investigator's Brochure, have predictable patterns, are reversible and can be monitored in the clinic with routine clinical observations and tests already outlined in the protocol. Therefore after a discussion with the PIs, an intermediate yet lower dose was evaluated as allowed in the C16003 protocol and supported by available pharmacokinetic data in order to further characterize dose-related toxicities. Six patients were treated at the intermediate dose of 2.0 mg/m^2, a dose approximately half way between the two existing dose levels of 2.23mg/m^2 and 1.68mg/m^2 (a dose without any DLTs). Given that no patient (0/6) experienced a DLT, the MTD of PO ixazomib administered twice-weekly is determined to be 2.0mg/m^2. This study is now accruing patients in 4 MTD expansion cohorts.

As of 12 January 2011, in Study C16004 where ixazomib is administered weekly (n=22), patients have received a median of 2 cycles (range, 1–8); 4 pts are currently receiving therapy. Dose escalation is continuing. The most common treatment emergent adverse events of any grade irrespective of causality (>20%) in this specific study are fatigue (41%), nausea (27%), and diarrhea (27%). There has not been any treatment related AEs ≥ Grade 3, any drug-related SAEs, or deaths on- study. In this heavily pretreated patient population, 4 patients have achieved stabilization of disease.

In Study C16005, ixazomib is administered in combination with lenalidomide and low-dose dexamethasone. This study has recently started to enroll patients (n=2 as of 12 January 2011) and dose escalation is ongoing. To date, there have not been any treatment related AEs ≥ Grade 3, any drug-related SAEs, or deaths on-study. Treatment emergent adverse events of any grade and irrespective of causality have been reported in 1 patient, and include nausea, vomiting, diarrhea, and anemia. Both patients in this study have achieved a PR after 1 cycle of therapy.

In the 2 ongoing studies investigating IV ixazomib in advanced solid tumors and advanced lymphoma (studies C16001 and C16002, respectively), a total of 93 patients have been treated thus far at single agent doses of 0.125 to 2.34 mg/m^2 twice-weekly (C16001) and 0.125 to 1.76 mg/m^2 weekly (C16002). The most frequent (> 10%) TEAEs of any grade irrespective of causality to IV ixazomib (pooled IV data), include fatigue (56%), thrombocytopenia (39%), nausea (33%), vomiting (32%), anorexia (31%), fever (29%), diarrhea (26%), constipation (22%), cough and headache (19% each), chills (18%), anemia (17%), abdominal pain (16%), shortness of breath (15%), and back pain and peripheral edema (14% each). As described below, the MTD has been established in Study C16001 but dose escalation in Study C16002 is ongoing.

As of 12 January 2011, in Study C16002 where ixazomib is administered weekly, (n=15), patients have received a median of 2 cycles (range, 1-10); 6 patients have experienced treatment-related AEs ≥ Grade 3; only

thrombocytopenia (n=2) and neutropenia (n=2) were seen in > 1 patient at any point during the course of therapy. One patient at the 1.76mg/m^2 dose level who experienced Grade 4 neutropenia that lasted more than 7 days (meeting the definition of a DLT). One patient at the 1.4mg/m^2 dose level achieved PR; and 5 patients have achieved disease stabilization. The next dose level, 2.34mg/m^2, is open for accrual.

In Study C16001, 78 evaluable patients with advanced non-hematologic malignancies have been treated across 7 dose levels. Patients have received a median of 2 cycles (range, 1-10); 6 patients are currently receiving therapy. Thirteen patients have had stabilization of the underlying disease including tumor reductions of 14% and 18% in 2 patients with renal cell carcinoma. The MTD has been determined in this study. At the 1.0 mg/m^2 dose level, 1 out of 6 patients experienced a DLT (transient Grade 3 rash); no drug-related SAEs were reported. No additional DLTs were reported as the dose was escalated up to 1.76 mg/m^2. At the 2.34 mg/m^2 dose level, 3 out of 3 patients were admitted to the hospital with DLTs (1 reversible Grade 3 acute renal failure and 2 reversible Grade 4 thrombocytopenia). All 3 patients recovered; 1 patient, who had experienced thrombocytopenia, continued on study at a reduced dose of ixazomib for an additional 3 cycles before disease progression. Given these AEs, the MTD of IV ixazomib administered twice-weekly is determined to be 1.76 mg/m^2.

As of 12 January 2011, 56 patients (6 in the dose escalation phase, 50 from the dose expansion phase) have been treated at the MTD of 1.76 mg/m^2. In these patients, fatigue, thrombocytopenia, nausea, vomiting, anorexia, fever, constipation, cough, diarrhea, chills, anemia, rash, headache, dehydration, shortness of breath, back pain, hyponatremia, abdominal pain, and peripheral edema are the most common treatment-emergent AEs. One patient treated at the MTD experienced renal toxicity, 1 patient experienced Grade 3 transient peripheral sensory neuropathy during Cycle 2, and 1 experienced Grade 3 peripheral neuropathy at the end of treatment after completion of 3 cycles. Fifteen SAE cases have been reported in the 1.76 mg/m^2 dose cohort where the investigators considered ixazomib and alternative etiologies as a possible cause (1 each, Grade 3 reversible: depressed level of consciousness, pneumonitis, pneumonia, ileus, pain in extremity, dyspnea, and acute renal failure; 3 each, Grade 3 reversible: fatigue and dehydration; 1 Grade 2 shingles and rash).

During enrollment in the expansion cohort of Study C16001 (dosing at 1.76 mg/m^2), 1 patient (among 50 patients treated as of 10 December 2010) has experienced acute renal failure (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE][i], version 3.0. Both cases of acute renal failure reported to date (the other patient was treated at the 2.34 mg/m^2 dose level) share the following features: (1) a pre-existing kidney condition (status post-nephrectomy due to kidney cancer and prior hydronephrosis due to disease progression); (2) prior exposure to other antineoplastic drugs associated with nephrotoxic potential; (3) diarrhea and/or poor oral intake; (4) use

of nonsteroidal anti-inflammatory drugs (NSAIDs) during the 24 to 48 hours before the onset of the AE; (5) the event occurred after a total of 4 doses of study drug had been administered (1 patient received all 4 doses within Cycle 1 while the second patient received them over the course of 2 treatment cycles); and (6) concomitant with event, the patient experienced thrombocytopenia.

The emerging safety profile indicates that ixazomib is generally well tolerated with manageable and reversible treatment-emergent adverse events (TEAEs) or adverse reactions. The MTD has been established in the 2 trials administering ixazomib twice-weekly (Study C16001; IV dosing and Study C16003; PO dosing) with dose escalation continuing in the 3 other studies. As of 12 January 2011, the most common treatment-related adverse drug reactions reported with ixazomib use, pooled from the 5 phase 1 early human studies (including both IV and oral formulations), include thrombocytopenia and maculopapular rash, with or without pruritus. Other treatment-emergent side effects reported across these studies, which may have been due to either the patient's disease or ixazomib, include nausea, vomiting, diarrhea, constipation, anorexia, fatigue, anemia, fever, abdominal pain, cough, headache, shortness of breath, upper respiratory infection, peripheral edema, chills, and back pain. The most frequent (> 10%) TEAEs of any grade reported across the 3 phase 1 studies using the oral formulation of ixazomib (ie, C16003, C16004, and C16005) , irrespective of causality to ixazomib, include fatigue (40%), nausea (30%), diarrhea (36%), vomiting and anemia (20% each), upper respiratory infection (18%), thrombocytopenia (16%), cough (14%), and headache, rash, and abdominal pain (12% each).

Please refer to the IB for further information. The most frequent AEs were anticipated based on preclinical data and previous experience with bortezomib and are noted in the informed consent documents. While the potential toxicities may be severe, they are managed by routine clinical monitoring and standard medical interventions. Based on bortezomib's proven utility in the treatment of multiple myeloma and MCL and ixazomib's increased tissue distribution and activity in several xenograft models, it is anticipated that ixazomib, directed against the same components of the ubiquitin-proteasome system (UPS), will prove efficacious in the treatment of similar, if not additional, malignancies.

1.19b Potential Risks of ixazomib: ixazomib is structurally similar to bortezomib which has a well-defined safety profile. Bortezomib (VELCADE®) is approved by the FDA and EMA for the treatment of patients with multiple myeloma. Based on observations from nonclinical toxicology studies of ixazomib and the preliminary clinical observations from the ongoing phase 1 studies, the potential safety risks of ixazomib are generally consistent with the class-based effects of proteasome inhibition, are similar to what has been previously reported with bortezomib, and are noted in the ixazomib IB.
Thrombocytopenia, fatigue, nausea, vomiting, diarrhea and rash (erythematous, generalized, macular, macular-papular, and popular) with

or without pruritus have been listed in the ixazomib IB as adverse drug reactions reported with ixazomib. 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.

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines. 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. This is the responsibility of the sponsor-investigator.

Additional details on the potential risks of ixazomib may be found in the current IB.

1.19c Daratumumab in multiple myeloma

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. This target is distinct from those of other approved agents for multiple myeloma therapy. Daratumumab is currently approved for treatment of relapsed myeloma, that are refractory to a proteasome inhibitor and an IMiD and in combination with VMP for newly diagnosed MM.

Nonclinical Studies with daratumumab
Based on preclinical data, daratumumab may utilize multiple effector cell functions, resulting in immune mediated killing of tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary multiple myeloma cells, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins. Daratumumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro. Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro. The precise role of some or all of these effector functions in reducing tumor burden in patients is unknown. In toxicology studies in cynomolgus monkeys and chimpanzees, the major observed toxicities were cytokine release syndrome and thrombocytopenia. A minor decrease in red blood parameters was also observed. Cytokine release was seen only following the first dose and was markedly reduced following implementation of a 10-mg predose of daratumumab. The effect on platelets and red blood cells was reversible.

For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the latest version of the Investigator's Brochure (Daratumumab IB).

Clinical studies with daratumumab

Single agent studies: Two large single agent studies have been reported to date; GEN501 and MMY2002. In the GEN501 study, daratumumab was administered at doses of 0.005 to 24 mg per kilogram of body weight during the dose escalation phase.[19] No maximum tolerated dose was identified. In the dose-expansion phase, 30 patients received 8 mg per kilogram of daratumumab and 42 received 16 mg per kilogram, administered once weekly (8 doses), twice monthly (8 doses), and monthly for up to 24 months. In the expansion phase, the median time since diagnosis was 5.7 years. Patients had received a median of four prior treatments; 79% of the patients had disease that was refractory to the last therapy received (64% had disease refractory to proteasome inhibitors and immunomodulatory drugs and 64% had disease refractory to bortezomib and lenalidomide), and 76% had received autologous stem-cell transplants. Infusion-related reactions were mild (71% of patients had an event of any grade, and 1% had an event of grade 3), with no dose-dependent adverse events. The most common adverse events of grade 3 or 4 (in ≥5% of patients) were pneumonia and thrombocytopenia. The overall response rate was 36% in the cohort that received 16 mg per kilogram (15 patients had a partial response or better, including 2 with a complete response and 2 with a very good partial response) and 10% in the cohort that received 8 mg per kilogram (3 had a partial response). In the cohort that received 16 mg per kilogram, the median progression-free survival was 5.6 months (95% confidence interval [CI], 4.2 to 8.1), and 65% (95% CI, 28 to 86) of the patients who had a response did not have progression at 12 months.

In the MMY2002 study, patients with multiple myeloma who were previously treated with at least three lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or were refractory to both proteasome inhibitors and immunomodulatory drugs, were randomized to receive intravenous daratumumab 8 mg/kg or 16 mg/kg in in the initial part of the study.[20] Patients received 8 mg/kg every 4 weeks, or 16 mg/kg per week for 8 weeks (cycles 1 and 2), then every 2 weeks for 16 weeks (cycles 3–6), and then every 4 weeks thereafter (cycle 7 and higher). In the second part of the study, the dose of 16 mg/kg was taken forward. One-hundred-six patients with a median of five previous lines of therapy (range 2–14) were treated at the 16-mg/kg dose. 85 (80%) patients had previously received autologous stem cell transplantation, 101 (95%) were refractory to the most recent proteasome inhibitors and immunomodulatory drugs used, and 103 (97%) were refractory to the last line of therapy. Overall, responses were seen in 31 patients (29·2%,)—three (2·8%) with a stringent CR, ten (9·4%) with a VGPR, and 18 (17·0) with a PR. Median duration of response was 7·4 months (95% CI 5·5–not estimable) and progression-free survival was 3·7 months and the 12-month overall survival was 64·8%. Daratumumab

was well tolerated; fatigue (40%) and anemia (33%) were the most common adverse events.

Daratumumab-lenalidomide combinations: Preclinically, using bone marrow mononuclear cells from patients with multiple myeloma, increased killing of tumor cells was demonstrated when daratumumab was combined with lenalidomide as compared with that of either agent alone.

In an open-label phase 1/2 study DARA 2-16 mg/kg was combined with standard dose of lenalidomide and dexamethasone, leading to a recommended phase 2 dose of daratumumab 16 mg/kg along with lenalidomide 25 mg days 1-21 and dexamethasone 40 mg weekly. Daratumumab 16 mg/kg was administered weekly during the first two 28-day cycles, every other week during Cycles 3 through 6, and monthly in Cycle 7 and beyond until disease progression or unacceptable toxicity. LEN 25 mg was administered orally on Days 1 through 21 of each cycle, and DEX 40 mg was given weekly. Thirty two patients with median of 2 prior lines of therapy were enrolled.

The most common (>25%) TEAEs included neutropenia (81%), muscle spasms (44%), cough (38%), diarrhea (34%), fatigue and hypertension (28% each). Eighteen (56%) patients had IRRs and these were generally mild to moderate and occurred mostly during the first cycle. IRRs included cough (25%), allergic rhinitis, nausea, and vomiting (9% each), as well as dyspnea, nasal congestion, and hypertension (6% each). The overall response rate was 88%, with 11 (34%) partial responses and 17 (53%) ≥very good partial responses (VGPRs) that included 7 (22%) stringent complete responses, 1 (3%) complete response, and 9 (28%) VGPRs. The median time to first and best response was 1 month and 4.5 months, respectively. Results of this study confirm the efficacy of combining daratumumab with lenalidomide and dexamethasone.

In a phase 3 trial, 498 patients with relapsed or relapsed and refractory multiple myeloma were randomly assigned to receive bortezomib and dexamethasone, alone or in combination with daratumumab. The progression-free survival was significantly higher in the daratumumab group than in the control group; the 12-month rate of progression-free survival was 60.7% in the daratumumab group versus 26.9% in the control group. After a median follow-up period of 7.4 months, the median progression-free survival was not reached in the daratumumab group and was 7.2 months in the control group (HR, 0.39; P<0.001). The overall response rate was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, P<0.001), as were the rates of very good partial response or better (59.2% vs. 29.1%, P<0.001) and complete response or better (19.2% vs. 9.0%, P=0.001). The most common grade 3 or 4 adverse events were thrombocytopenia, anemia, and neutropenia. Infusion-related reactions were associated with daratumumab in 45.3% of the patients; these reactions were mostly grade 1 or 2 (grade 3 in 8.6% of the patients), and in 98.2% of these patients, they occurred during the first infusion.

In another phase 3 trial, 569 patients with multiple myeloma who had received one or more previous lines of therapy were randomly assigned to receive lenalidomide and dexamethasone alone or in combination with daratumumab. At a median follow-up of 13.5 months OFS superior in the daratumumab arm. The Kaplan-Meier rate of progression-free survival at 12 months was 83.2% (95% CI, 78.3 to 87.2) in the daratumumab group, as compared with 60.1% (95% CI, 54.0 to 65.7) in the control group. Overall response rate was higher in the daratumumab group (92.9% vs. 76.4%, P<0.001), as was the rate of complete response or better (43.1% vs. 19.2%, P<0.001). In the daratumumab group, 22.4% of the patients were minimal residual disease negative (1 tumor cell per 105 white cells), compared with 4.6% in the control group (P<0.001). The most common adverse events of grade 3 or 4 during treatment were neutropenia, thrombocytopenia, and anemia. Daratumumab-associated infusion-related reactions occurred in 47.7% of the patients and were mostly grade 1 or 2.

1.19d ***Rationale for current study:*** Ixazomib represents the next generation proteasome inhibitor with several advantages including oral bioavailability as well as different proteasome binding characteristics. The trials so far have examined the activity of the drug in the setting of prior bortezomib treatment, since bortezomib is commonly used for relapsed patients. However, it is important to understand the single agent activity of the new drug in patients who have not received or received a limited amount of bortezomib and to further characterize the benefit of combining dexamethasone with ixazomib.

Rationale for addition of cohorts B and C: Ixazomib as a single agent has shown activity in this cohort of relapsed, relatively proteasome inhibitor naive population. A proportion of patients had dexamethasone added to ixazomib as originally planned, for lack of optimal response or disease progression. The goal of this trial initially was to assess the efficacy of single agent ixazomib in this patient population. The current practice for most of the myeloma drugs including the newer drugs such as lenalidomide or bortezomib is to administer them in combination with dexamethasone. Given these factors, it would be of significant interest to assess the efficacy of dexamethasone added to ixazomib right from the beginning as that might provide better disease control and long-term efficacy as compared to adding it for suboptimal response. We propose to add another cohort of patients in order to assess the efficacy and tolerability of ixazomib in combination with dexamethasone. In addition, ixazomib trials that are ongoing or in development in combination with other myeloma agents are using a lower dose of ixazomib at 4 mg weekly.(Kumar*, et al* 2012) In the current trial, we are using a dose of 5.5 mg based on the initial phase 1 single agent studies. Given that the future studies in combination with other active drugs like lenalidomide are going to use the 4 mg dose, it is of considerable interest to explore this dose also in the dexamethasone combination setting to better understand the contribution of the drugs being combined.

Rationale for addition of cohort D: One of the most effective combinations has been that of cyclophosphamide and bortezomib substantiating in vitro studies suggesting an excellent synergy between alkylating agents and proteasome inhibitors.[4,5] Previously, we have shown that the combination of cyclophosphamide and dexamethasone with bortezomib provides a very effective regimen with responses comparable to that seen with IMiD combinations. This was also confirmed in the studies looking at combining melphalan with bortezomib.[6] In fact, in the randomized EVOLUTION trial the combination of weekly cyclophosphamide with bortezomib and dex appeared to have higher response rate and depth of response compared to other three and four drug combinations that included bortezomib and lenalidomide.[5] Ongoing trials are examining the combination of ixazomib, cyclophosphamide and dexamethasone in other settings, but the true clinical activity of this combination in the setting of minimal prior exposure to bortezomib is unknown and is an important question for continued development of an all-oral combination regimen in myeloma.

Rationale for addition of cohort E: Daratumumab has been added to the current combinations such as Rd, Pd, VRd, KRd, and IRd in various clinical trials of newly diagnosed and relapsed myeloma, with excellent efficacy. The combination of ixazomib, cyclophosphamide and dexamethasone (ICd) has shown activity in newly diagnosed as well as relapsed MM. It is of scientific and clinical interest to examine the feasibility and efficacy of adding daratumumab to ICd.

2.0 Goals

2.1 Primary

2.11 Arm A (Permanently closed to accrual per Addendum 5): To determine the confirmed overall response rate (>=PR) of ixazomib, used as a single agent in patients with relapsed multiple myeloma, who are proteasome inhibitor naive (including bortezomib) naïve OR have received less than 6 cycles of therapy with bortezomib and had a better than PR with no progression at the time of discontinuation.

2.12 Arm B: To determine the confirmed overall response rate (>=PR) of ixazomib at a 4 mg dose level in combination with dexamethasone in patients with relapsed multiple myeloma, who are proteasome inhibitor naive (including bortezomib) naïve OR have received less than 6 cycles of therapy with bortezomib and had a better than PR with no progression at the time of discontinuation

2.13 Arm C: To determine the confirmed overall response rate (>=PR) of ixazomib at a 5.5 mg dose level in combination with dexamethasone in patients with relapsed multiple myeloma, who are proteasome inhibitor naive (including bortezomib) naïve OR have received less than 6 cycles of therapy with bortezomib and had a better than PR with no progression at the time of discontinuation

2.14 Arm D: To determine the confirmed overall response rate (>=PR) of ixazomib in combination with cyclophosphamide and dexamethasone in

patients with relapsed multiple myeloma, who are proteasome inhibitor naive (including bortezomib) naïve OR have received less than 6 cycles of therapy with bortezomib and had a better than PR with no progression at the time of discontinuation

2.15 Arm E (newly added with Addendum 23): To determine the confirmed overall response rate (>=PR) of ixazomib in combination with cyclophosphamide, daratumumab, and dexamethasone in patients with relapsed multiple myeloma

2.2 Secondary

2.21 Arm A: To determine the overall response rate of ixazomib in combination with dexamethasone, when dexamethasone is added to ixazomib for lack of response or for progression.

2.22 Arm A: To determine the event free survival and overall survival among patients with relapsed myeloma following treatment with ixazomib with dexamethasone added for lack of response or progression.

2.23 Arms B and C: To determine the event free survival and overall survival among patients with relapsed myeloma following treatment with ixazomib at two different doses, in combination with dexamethasone.

2.24 Arm D: To determine the event free survival and overall survival among patients with relapsed myeloma following treatment with ixazomib in combination with cyclophosphamide and dexamethasone.

2.25 Arm E (Addendum 23): To determine the event free survival and overall survival among patients with relapsed myeloma following treatment with ixazomib in combination with cyclophosphamide, daratumumab, and dexamethasone.

3.0 Patient Eligibility

3.1 Registration - Inclusion Criteria

3.11 Age ≥18 years.

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

- Calculated creatinine clearance (using Cockcroft-Gault equation below)* >=30 mL/min
- Absolute neutrophil count ≥1000/mL
- Untransfused Platelet count ≥75000/mL
- Hemoglobin ≥8.0 g/dL
- Total bilirubin <= 1.5 x the upper limit of the normal range (ULN).
- Aspartate aminotransferase (AST) <= 3x ULN
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <= 3x

*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)

3.13 Patients with relapsed multiple myeloma who have already received one or more standard treatment regimens.

3.14 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.
- For patients with EMD measurable disease by CT or MRI or the CT portion of the PET/CT: Must have at least one lesion that has a single diameter of ≥2 cm. Skin lesions can be used if the area is ≥2cm in at least one diameter and measured with a ruler.
- Plasma cell count ≥0.5 X 10^9/L or 5 percent of the peripheral blood white cells
- Plasma cell count if determined by flow cytometry, ≥200/150,000 events

3.15 ECOG performance status (PS) 0, 1, 2 (Appendix I).

3.16 Provide informed written consent.

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

3.18 Willing to return to consenting Mayo Clinic institution for follow-up during the active Monitoring Phase of the study.

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.*

3.19a Recovered (ie, < Grade 1 toxicity) from the reversible effects of prior antineoplastic therapy.

3.19b **Arms A – D only:**
Patients should be proteasome inhibitor naïve (including bortezomib and carfilzomib) OR have received less than 6 cycles of therapy with a bortezomib or carfilzomib containing regimen and were not refractory to the bortezomib or carfilzomib based regimen (less than a PR or progression on or within 60 days of discontinuation)

3.19c **Arm E only:**
Negative hepatitis B test (defined by a negative test for hepatitis B surface antigen [HBsAg], or antibodies to hepatitis B surface and/or core antigens [antiHBs or antiHBc)
Note: Patients with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. Those who are PCR positive will be excluded.

3.2 Registration - Exclusion Criteria

3.21 Recent prior chemotherapy
- Alkylators (e.g. melphalan, cyclophosphamide) ≤14 days prior to registration.
- Anthracyclines ≤ 14 days prior to registration
- High dose corticosteroids, immune modulatory drugs (thalidomide or lenalidomide) ≤7 days prior to registration.

3.22 Prior therapy with any proteasome inhibitor other than bortezomib, carfilzomib, or ixazomib,

3.23 Concomitant high dose corticosteroids other than what is part of treatment protocol (concurrent use of corticosteroids). EXCEPTION: Patients may be on chronic steroids (maximum dose 20 mg/day prednisone equivalent) if they are being given for disorders other than myeloma, i.e., adrenal insufficiency, rheumatoid arthritis, etc.

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

3.25 Any of the following:
- Pregnant women or women of reproductive ability who are unwilling to use 2 effective methods of contraception from the time of signing the informed consent form through 90days after the last dose of study drug
- Nursing women
- Men who are unwilling to use a condom (even if they have undergone a prior vasectomy) while having intercourse with any woman, while taking the drug and for 30 days after stopping treatment.

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

3.27 Other concurrent chemotherapy, radiotherapy, 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.

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

3.29a Major surgery within 14 days before study registration.

3.29b Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment.

3.29c Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, 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.

3.29d 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.

Arm E only:

3.29j Refractory to any combination of a proteasome inhibitor and Daratumumab.

3.29k Known chronic obstructive pulmonary disease with a forced expiratory volume in 1second (FEV1) <50% of predicted normal.
(**Note** that FEV1 testing is required for subjects suspected of having chronic obstructive pulmonary disease and subjects must be excluded if FEV1 <50% of predicted normal.)

3.29l Known moderate or severe persistent asthma within the past 2 years or currently has uncontrolled asthma of any classification (see Asthma Guidelines)

[redacted]

4.0 Test Schedule

	Days Prior to Registration		Days 8, 15, 22[6]	Every Cycle [1]	End of treatment[4]
	≤30 days	≤14 days			
Complete medical history	X			X[13]	X
Adverse Event monitoring		X		X[15]	X
Physical exam, including weight and vital signs		X		X[13,15]	X
Height	X				
Performance status (ECOG scale)		X		X[15]	X
CBC with diff. (includes hemoglobin, absolute neutrophil count and platelet count)		X	X[10]	X[15]	X
Electrocardiogram		X			
Forced expiratory volume in 1 second (FEV1) **Note:** Arm E patients only		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[15]	X
LDH, $Beta_2$-microglobulin, C-reactive protein, circulating plasma cells		X			
Viral hepatitis panel including HBsAg, HB core antibody, and HB antibody **Note:** Arm E only patients only	X[14]			X[14]	X[14]
Urinalysis		X			
Electrophoresis of serum and urine		X		X[2,15]	X[2]
Affected Immunoglobulin[8]		X		X[15]	X
Immunofixation serum and urine	X			X[5,15]	X
Immunoglobulin free light chain[9]		X		X[15]	X
X-ray skeletal survey or WBLDCT; PET/CT, MRI	X			X[16]	

Bone marrow aspirate and biopsy, myeloma FISH, metaphase cytogenetics, and flow cytometry	X			X[5,11]	
Chest x-ray	X				
Serum pregnancy test		X[3]			
Medication Diary[7]				X	

1) All scheduled visits will have a window of ± 7 days unless otherwise stated. After completing 4 cycles of therapy, patients can elect to come to the enrolling Mayo site every two cycles as long as all the required testing can be performed at local clinic and toxicity check can be performed over phone.
2) Urine electrophoresis required only if used to assess disease response..
3) For women of childbearing potential only. Must be done ≤7 days prior to registration.
4) End of treatment labs to be obtained at the time of study discontinuation or within 30 days. Tests used to confirm progression, if done can be used as end of treatment labs. Patients will go to event monitoring at progression while receiving dexamethasone with ixazomib.
5) Only required to document CR.
6) Only for first 2 cycles.
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.
9) Serum FLC to be followed in patients with light chain measurable disease.
10) These tests may be obtained locally and results send to enrolling institution,
11) Cytogenetics and FISH are not required.
12) Urine electrophoresis required only if used to assess disease response.
13) Medical history and physical examination can be performed every 2 cycles after the initial 4 cycles and there are no ongoing toxicities.
14) HBV-DNA testing required for patients with serologic evidence of prior HBV infection every 12 weeks during treatment, at EOT, and 12 weeks after last dose of study treatment.
15) Required evaluations can be done through local facility, phone contact, or by local lab as applicable if patient is unable to return to Mayo facility and is approved by study chair.
16) For patients with EMD only: Same modality should be used at baseline and for serial evaluation. Assessment of EMD lesions should be performed at end of Cycle 1 and every three cycles or more frequently if clinically indicated. For patients with only skin involvement, skin lesions should be measured with a ruler with images maintained in the medical record.

5.0 Stratification Factors:

Stratification Factors – Arms B and C (closed)

5.1 Bortezomib or Carfilzomib exposure none versus limited
5.2 Lenalidomide refractory versus no

Grouping Factors as of Addendum 23

5.3 Treatment: Arm D versus Arm E

6.0 Registration/Randomization Procedures

6.1 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.

6.11 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.

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

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

6.5 All required baseline symptoms (see Section 10.3) must be documented and graded.

6.6 **As of amendment 27**: Treatment on this protocol must commence under the supervision of a medical oncologist or hematologist from the enrolling institution

6.7 Study drug availability checked.

7.0 Protocol Treatment

As of Amendment 30, due to the commercial availability of Ixazomib, protocol treatment on this study will be discontinued. Patients may complete any current cycles in progress plus one additional cycle before being removed from protocol treatment.

7.1 **Arm A (Permanently closed to accrual per Addendum 5) Treatment Schedule** -

Agent	Dose Level	Route	Day
Ixazomib	5.5 mg	PO	1, 8, 15
Dexamethasone*	20 mg	PO	1, 2, 8, 9, 15, 16

* Dexamethasone is added only for lack of a minor response by end of Cycle 2 or lack of a partial response by end of Cycle 4 (these responses can be unconfirmed) or if there is disease progression at any time (confirmation of PD is not required). On-study measurements will be used throughout and no new baseline will be established.

Arm B (Permanently closed to accrual per Addendum 14) Treatment Schedule –

Agent	Dose Level	Route	Day
Ixazomib**	4 mg	PO	1, 8, 15
Dexamethasone*	40 mg	PO	1, 8, 15

* Dexamethasone is started Day 1 Cycle 1

Arm C (Permanently closed to accrual per Addendum 14) Treatment Schedule –

Agent	Dose Level	Route	Day
Ixazomib**	5.5 mg	PO	1, 8, 15
Dexamethasone*	40 mg	PO	1, 8, 15

* Dexamethasone is started Day 1 Cycle 1

Arm D Treatment Schedule –

Agent	Dose Level	Route	Day
Ixazomib	4 mg	PO	1, 8, 15
Cyclophosphamide (**Discontinue after 18 cycles**)	300 mg/m^2	PO	1, 8, 15, 22
Dexamethasone*	40 mg	PO	1, 8, 15, 22

* Dexamethasone is started Day 1 Cycle 1

The combination of ixazomib, cyclophosphamide and dexamethasone has been studied in newly diagnosed and relapsed patients in separate trials. Doses up to 500 mg/m^2 weekly of cyclophosphamide have been combined with ixazomib, 4mg on days 1, 8, 15 and dexamethasone 40 mg weekly.

Arm E Treatment Schedule –

Agent	Dose Level	Route	Day
Ixazomib	4 mg	PO	1, 8, 15
Cyclophosphamide **(Discontinue after 12 cycles)**	300 mg/m^2	PO	1, 8, 15, 22
Daratumumab	16 mg/kg	IV	Days 1, 8, 15, 22 for cycles 1-2; Days 1, 15 for cycles 3-6; and Day 1 for subsequent cycles
Dexamethasone*	40 mg	PO/IV**	1, 8, 15, 22

* Dexamethasone is started Day 1 Cycle 1
**Dexamethasone should be given IV (PO only if IV is unavailable), approximately 1 hour or less prior to daratumumab infusion. On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home. On days when daratumumab is not scheduled, PO may be taken at home (see Section 9.9b).

7.2 Ixazomib

- Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Ixazomib 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.
- Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose
- Procedures for ixazomib dose reductions and delays are summarized in Section 8.2, along with the criteria that must be met for retreatment with study drug. If a dose is missed due to toxicity, the dose will not be made up.
- Oral ixazomib is supplied by Takeda Pharmaceuticals. See Section 15.1 for details on ixazomib description, formulation, storage, and accountability.

7.3 Cyclophosphamide (Cycles 1-18 for Arm D and cycles 1-12 for Arm E)

- Subjects will receive cyclophosphamide orally once weekly on days 1, 8, 15 and 22 of the 28 day cycle.
- Cyclophosphamide is taken with water on a full or empty stomach. Subjects should not crush or chew capsules. Missed doses will not be made up.
- Procedures for dose reductions and delays are summarized in Section 8.3.
- Cyclophosphamide is commercially obtained

7.4 Daratumumab

- Subjects will receive daratumumab intravenously weekly for 8 weeks, then every other week for 16 weeks and then every 4 weeks.
- Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated.
- Vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other infusions, vital signs should be measured immediately before the start of infusion and at the end of the infusion.
- Missed doses will not be made up. Procedures for dose reductions and delays are summarized in Section 8.5.

- There are no planned dose reductions.
- Daratumumab is provided by Janssen. See Section 15.4 for details on daratumumab description, formulation, storage, and accountability.

  As of amendment 27:
  In the event patient is unable to come to the enrolling site for daratumumab infusion due to extenuating circumstances, commercial drug can be used for administration at a facility accessible to the patient. In that event, the treating investigator will work closely with the external provider to ensure safe and appropriate delivery of the planned dose. This instance will have to be reported to the IRB as a deviation.

- Daratumumab administration: See table below for general infusion guidelines.
  If patients tolerate the first 3 infusions, consideration can be given for a 90 minute infusion as per institutional guidelines.

Refer to section 9 for prophylaxis and treatment of infusion reactions

	Dilution volume (mL)	Initial rate (first hour)	Rate increment	Maximum rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

a Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.
b Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions.

7.5 Dexamethasone

- Dexamethasone may be self-administered by the subject on an outpatient basis.
- Dexamethasone may be permanently discontinued after 12 cycles at the treating physician's discretion or sooner if needed to manage toxicity related to dexamethasone. Dexamethasone as pre-treatment prior to daratumumab should continue.
- Missed doses of dexamethasone will not be made up. Procedures for dose reductions and delays are summarized in Section 8.2.
- Dexamethasone is commercially available. Accurate records will be kept in the source documents of all drug administration (including dispensing and dosing).

7.6 Treatment at enrolling institution

For this protocol, the patient must return to the consenting institution for daratumumab infusions as per treatment schedule and for evaluation prior to each cycle. Treatment by a

local medical doctor (LMD) is not allowed. **As of amendment 27**: **Exception noted above in 7.4.**

As of amendment 27
The patient must return to the enrolling 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.

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.

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 Arms A-D, if ixazomib is discontinued, the patient will proceed to event monitoring (see Section 18.0). For Arm E, if ixazomib and daratumumab are discontinued, the patient will proceed to event monitoring (see Section 18.0).

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

Instruction for initiation of a new cycle of therapy or restarting therapy after interruption during a cycle for toxicities

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 treatment 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, the subject will be evaluated weekly and a new cycle of therapy will be held until the toxicity has resolved as described above.

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, the patient will be removed from protocol therapy and will go to event monitoring.

8.1 Dose Levels for ixazomib and cyclophosphamide (Based on Adverse Events in Tables 8.11 and 8.1*2*)

Dose Level	**Ixazomib**				**Cyclophosphamide**
	Arms A and C	Arm B	Arm D	Arm E	Arms D and E
Starting Dose	5.5 mg Days 1, 8, 15	4.0 mg Days 1, 8, 15	4.0 mg Days 1, 8, 15	4.0 mg Days 1, 8, 15	300mg/m2/week Days 1,8,15,22
-1	4.0 mg Days 1, 8, 15	3.0 mg Days 1, 8, 15	3.0 mg Days 1, 8, 15	3.0 mg Days 1, 8, 15	300mg/m2/week Days 1,8,15
-2	3.0 mg Days 1, 8, 15	2.0 mg Days 1, 8, 15	2.0 mg Days 1, 8, 15	2.3 mg Days 1, 8, 15	200mg/m2/week Days 1,8,15
-3	2.0 mg Days 1, 8, 15	Discontinue	2.0 mg Days 1, 15	Discontinue	100mg/m2/week Days 1,8,15
-4	Discontinue		Discontinue		Discontinue

8.12 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 / Cyclophosphamide	Days 2-22: Ixazomib and cyclophosphamide doses 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 and cyclophosphamide may be reinitiated with 1 dose level reduction (see table 8.1). The subsequent cycle will use the reduced dose. Dose reduction should be applied to only one drug at a time, starting with cyclophosphamide and alternating with ixazomib. 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	Newly developed Grade 1 peripheral neuropathy with pain, ≥ Grade 2 peripheral neuropathy,	Ixazomib	Reduce dose of ixazomib to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring.
	Grade 2 neuropathy with pain or Grade 3 peripheral neuropathy	Ixazomib	Omit ixazomib until toxicity resolves 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	Discontinue study drug for grade 4 peripheral neuropathy.
Renal and urinary disorders	Cystitis non infective >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 and cyclophosphamide until resolution to Grade < 1 or baseline. If patient is also receiving Dex, hold both drugs. Restart at next lower dose. If a patient is already at the lowest drug level, go to event monitoring.
	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.

8.2 Dose Levels for Dexamethasone (Based on Adverse Events in Tables 8.21)

*In Arm A, Dexamethasone is added only for lack of a minor response by end of Cycle 2 or lack of a partial response by end of Cycle 4 (these responses can be unconfirmed) or if there is disease progression at any time (confirmation of PD is not required). In Arms B, D, and E, Dexamethasone is started on Day 1 Cycle 1.

8.21 Dose modifications based on adverse events during a cycle

Dose Level	Dexamethasone*		
	Arm A (Permanently closed to accrual)	**Arms B and C (Permanently closed to accrual)**	**Arms D and E**
0	20 mg Days 1, 2, 8, 9, 15, 16	40 mg Days 1, 8, 15	40 mg Days 1, 8, 15, 22
-1	20 mg Days 1, 8, 15	20 mg Days 1, 8, 15	20 mg Days 1, 8, 15, 22
-2	10 mg Days 1, 8, 15	12 mg Days 1, 8, 15	12 mg Days 1, 8, 15, 22
-3	5 mg Days 1, 8, 15	4 mg Days 1, 8, 15	4 mg Days 1, 8, 15, 22

→ → ***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.

→ → *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****
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 selfcare 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.
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.

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.

8.3 Daratumumab Dose Modification

Dose modification of daratumumab is not permitted, but dose delay is the primary method for managing daratumumab-related toxicities. The attribution of the toxicity to individual drug (s) will be performed by the treating physician.

8.31 Daratumumab-Related Toxicity Management

Refer to Section 9.9i for details on management of infusion-related reactions. ONLY if any of the following criteria are met and the event cannot be ascribed to the other drugs, the daratumumab infusion must be omitted to allow for recovery from toxicity. The criteria for a dose omit are:

- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia, if this is the second occurrence despite growth factor support
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

If a daratumumab administration does not commence within the prespecified window (Table) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

Table 8.6 Daratumumab-Related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Re-start
1 and 2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)`	>1 week	next planned biweekly dosing date
7+	Every 4 weeks (Q4W)	>2 weeks	next planned every 4 weeks dosing date

A missed dose will not be made up. Doses of daratumumab may be delayed up to 4 weeks. If a dose is delayed, then the dates of the subsequent doses must be adjusted. Any adverse event deemed to be related to daratumumab and unrelated to the other drugs that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab.

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

9.4 Antiemetics may be used at the discretion of the attending physician. Volume depletion should be corrected before initiation of study drug.

9.5 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

9.6 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.

Interference with Serological Testing: Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received Daratumumab. Type and screen patients prior to starting Daratumumab.

9.7 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.

9.8 Acute renal failure have been reported with ixazomib (see Section 1.4.3). Volume depletion should be corrected before initiation of study drug. Nonsteroidal anti-inflammatory drugs (NSAIDs) induced prevalence of nephrotoxicity is relatively low; however, given the wide use of these agents many persons are at risk, including for example, patients with cardio-renal disease, dehydration, and the aging kidney. NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function

9.9 Herpes Zoster prophylaxis with acyclovir 400 mg PO BID is recommended while on study therapy and for 1 month beyond the end of therapy

9.9a The following medications and procedures are prohibited during the study.
Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment

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.

9.9b 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. The rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body or more generalized. The rash has been transient and has resolved either spontaneously or with standard symptomatic measures such as oral or topical steroids and/or antihistamines. Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. A rare risk is Stevens Johnson Syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice.

Thrombocytopenia: Thrombocytopenia has been reported 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 8-2 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.

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

filgrastim 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 **dosing** should be modified when neutropenia occurs, as noted in the dose modification recommendations in Table 8-2. Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts.

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.

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.

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.

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.

Guidelines for Prevention of Infusion Reactions

Pre-infusion Medication: On daratumumab infusion days, subjects will receive the following medications prior to infusion:

- Acetaminophen (paracetamol) 650-1000 mg IV or orally (PO) approximately 1 hour or less prior to daratumumab infusion
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) approximately 1 hour (or less) prior to infusion
- Dexamethasone 40 mg IV or PO (only if IV is not available), approximately 1 hour or less prior to daratumumab infusion. On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home.

Post-infusion Medication: For subjects with higher risk of respiratory complications (ie, subjects who have a FEV1 <80%), the following postinfusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Dexamethasone 4 mg day after infusion
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salbumatol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic.

Management of Infusion-related Reactions (or any reaction during infusion)

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation must be available at the bedside.

If any infusion-related reactions develop, then the infusion should be temporarily interrupted. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.
- If an infusion is paused or the infusion rate is decreased, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

Infusion-Related Events of Grade 1 or Grade 2: If the investigator assesses an adverse event to be related to the daratumumab infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used

before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the subject experiences a Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from the onset, then the subject must be withdrawn from treatment.

Infusion-Related Reactions of Grade 3 or Higher: For infusion-related adverse events that are Grade 4, the infusion should be stopped and treatment with daratumumab will be discontinued for that subject.

For infusion-related adverse events that are Grade 3, the daratumumab infusion must be stopped, and the subject must be observed carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

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 site:

[redacted]

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 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). 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 10.52 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).

- **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 15.17 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.17 of the protocol.

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 SAME Arm**

NOTE: The combination of an investigational agent with a commercial agent is considered investigational.

Routine Reporting

- 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 10.52.

  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.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for CTEP 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 by the Cooperative Group to the FDA via MedWatch.

- 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.

10.32 Special Situations for Expedited Reporting

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

An expedited report or notification form may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events where the AE is listed in Section 15.0 of the protocol or the consent form* as **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will **supercede** the standard Expedited Adverse Event Reporting Requirements (Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/adverse events form 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 3
	Platelet count decreased	Grade 3
	White blood count	Grade 3
	Lymphocyte count	Grade 3
Blood and lymphatic system disorders	Anemia	Grade 3
Metabolism and Nutrition disorders	Hyperglycemia	Grade 3

[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.

*The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure.

10.321 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).

10.322 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.

10.323 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.

10.324 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.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.32 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. Contact Takeda/Millennium Pharmacovigilance and Janssen (see 10.6)

   Sponsor-investigator must report **all SAEs**, regardless of expectedness or relationship with any study drug, to Millennium Pharmacovigilance (or designee) as soon as possible, but **no later than 5 calendar days** of the sponsor-investigator's observation or awareness of the event. In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Subinvestigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and subinvestigator(s). Millennium Pharmacovigilance (or designee) may request follow-up information to a reported SAE, which the sponsor-investigator will be responsible for providing to Millennium Pharmacovigilance (or designee)

   The SAE report must include event term(s), serious criteria, and the investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration.

   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. 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 Section. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

   Suggested Pregnancy Reporting Form:
   - Pregnancy Report Form (a sample is provided in Appendix V)

   Suggested Reporting Form:
   - SAE Report Form (provided by Takeda)
   - US FDA MedWatch 3500A:
   - Any other form deemed appropriate by the sponsor-investigator

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax 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.

10.5 Other Required Reporting

10.51 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:

			Each

SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	evaluation
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
General disorders and administration site conditions	Edema limbs	X	X
	Fatigue	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of Stools	X	
	Diarrhea		X
	Constipation		X
Infections and infestations	Sepsis	X	X
Blood and lymphatic system disorders	Febrile neutropenia	X	X
	Anemia	X	X
Skin and subcutaneous tissue disorders	Rash, maculopapular	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X
	Cognitive disturbance	X	X

10.52 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:

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

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

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 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.

10.53 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).

10.6 Other Reporting Instructions for Industry Partners

10.61 Special reporting requirements for Takeda

Serious Adverse Event Definition

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

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but

may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

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 [redacted]
- **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 [redacted]

  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

[redacted]

Suggested Reporting Form:

- SAE Report Form (provided by Takeda)
- US FDA MedWatch 3500A: [redacted]
- Any other form deemed appropriate by the sponsor-investigator

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

- [redacted]

- [redacted]
- 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

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events
If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Takeda 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 Takeda 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:

Pregnancy Report Form (provided by Takeda)

10.62 Special reporting requirements for Janssen

Overview
As the sponsor of the Study, PRINCIPAL INVESTIGATOR shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The PRINCIPAL INVESTIGATOR will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

1. Management of Safety Data
This Study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: DARZALEX™ (daratumumab)

2. Definitions

2.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])
This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

2.2. Adverse Events of Special Interest (Arm E only)

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions ≥ grade 3
- Infections ≥ grade 4
- Cytopenias ≥ grade 4
- HBV Reactivation Other malignancies

Any Adverse Event of Special Interest that is to be reported should be recorded on a Serious Adverse Event Report Form (MedWatch Form) and be reported within 24 hours of knowledge of the event.

2.3. Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

2.4. Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

2.5. Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

2.5.1. Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)

- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]
- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

2.5.2. Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

3. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

[redacted]

For DARZALEX™ (daratumumab),the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure

4. <u>Special Reporting Situations</u>

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

5. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

6. Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs, LLC

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

6.1. SAEs, Adverse Events of Special Interest, and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The PRINCIPAL INVESTIGATOR will transmit all SAEs, adverse events of special interest, and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 10,Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, **within 24 hours becoming aware**, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE or special situation is required.

- The PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 10 from this Exhibit within **24 hours of such report or correspondence being sent to applicable health authorities.**

6.2. Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

6.3. PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

7. Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the PRINCIPAL INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

8. Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

11.0 Treatment Evaluation

11.1 Terms and definitions

Definitions for EMD response is similar to those used for patients with lymphoma (Cheson et al. Revised Response Criteria for Malignant Lymphoma). EMD measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).

Response is based on CT alone or the CT component of PET/CT or MRI where applicable and the PET.

PET/CT scans are required at baseline for all patients with EMD.

- **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-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.
  - Cases in which there are multiple peaks of same monoclonal 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-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.

- **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), progressive disease (PD) and relapse from CR (RFCR).

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

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) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results.***

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

- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-spike or urine M-spike, but has had a detectable monoclonal 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 monoclonal 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**	**24 hr UPEP[2]**	**Ig FLC**

Serum M-spike ≥1 g/dl, and urine M-spike≥ 200 mg/24 hrs	X	X	
Serum M-spike ≥ 1 g/dl, but urine M-spike < 200 mg/24 hrs	X		
Serum M-spike<1 g/dl, and urine M-spike≥ 200 mg/24 hrs		X	
Serum M-spike < 1 g/dl, urine M-spike < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X

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

[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] *Bone marrow biopsy results do not need to be confirmed (i.e. repeated after documented response).*

11.3 Confirmed response

In order to be classified as a 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.

- Bone marrow aspirate and biopsy are **only** required to document or confirm 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.
- 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 or relapse 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 CRITERIA [a]**
Stringent complete response (sCR)[e]	• CR as defined below plus all of the following • Normal serum FLC ratio • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [b] • Not applicable for those patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike at baseline
Complete response (CR)	• Negative immunofixation of the serum and urine • < 5% plasma cells in bone marrow • Disappearance of any soft tissue plasmacytomas • If at on study, the only measurable parameter was FLC, normalization of FLC ratio • For patients with extramedullary plasmacytoma present at baseline: a) FDG-avid or PET positive prior to therapy: Mass of any size permitted if PET negative and b) Variably FDG-avid or PET negative: Regression to normal size on CT. For patients with only skin involvement, these same criteria apply to skin lesions measured with a ruler. • For patients with plasma cell leukemia at baseline, complete absence of circulating plasma cells
Very good partial response (VGPR)[d,e]	• PR as defined below plus all of the following: • Serum and urine M-component detectable by immunofixation but not on electrophoresis or • If at on study, serum measurable, ≥ 90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h • If at on study, the only measurable parameter was FLC, ≥ 90% or greater reduction in the difference between involved and uninvolved free light chain levels • Not applicable for those patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike at baseline
Partial Response (PR)	• One of the following: ▪ If at on study, serum and urine measurable, a ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to <200 mg per 24 h ▪ If at on study, only serum measurable (but urine not), a ≥ 50% reduction of serum M-protein ▪ If at on study, urine measurable (but serum not), a reduction in 24-h urinary M-protein by ≥ 90% or to <200 mg per 24 h ▪ If at on study, the only measurable parameter was FLC, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels • In addition to the above criteria, if a plasmacytoma present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required • For patients with extramedullary plasmacytoma present at baseline: ≥50% decrease in SPD of up to 6 largest dominant masses and a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved sites OR b) Variably FDG-avid or PET negative: regression on CT or by measurements with a ruler in patients with only skin involvement

Minor Response (MR)	• ≥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 • In addition to the above criteria, if a plasmacytoma present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR or progressive disease
Progressive disease (PD)	Any one or more of the following: • Increase of 25% from lowest value in[d]: ▪ 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 parameter was FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl) [c] ▪ Bone marrow plasma cell percentage (absolute % must be ≥10%)[c] ▪ Appearance of a new lesion(s), ≥50% increase from nadir in SPD of more than one lesion, or ≥50% increase in longest diameter of a previous lesion >1 cm in short axis. Lesions PET positive if PET positive prior to therapy ≥50% increase in circulating plasma cells (minimum of 200/mcl) Or any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder ▪ Development of new soft tissue plasmacytomas or bone lesions ▪ Hypercalcemia (≥11.5 mg/dl) ▪ Decrease in hemoglobin of ≥2 g/dl ▪ Serum creatinine level ≥2 mg/dll

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy; complete and 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] 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 CR will not be considered progression.
[d] 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[e]Does not apply to EMD or PCL

12.0 Descriptive Factors

12.1 Prior bortezomib treatment: Yes vs. no.

12.2 Prior stem cell transplant: Yes vs. no.

12.3 Parameters of hematologic response (pick all that apply): serum M-spike ≥ 1 g/Dl (distinguish between SPEP measurement versus quantitative IgA measurement), serum immunoglobulin free light chain ≥10 mg/dL, urine M-spike ≥200 mg/24 hours.

12.4 Prior carfilzomib treatment: Yes vs. no

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 Arm A only (Permanently Closed to Accrual: Patients who do not achieve an MR (or uMR) by end of cycle 2 or a PR (or uPR) by end of cycle 4 (these responses can be unconfirmed) and those who develop progressive disease (confirmation of PD is not required) while receiving ixazomib alone will continue treatment with the addition of dexamethasone.

13.3 Arm A: Patients who develop progressive disease (confirmed or unconfirmed per physician discretion) **despite addition of dexamethasone** while receiving therapy will go to the event-monitoring phase per Section 18.0.

Arms B, C, D, E: Patients who develop progressive disease (confirmed or unconfirmed per physician discretion) at any time will go to event-monitoring phase per Section 18.0.

Note: Patients who develop progressive disease can be re-registered and move to a different arm.

13.4 Patients who go off protocol treatment for reasons other than PD will go to event-monitoring phase per Section 18.0.

13.5 Criteria for Patient Discontinuation of Protocol Treatment

Patients may discontinue protocol treatment and go to the event-monitoring phase per Section 18.0 for the following reasons:

- Progressive multiple myeloma despite addition of dexamethasone
- Patient withdraws consent to continue in 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
- 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 Treatment procedures per Section 4.0 if a patient discontinues protocol treatment 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:

- Determination of unexpected, significant, or unacceptable risk to patients
- 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
- Insufficient complete and/or evaluable data
- Manufacturing difficulties/concerns
- Plans to modify, suspend, or discontinue the development of the drug

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 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 must be submitted. No further data submission is necessary.

13.8 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.

13.9 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

No correlative studies planned

15.0 Drug Information

15.1 Ixazomib (**MLN9708, Ninlaro®)**

15.11 **Background**: Ixazomib is a second-generation small molecule inhibitor of the 20S proteasome that is under development for the treatment of multiple myeloma, other plasma cell dyscrasias, nonhematologic malignancies, and pediatric acute lymphoblastic leukemia and lymphoma.

Ixazomib (MLN2238) refers to the biologically active, boronic acid form of the drug substance, ixazomib citrate. 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 different capsule strengths are manufactured: 0.2, 0.5, 2.0, 2.3, 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 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 mg), individually packaged in blisters:
Do not store above 25°C. Do not freeze. Ixazomib capsules (2.3 mg, 3 mg, 4 mg, and 5.5 mg), individually packaged in blisters: 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 at least 1 hour before or at least 2 hours after food.

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

Health care providers should instruct patients and caregivers that only one dose of ixazomib should be taken at a time, and only at the prescribed interval (e.g. one capsule, once a week, on Days 1,8, and 15 of a 28-day cycle). The importance of carefully following all dosage instructions should be discussed with patients starting treatment.

15.15 **Pharmacokinetic (PK) 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. The absolute oral bioavailability of ixazomib is ~58%. 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. Protein binding is 99% to plasma proteins and the extent of binding is not altered by severe renal impairment, moderate-severe hepatic impairment.

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. Ixazomib is not dialyzable and therefore can be administered without regard to the timing of 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 C_{max} and $AUC_{0\text{-}last}$ were reduced in the presence of rifampin by approximately 54% and 74%, respectively. As a result, the coadministration of strong CYP3A inducers with ixazomib is not recommended. 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 like 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%): peripheral edema, peripheral neuropathy, peripheral sensory neuropathy, skin rash, diarrhea, constipation, nausea, vomiting, thrombocytopenia, neutropenia, back pain, eye disease, upper respiratory infection
Common (≥1% to <10%): Herpes zoster, hepatic insufficiency, blurred vision, conjunctivitis, xerophthalmia, pneumonia
Uncommon (≥0.1% to <1%): cholestatic hepatitis, hepatocellular hepatitis, hepatotoxicity, liver steatosis, peripheral motor neuropathy, reversible posterior leukoencephalopathy syndrome, Stevens-Johnson syndrome, Sweet's syndrome, thrombotic thrombocytopenic purpura, transverse myelitis, tumor lysis syndrome, thrombotic microangiopathy

Herpes zoster – antiviral prophylaxis should be considered in patients being treated with ixazomib to decrease the risk of herpes zoster reactivation.
Overdose – There is no known specific antidote for ixazomib overdose. . Symptoms of overdose are generally consistent with the known risks of ixazomib and reports have been associated with serious adverse events such as nausea, aspiration pneumonia, multiple organ failure, and death. 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. Gastric lavage may be considered, but it should be kept in mind that ixazomib absorption is rapid. Ixazomib is not readily dialyzable.

15.18 **Drug procurement:** 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. Make sure that patients are instructed to take exactly as directed to avoid overdose.

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. 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.

15.199c Monitor LFT's. Rarely hepatotoxicity has been seen.

15.2 **Daratumumab (Darzalex®, Darzalex Faspro™, JNJ-54767414)**
Please consult the most current Investigator's Brochure and package insert for complete drug information.

15.21 Background: Daratumumab is an immunoglobulin G1 kappa (IgG1κ)

human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.
CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other cell types and tissues and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). Myeloid derived suppressor cells (MDSCs) and a subset of regulatory T cells (CD38+Tregs) expresses CD38 and is susceptible to daratumumab mediated cell lysis.

15.22 **Formulation**:

- . Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number

15.23 **Preparation and storage**:

-

  Daratumumab IV and SC study drug vials must be stored in the original carton in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab IV or SC does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

  Daratumumab IV will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration.

  Daratumumab and hyaluronidase-fihj SC injection is directly drawn from the vial into a syringe and is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles. After the solution is withdrawn into the syringe, replace the transfer needle with a syringe cap. To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

15.24 **Administration:**

- Administer pre-infusion and post-infusion medications. Refer to section 7 of the protocol.
- IV administration: Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES)

filter (pore size 0.22 or 0.2 micrometer). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.

- Infusion should be completed within 15 hours.
- Refer to section 7 of the protocol for infusion rates
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.
- Do not infuse **daratumumab** concomitantly in the same intravenous line with other agents.

15.25 **Pharmacokinetic information for IV administration**:
The pharmacokinetics (PK) of daratumumab following intravenous administration were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg, and included the recommended 16 mg/kg dose and regimen. Over the dose range from 1 to 24 mg/kg, increases in area under the concentration-time curve (AUC) were more than dose-proportional The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (332) µg/mL.

The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (332) µg/mL. At the recommended dose of 16 mg/kg, the mean ± SD central volume of distribution was 4.7 ± 1.3 L when daratumumab was administered as monotherapy and 4.4 ± 1.5 L when daratumumab was administered as combination therapy.

Daratumumab showed target-mediated disposition with rapid clearance (CL) at low doses and slower CL at higher doses and with multiple doses. Following the first administration at the recommended dose of 16 mg/kg, non-compartment model derived CL was 0.42 ± 0.42 mL/hr/kg and the half-life (t1/2) was 9.0 ± 4.3 days.

The model-derived half-life associated with linear elimination was approximately 18±9 days. Apparent steady state seems to be reached approximately 5 months into the every 4 week
dosing period of the 16 mg/kg with a schedule of weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter.

Following the administration of the recommended dose of 1,800 mg daratumumab and 30,000 units hyaluronidase subcutaneously once weekly for 8 weeks, the mean ± standard deviation (SD) maximum trough concentrations (Ctrough following the 8th dose) were 593±306 µg/mL compared to 522±226 µg/mL for daratumumab 16 mg/kg administered intravenously, with a geometric mean ratio of 108% (90% CI: 96, 122). The estimated median daratumumab area under the concentration-time curves (AUC0-7 days) and daratumumab peak concentration (Cmax) following the 8th dose were comparable between subcutaneous and intravenous daratumumab (4017 µg/mL•day vs. 4,019 µg/mL•day for AUC0-7 days and 592 µg/mL vs. 688 µg/mL for Cmax).
The absolute bioavailability of daratumumab-hyaluronidase is 69%, with peak concentrations occurring around 3 days (Tmax). The estimated mean (coefficient of variation, CV) volume of distribution for the central compartment is 5.2 L

(37%) and peripheral compartment was 3.8 L with the daratumumab-hyaluronidase formulation. Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. The estimated mean (CV%) linear clearance of daratumumab is 119 mL/day. The estimated mean (CV%) elimination half-life associated with linear clearance is 20 days (22%).

Special Populations

Geriatric use: Based on population PK analyses in patients receiving monotherapy or combination therapies, age (range: 31-93 years) had no clinically important effect on the PK or effectiveness of daratumumab. The most common serious adverse events that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis.

Renal Impairment: The population PK analysis included 592 patients receiving IV daratumumab 16 mg/kg with normal renal function (creatinine clearance [CrCL] ≥90 mL/min), 757 patients with mild renal impairment (CrCL <90 and ≥60 mL/min), 604 patients with moderate renal impairment (CrCL <60 and ≥30 mL/min), and 6 patients with severe renal impairment or end stage renal disease (CrCL <30 mL/min). No clinical differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function in both daratumumab IV and SC. .

Hepatic Impairment: The population PK analysis included 1,742 patients with normal hepatic function (TB and AST ≤ULN) , 224 with mild hepatic impairment (TB 1.0× to 1.5× ULN or AST>ULN) patients, and 10 patients with moderate (TB>1.5 to 3xULN; n=9) or severe hepatic impairment (TB >3xULN; n=1). No clinical differences in the exposure to daratumumab were observed between patients with hepatic impairment and those with normal hepatic function. The effect of moderate (TB>1.5× to 3× ULN and any AST) or severe (TB>3× ULN and any AST) hepatic impairment on daratumumab IV or SC pharmacokinetics is unknown. Population PK analysis demonstrated no clinically important differences in the exposure to daratumumab were observed between patients with normal hepatic function and mild hepatic impairment in studies of both daratumumab IV and SC. There were few patients with moderate-severe hepatic impairment to make meaningful conclusions for these populations.

15.26 **Potential Drug Interactions**: Clinical PK assessments with daratumumab IV and SC formulations and lenalidomide, bortezomib, thalidomide, pomalidomide, melphalan ,prednisone, cyclophosphamide, dexamethasone, and carfilzomib indicated no clinically relevant drug-drug interactions.

Effects on laboratory tests:
Interference with Indirect Antiglobulin Tests: Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching and may persist for up to 6 months after the last daratumumab administration. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or genotyping. Since the Kell blood group system is also sensitive to DTT

treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, non-cross matched ABO/RhD compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests: Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

15.27 **Known potential toxicities**:

Very common known potential toxicities, ≥ 10%:

Blood and lymphatic system disorders: neutropenia, thrombocytopenia, anemia, lymphopenia
Gastrointestinal disorders: nausea, vomiting, diarrhea, constipation
Infections and infestations: upper respiratory tract infection, bronchitis pneumonia, nasopharyngitis
Injury, poisoning, and procedural complications: infusion related reaction
Metabolism and nutrition disorders: hypokalemia, hyperglycemia, decreased appetite
Musculoskeletal and connective tissue disorders: muscle spasms, back pain, arthralgia, pain in extremity, bone pain, musculoskeletal chest pain
Nervous system disorders: dizziness, headache, tremor, headache
Psychiatric disorders: Insomnia, anxiety
Respiratory, thoracic, and mediastinal disorders: cough, dyspnea, nasal congestion, upper respiratory tract infection, pneumonia
Vascular disorders: hypertension
General disorders and administration site conditions: fatigue, pyrexia, chills, peripheral edema, asthenia, non-cardiac chest pain, pain,

Common known potential toxicities, 1% - <10%:

General disorders and administration site conditions: injection site reaction, peripheral edema
Infections and infestations: respiratory tract infection, influenza, lower respiratory tract infection, sepsis, sinusitis, rhinitis, pharyngitis, viral respiratory tract infection, nasopharyngitis, respiratory syncytial virus infections, laryngitis, tonsillitis, lung infection, herpes zoster
Blood and lymphatic disorders: febrile neutropenia
Cardiac disorders: atrial fibrillation
Respiratory, thoracic, and mediastinal disorders: pulmonary edema, hypoxia, laryngeal edema, pneumonitis, bronchospasm

Uncommon and rare known potential toxicities, <1%:
Infections and infestations: pharyngitis, metapneumovirus infection, tracheitis, acute sinusitis, bronchiolitis, epiglottitis, oropharyngeal candidiasis, rhinovirus infection, tracheobronchitis, upper respiratory tract bacterial infection, bronchitis bacterial, viral or bacterial laryngitis, pharyngitis, viral rhinitis, respiratory syncytial virus, infectious pneumonia
Blood and Lymphatic Disorders: neutropenic sepsis, neutropenic infection
Daratumumab IV and SC studies demonstrated that the incidence of anti-daratumumab antibodies was low [<1%] following daratumumab administration in multiple myeloma (IV/SC) and amyloidosis (SC) participants. Treatment emergent anti-rHuPH20 antibodies developed in 7.1% (60/840) of participants who received daratumumab SC in monotherapy and combination clinical studies.

Hepatitis B virus (HBV) reactivation, in some cases fatal, have been reported in patients treated with daratumumab. HBV screening should be performed in all patients before initiation of treatment with daratumumab and as clinically indicated. Treatment interruption may be warranted in the event of HBV reactivation while on daratumumab.

Please refer to the Investigator Brochure for a more comprehensive list of treatment-emergent adverse events.

15.28 **Drug procurement:** Daratumumab (Darzalex®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Note: patients will be charged for the administration of the Daratumumab.

15.29 **Nursing Guidelines:**

15.291 Daratumumab can cause severe infusion reactions, usually during the first infusion. Patients who have experience a reaction may experience further reactions with subsequent infusions. Most reactions occur during or within 4 hours of infusion, however may occur up to 48 hours after an infusion. Warn patient of this possibility. Monitor patient throughout infusion for bronchospasm, hypoxia, SOB, and hypertension. Patients may also experience symptoms of anaphylaxis. Administer emergency medication as ordered.

15.292 Patients may experience infections, including URI and pneumonia. Patients who have an ongoing infection should not receive agent.

15.293 Patients may experience gastrointestinal side effects including diarrhea and nausea. Treat symptomatically and monitor for effectiveness.

15.294 Warn patients about the possibility of peripheral neuropathy, dizziness, and insomnia.

15.295 Fatigue is common. Instruct patient in energy conserving lifestyle.

15.296 Rarely patients may experience cardiac issues including, atrial-fibrillation, peripheral edema, and hypertension. Instruct patient to report any chest pain, heart palpitations, and swelling to the study team.

15.297 Monitor CBC w/diff as cytopenias (thrombocytopenia, neutropenia, anemia, and lymphopenia) have been seen. Instruct patient to report any unusual, bruising, bleeding and/or infections/fever to the study team.

15.298 If using SQ, injection should be in the abdomen over 3-5 minutes. There is no data on SQ injections on other parts of the body.

15.3 Dexamethasone for Oral Administration (DXM)

15.31 **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.

15.32 **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)

15.33 **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.

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

15.35 **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

15.36 **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)

15.37 **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.

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

15.39 Nursing Guidelines:

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

15.392 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.

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

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

15.395 Monitor blood glucose frequently.

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

15.397 Advise patient that easy bruising is a side effect.

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

15.41 **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.

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

15.43 **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.

15.44 **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.

15.45 **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)

15.46 **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.

15.47 **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.

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

15.49 **Nursing Guidelines:**

15.491 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.

15.492 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.

15.493 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.

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

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

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

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

15.498 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.

15.499a Advise female patients of possible menstrual changes or amenorrhea.

15.499b Patients on anticoagulant therapy should have INR levels carefully monitored as cytoxan increases their effect.

15.499c Monitor electrolytes and for signs/symptoms of SIADH and tumor lysis syndrome.

15.499d Monitor digoxin levels closely as cytoxan may decrease these levels.

15.499e 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 II study designed to assess the proportion of confirmed responses as well as the toxicity associated with ixazomib with or without dexamethasone ,ixazomib with dexamethasone and cyclophosphamide, and ixazomib with dexamethasone, cyclophosphamide, and daratumumab in patients with relapsed multiple myeloma.

16.11 Primary Endpoint:

The primary endpoint of this trial is the proportion of confirmed responses (sCR, CR, VGPR, PR) with single agent ixazomib (Arm A) or ixazomib in combination with dexamethasone (Arms B and C) or ixazomib in combination with dexamethasone and cyclophosphamide (Arm D) or ixazomib in combination with dexamethasone, cyclophosphamide, and daratumumab (Arm E). Throughout Section 16.0, confirmed response will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for confirmed response, with the exception of patients who are determined to be a major treatment violation.

16.12 Sample Size:

The single stage study design to be used is fully described below. Twenty-nine evaluable patients are required to assess the primary endpoint. We anticipate accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the maximum total sample size will be 33 patients.

As of Addendum 5 Arms B and C will be added to this study. The single stage study design to be used for each arm is fully described below. Thirty-two evaluable patients are required to assess the primary endpoint. We anticipate accruing an additional 3 patients in each arm to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the maximum total sample size in each arm will be 35 patients. The overall maximum total sample size including all arms will be increased to 103 patients.

As of Addendum 14, one additional patient will be randomized to Arm B or Arm C. This is to account for a miscommunication that resulted in an extra patient being consented for the study.

As of Addendum 15 Arm D will be added to this study. The single stage study design to be used is fully described below. Thirty-six evaluable patients are required to assess the primary endpoint. We anticipate accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the maximum total sample size in Arm D will be 40 patients. The overall maximum total sample size including all arms will be increased to 144 patients.

As of Addendum 23 Arm E will be added to this study. The single stage study design to be used is fully described below. Thirty-five evaluable patients are required to assess the primary endpoint. We anticipate accruing an additional 4

patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the maximum total sample size in Arm E will be 39 patients. The overall maximum total sample size including all arms will be increased to 183 patients.

16.13 Accrual Rate and Study Duration:
Based on prior Mayo Clinic accrual in this patient population we expect an accrual of about 3-4 patients per month. Therefore, accrual to this study should take about 9-12 months. The analysis can begin as soon as the last patient has been observed for at least 6 months, or about 1.5 years after the trial opens.

As of Addendum 5, accrual to Arm A has been completed and accrual will begin to Arms B and C. Based on accrual to Arm A, we expect Arms B and C to have a similar accrual of about 3-4 patients per month. Therefore, accrual to Arms B and C should take about 18-24 months. The analysis can begin as soon as the last patient has been observed for at least 6 months, or about 2.5 years after Addendum 4 is implemented.

As of Addendum 15, accrual to Arms B and C has been completed and accrual will begin to Arm D. Based on accrual in the previous arms, accrual to Arm D is expected to take approximately 14 months. The analysis can begin as soon as the last patient has been observed for at least 6 months, or about 1.75 years after Addendum 15 is implemented.

As of Addendum 23, accrual to Arm E will begin. Based on accrual in the previous arms, accrual to Arm E is expected to take approximately 24 months. The analysis can begin as soon as the last patient has been observed for at least 6 months, or about 2.5 years after Addendum 23 is implemented.

16.2 Statistical Design for Arm A (Permanently Closed to Accrual):

16.21 Decision Rule:

In a study including 193 evaluable relapsed multiple myeloma patients treated with single agent bortezomib, a proteasome inhibitor given by intravenous bolus, 27% of patients achieved a confirmed response (Richardson*, et al* 2003a). Ixazomib is a next generation proteasome inhibitor with different proteasome binding characteristics that is given orally. Since oral administration is preferred, a confirmed response rate at least equivalent to bortezomib in relapsed multiple myeloma patients treated with single agent ixazomib is of interest.

Therefore, the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. The following one-stage binomial design requires 29 patients to test the null hypothesis that the true success proportion in this patient population is at most 10%.

16.211 Final Decision Rule: If 5 or fewer successes are observed in the first 29 evaluable patients, we will consider this regimen ineffective in this

patient population and terminate this study. Otherwise, if the number of successes is at least 6, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.212 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 16.54.

16.22 Power and Significance Level: Assuming that the number of responses is binomially distributed, with a significance level of 6%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.10	0.15	0.20	0.25	0.30
Then the probability of declaring that the regimen is promising and warrants further study is…	0.06	0.26	0.54	0.77	0.91

16.23 Other Considerations: Toxicity, 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.

16.3 Statistical Design for Arms B and C (Permanently closed to accrual):

16.31 Patients will be randomized to a treatment regimen using a dynamic allocation procedure, which balances the marginal distribution of the stratification factors (see Section 5.2) between the treatment regimens.(Pocock and Simon 1975) The results of these studies will be analyzed independently and no direct comparisons will be made between the data from each of these treatment regimens.

16.32 Decision Rule (to be assessed independently in each arm):

The addition of dexamethasone to ixazomib from the beginning of treatment may result in improved response rates. Therefore, the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 20%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 40%. The following one-stage binomial design requires 32 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 20%.

16.321 Final Decision Rule: If 9 or fewer successes are observed in the first 32 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 10, this will be considered evidence of promising

activity and the treatment may be recommended for further testing in subsequent studies.

16.322 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 16.54.

16.33 Power and Significance Level: Assuming that the number of responses is binomially distributed, with a significance level of 9%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.20	0.25	0.30	0.35	0.40
Then the probability of declaring that the regimen is promising and warrants further study is…	0.09	0.26	0.50	0.73	0.88

16.34 Other Considerations: Toxicity, 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 Statistical Design for Arm D:

16.41 Decision Rule:

The addition of cyclophosphamide to ixazomib and dexamethasone may result in improved response rates. Therefore, the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 25%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 45%. The following one-stage binomial design requires 36 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 25%.

16.411 Final Decision Rule: If 12 or fewer successes are observed in the first 36 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 13, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.412 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 16.64.

16.42 Power and Significance Level: Assuming that the number of responses is binomially distributed, with a significance level of 9%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.25	0.30	0.35	0.40	0.45
Then the probability of declaring that the regimen is promising and warrants further study is…	0.09	0.26	0.51	0.74	0.89

16.43 Other Considerations: Toxicity, 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.

16.5 Statistical Design for Arm E:

16.51 Decision Rule:

The addition of cyclophosphamide and daratumumab to ixazomib and dexamethasone may result in improved response rates. Therefore, the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 50%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 70%. The following one-stage binomial design requires 35 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 50%.

16.511 Final Decision Rule: If 21 or fewer successes are observed in the first 35 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 22, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.512 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 16.64.

16.52 Power and Significance Level: Assuming that the number of responses is binomially distributed, with a significance level of 9%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.50	0.55	0.60	0.65	0.70
Then the probability of declaring that the regimen is promising and warrants further study is…	0.09	0.22	0.44	0.68	0.87

16.53 Other Considerations: Toxicity, 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.

16.6 Analysis Plan:

16.61 Primary Endpoint:

16. 611 Definition: The primary endpoint of this study is the proportion of confirmed responses with single agent ixazomib (prior to initiation of dexamethasone) (Arm A), with the combination of ixazomib plus dexamethasone from the start of therapy (Arms B and C), and with the combination of ixazomib plus dexamethasone and cyclophosphamide from the start of therapy (Arm D). A confirmed response is defined as sCR, CR, VGPR, or PR noted as the objective status on 2 consecutive evaluations while receiving single agent ixazomib (Arm A) or ixazomib plus dexamethasone (Arms B and C) or ixazomib plus dexamethasone and cyclophosphamide (Arm D) or ixazomib in combination with dexamethasone, cyclophosphamide, and daratumumab (Arm E). All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients who are determined to be a major treatment violation.

16. 612 Estimation: The proportion of successes will be estimated in each arm independently by the number of successes divided by the total number of evaluable patients. 95% confidence intervals for the true success proportion will be calculated by the exact binomial method.

16. 62 Definitions and Analyses of Secondary Endpoint (To be evaluated independently in each arm, except where noted):

16. 621 Arm A Only - Confirmed response rate with the addition of dexamethasone: The confirmed response rate for ixazomib with the addition of dexamethasone for lack of response or progression will be estimated by the number of patients who achieve a confirmed response at any time (with single agent ixazomib or ixazomib plus dexamethasone) divided by the number of evaluable patients. 95% confidence intervals for the true confirmed response rate will be calculated by the exact binomial method. In addition, the number of patients who did not achieve a confirmed response with ixazomib alone then had a confirmed response after the addition of dexamethasone to ixazomib will be evaluated.

16. 622 Overall survival: 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 (Kaplan and Meier, 1958). All evaluable patients will be included in this analysis.

16. 623 Event-free survival: The event-free survival time is defined as the time from registration to disease progression while receiving ixazomib and dexamethasone, death due to any cause, or subsequent treatment for multiple myeloma. Date of progression will be defined as the date that the criteria for progressive disease (per section 11.5) were first met after initiation of dexamethasone. If a patient goes off study and never received dexamethasone, they will be censored on the date they went off study. If a patient initiates dexamethasone but later discontinues dexamethasone due to toxicity and continues ixazomib alone, disease progression on ixazomib alone will be considered an event in this case. The distribution of event-free survival will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1958). All evaluable patients will be included in this analysis.

16. 63 Adverse Events: The maximum grade for each type of adverse event, regardless of causality, will be recorded and reported for each patient, and frequency tables will be reviewed to determine adverse event patterns. Adverse events will continue to be recorded and reported up to 30 days after the last day of study drug treatment.

16. 64 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 point estimates and confidence intervals

16. 65 Data & Safety Monitoring

16. 651 The principle investigator(s) and the study statistician will review the study at least every quarter 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. 652 Adverse Event Stopping Rule (to be evaluated in each arm independently): The stopping rule specified below is based on the knowledge available at study development. We note that the 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 treatments 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 either of the following:

- if 4 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, 25% 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.

16.7 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 or gender, 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 Mayo, has a population, which includes approximately 3% minorities. Based on prior Mayo 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:

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	1	2	0	3
Not Hispanic or Latino	60	120	0	180
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	61	122	0	**183**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	1	0	1
Black or African American	2	2	0	4
Native Hawaiian or other Pacific Islander	0	0	0	0
White	59	119	0	178
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects	61	122	0	**183**

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, 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) -

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study Form	≤2 weeks after registration
Baseline Adverse Event Form	
Pretreatment Measurement Form	
SPEP, UPEP, FLC , Serum and Urine Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey, 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

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	X[1]	X
Adverse Event Form	X	X
Measurement Form	X	X
SPEP, UPEP, FLC , Serum and Urine Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey	X[2]	X[2]
Interval Laboratory Form	X[3]	
End of Active Treatment/Cancel Notification Form		X
ADR/AER	At each occurrence (see Section 10.0)	

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. 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: QAS for MC1181.
3. Only when required by the Test Schedule (see Section 4.0).

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 6 months until PD or subsequent treatment for myeloma [2]	At PD or subsequent treatment for myeloma [2]	q. 12 months after PD or subsequent treatment for myeloma	Death	New Primary
Event Monitoring Form	X	X	X	X	At each occurrence

1. If a patient is still alive 2 years after registration, no further follow-up is required.
2. For documentation of progression, submit one report for one of the measures where progression was seen. Attention: QAS for MC1181.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: None

19.3 Ixazomib will be provided free of charge to study participants by Takeda/Millennium Pharmaceuticals, Inc. Janssen Pharmaceuticals will provide the Daratumumab free of charge to the study participants (infusion and related costs will be charged to the patient/patients insurance).

19.4 Other budget concerns: Protocol administration, study coordinator time, data management and statistical analysis efforts will be by funded by Millennium Pharmaceuticals, Inc.

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Appendix I

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.

Appendix II

Mayo Risk Stratification

High Risk

FISH deletion 17p

FISH t(4:14)

FISH t(14:16)

Metaphase cytogenetic del 13

Hypodiploidy

PCLI >3%

Appendix III

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

Appendix IV

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 _____ Study No. MC1181

Mayo Clinic No. _____

Appendix V

PATIENT MEDICATION DIARY Arm D

Please complete this diary on a daily basis. Write in the amount of the dose of 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.
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 no sooner than 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.
The Cyclophosphamide will be discontinued after 18 cycles.
If you experience any health/medical complaints or take any medication other than the study medications, 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							

My next scheduled visit is:

If you have any questions, please call:

Patient signature: _____ Date:_____

Appendix VI

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS) Page 1 of 4

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

REPORTER INFORMATION: (Please forward if an alternative physician is more appropriate)		
Reporter name: _____	Title: _____	
Address: _____	Telephone No.: _____	Fax No. _____
City, State/Province: _____	Postal Code: _____	Country: _____

FATHER'S INFORMATION ❒ Father Unknown	
Initials: _____ Date of Birth: ___/___/_____ DD MM Yr or Age: _____years	
Participating in an MPI clinical study? ❒ No ❒ Yes *If no*, what company product was taken: _____ *If yes, please provide:* Study drug: _____ Protocol No: _____ Center No: _____ Patient No: _____	
Medical / Familial / Social History (i.e. Include chronic illnesses: specify, familial birth defects/genetic/chromosomal disorders; habitual exposure: specify, alcohol/tobacco; drug exposure: specify, substance abuse and medication use. Please include drug treatment prior to or around the time of conception and/or during pregnancy) _____ _____	Race: _____ Occupation: _____ Number of children: _____

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

MOTHER'S INFORMATION:

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

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

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: _____

Name _____ Study No. MC1181

Mayo Clinic No. _____

Appendix VII

PATIENT MEDICATION DIARY (Arms A-C, closed)

Please complete this diary on a daily basis. Write in the amount of the dose of ixazomib 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.

Your study medication should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 150 mL of water (5 fluid ounces or 2/3 cup) should be taken with the capsules.

If you experience any health/medical complaints or take any medication other than ixazomib 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							
Dexamethasone							

Week of: _____

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

Week of: _____

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

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
ixazomib							
Dexamethasone							

Patient signature: _____ Date:_____

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

Name _____ Study No. MC1181

Mayo Clinic No. _____

Appendix VIII

PATIENT MEDICATION DIARY (Arm E)

Please complete this diary on a daily basis. Write in the amount of the dose of ixazomib 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.

Your study medication should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 150 mL of water (5 fluid ounces or 2/3 cup) should be taken with the capsules.

The Cyclophosphamide will be discontinued after 12 cycles.

If you experience any health/medical complaints or take any medication other than ixazomib 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: _____