Mayo Clinic Cancer Center

Phase 2 trial of Ixazomib, lenalidomide, dexamethasone and daratumumab in patients with newly diagnosed multiple myeloma

Study Chair: [redacted]

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

Takeda Study: X16079
Janssen Scientific Affairs (Janssen) Study: 54767414MMY2010
IND #132345

Drug Availability
Commercial Agents: Dexamethasone, Lenalidomide
Drug Company Supplied: Ixazomib (***Takeda***), Daratumumab (***Janssen***)

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Protocol Resources

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

*No waivers of eligibility per NCI

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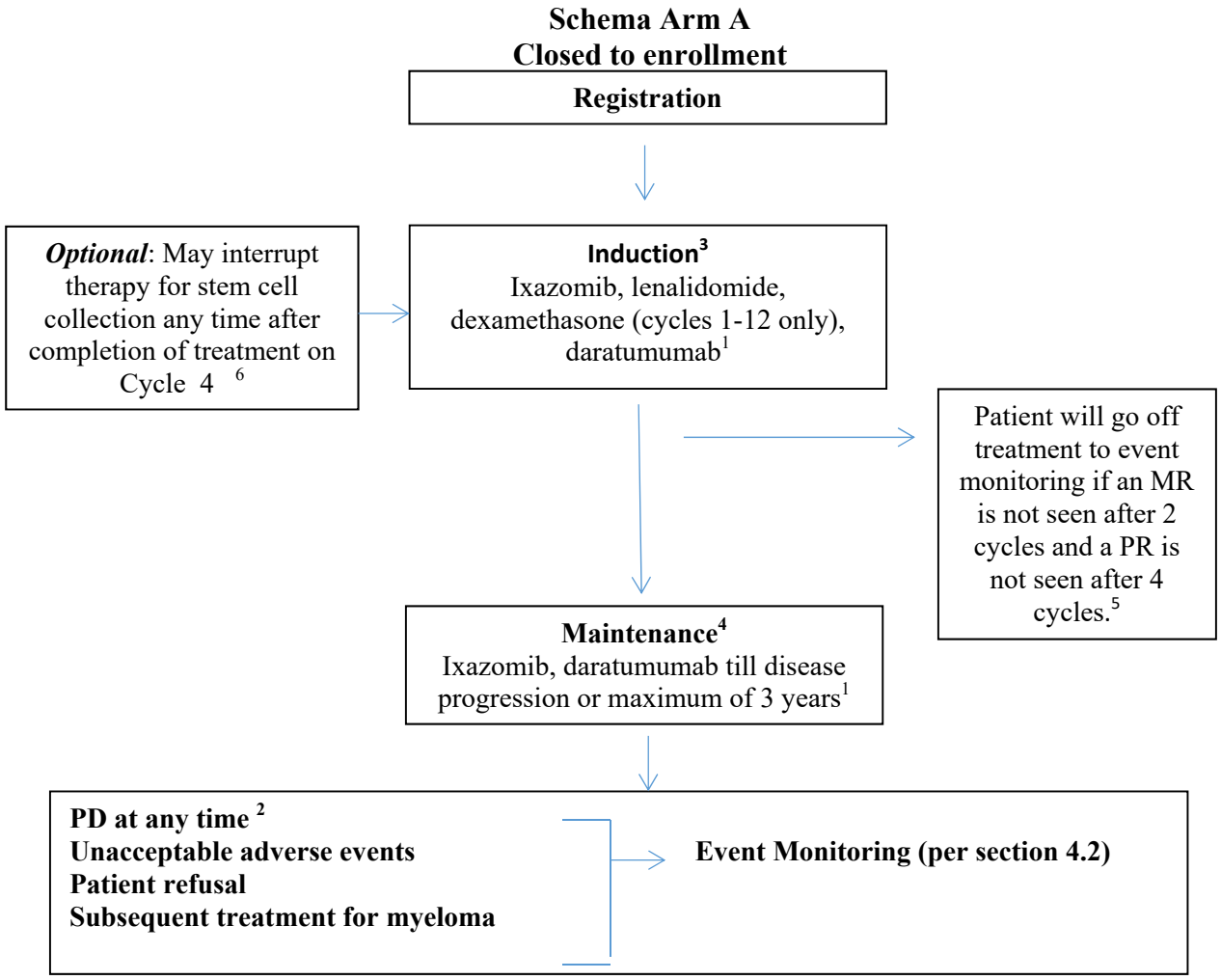


If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

[1] Cycle length = 28 days

[2] Confirmation of PD is not required. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the Patient Status Form.

[3] Induction cycles 1-12 cycles

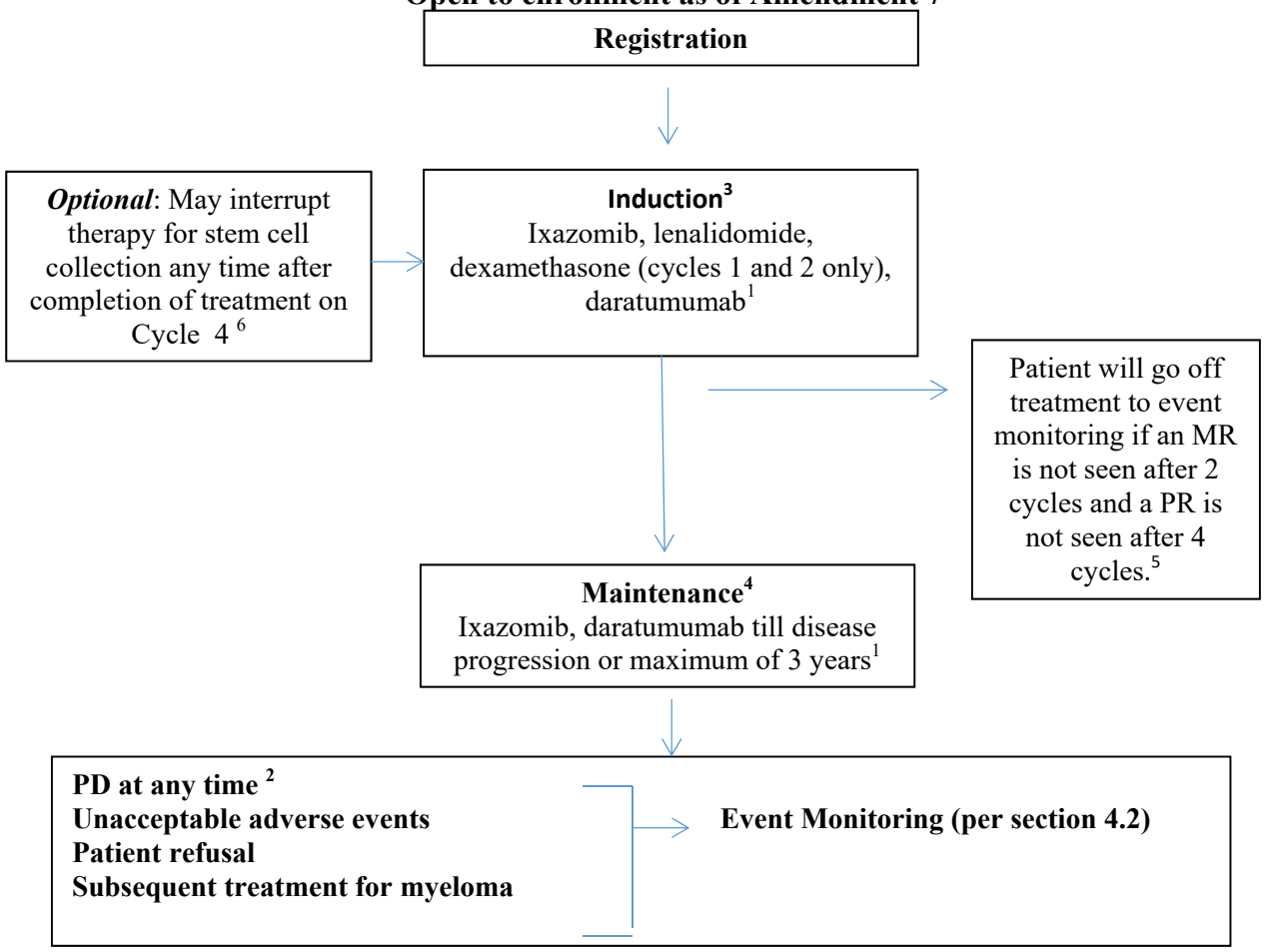
[4] Maintenance cycle 13 onwards

[5] Confirmation of MR or PR is not required.

[6] Patients may receive stem cell transplant (SCT) at physician discretion at any time after completion of treatment on Cycle 4. If patient goes to SCT, they will go to Survival and Disease Status Follow-Up/ Event Monitoring per Section 4.2. Details should be recorded on the Stem Cell Harvest and Transplant and Engraftment Forms

Generic name: Ixazomib Brand name(s):Ninlaro Mayo Abbreviation: MLN9708 Availability: Provided by Takeda Pharmaceuticals,	Generic name: Dexamethasone Brand name(s): Decadron Mayo Abbreviation: DXM Availability: Commercial
Generic name: Lenalidomide Brand name(s): Revlimid Mayo Abbreviation: REVLIMID Availability: Commercial Revlimid REMS program	Generic name: Daratumumab Brand name(s): Darzalex Mayo Abbreviation: DARATUMUMAB Availability: Provided by Janssen

Schema Arm B
Open to enrollment as of Amendment 7



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1.0 Background

1.1 ***Multiple Myeloma:*** Multiple myeloma is a malignancy of the differentiated plasma cells, that affect the older patient with a median age at onset of 65-70 years and a slight male predominance. It is characterized by clonal expansion of plasma cells leading to increased production of monoclonal protein in the majority of patients accompanied by end organ damage in the form of lytic bone disease, hypercalcemia, anemia and renal insufficiency. Nearly 24,000 patients with myeloma are diagnosed in the United States each year, and despite considerable improvements in therapy, myeloma remains incurable and uniformly fatal with a median overall survival of around 8 years. Recent improvements in therapies have significantly improved the survival outcomes, but given the inevitable relapses seen in these patients, new approaches to therapy are clearly needed. As the efficacy of therapies have increased and newer classes of drugs have been approved for treatment of myeloma, there is increasing interest on improving the depth of response with the initial therapy of myeloma.

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

Of particular interest is the VRd regimen, which has shown high efficacy rates and is increasingly used for initial therapy in the community.[5,9] VRd regimen has been associated with high response rates approaching 100% and deep responses with very good partial response rates and complete response rates of over 70 and 40% respectively. It has proven to be a highly effective initial therapy for patients planning stem cell transplantation with no significant effect on the ability to successfully mobilize stem cells.

In the initial phase 1/2 trial of the VRD regimen, 66 patients with newly diagnosed myeloma received 3-week cycles of bortezomib (days 1, 4, 8, 11), lenalidomide (days 1-14), and dexamethasone (days 1, 2, 4, 5, 8, 9, 11, 12). Phase 2 dosing was determined to be bortezomib 1.3 mg/m^2, lenalidomide 25 mg, and dexamethasone 20 mg. Most common

toxicities included sensory neuropathy, fatigue, lymphopenia, neutropenia and thrombocytopenia. All patients had a partial response 74% achieving very good partial response or better. In the EVOLUTION trial, patients were randomized to receive bortezomib 1.3 mg/m^2 d 1, 4, 8, 11 and dexamethasone 40 mg d 1, 8, 15, with either cyclophosphamide 500 mg/m^2 d 1, 8 and lenalidomide 15 mg d 1–14 (VDCR), lenalidomide 25 mg d1-14 (VRd), cyclophosphamide 500 mg/m^2 d 1, 8 (VCD) or cyclophosphamide 500 mg/m^2 d 1, 8, 15 (VCD-mod) in a 21 day cycle (maximum 8 cycles).[9,10] This was followed by bortezomib 1.3 mg/m^2 (d 1, 8, 15, 22) for four 42-day maintenance cycles in all arms. VGPR or better was seen in 58, 51, 41 and 53% (CR rate of 25, 24, 22 and 47%) of patients (VDCR, VRd, VCD and VCD-mod arms, respectively); the corresponding progression-free survival (PFS) at 1 year was 86, 83, 93 and 100%, respectively. In a recently presented phase 3 trial, the combination of VRd was associated with increased response rates, deeper responses, increased PFS and improved overall survival compared with lenalidomide and dexamethasone. In the SWOG0777 trial, 525 patients with newly diagnosed myeloma were randomized to lenalidomide with or without bortezomib. Median PFS was 43 months (VRd) versus 30 months (Rd); log-rank P value = 0.0018. Median OS was 75 months (VRd) versus 64 months (Rd); HR = 0.71; two-sided log-rank P value = 0.0250.

1.3 ***Ixazomib***: MLN9708, which has been formulated for both intravenous (IV) and oral (PO) administration, is a small molecule proteasome inhibitor. It is the citrate ester of the biologically active boronic acid form, MLN2238. In water or aqueous systems, Ixazomib citrate 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 MLN9708. 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.

<u>*Nonclinical Pharmacology*</u>: MLN2238 refers to the biologically active, boronic acid form of the drug substance, ixazomib citrate (MLN9708). Ixazomib citrate refers to the citrate ester of MLN2238. In water or aqueous systems, the equilibrium shifts from ixazomib citrate to the biologically active boronic acid form MLN2238. All doses and concentrations are expressed as the boronic acid, MLN2238.

<u>*In Vitro Pharmacology*</u>: MLN2238 preferentially binds the β5 site of the 20S proteasome; at higher concentrations, it also inhibits the activity of the β1 and β2 sites. MLN2238 inhibits ß5 site 20S proteasome activity in vitro, with a half-maximal inhibitory concentration (IC50) of 3.4 nM. Potency is reduced roughly 10-fold versus ß1 (IC50 31 nM) and 1,000-fold versus ß2 (IC50 =3500 nM). MLN2238 was also tested for inhibition against a panel of 103 kinases, 18 receptors (neurotransmitter, ion channel, brain and gut receptors), and 9 serine proteases. In all cases, the IC50 values were > 10 μM. MLN2238 and bortezomib have different β5 proteasome dissociation half-lives (t1/2), reflecting differences in their on-off binding kinetics (the β5 proteasome dissociation t1/2 for MLN2238 and bortezomib are 18

and 110 minutes, respectively). Based on these favorable characteristics, ixazomib is anticipated to be effective against multiple myeloma. (ixazomib Investigator's Brochure (IB). Proteasome inhibition results in the accumulation of poly-ubiquitinated substrates within the cell and leads to cell cycle disruption, with concomitant activation of apoptotic pathways and cell death. Consistent with inhibition of ß5 20S activity, MLN2238 demonstrated potent activity against cultured MDA-MB 231 human breast cancer cells in the WST cell viability assay. In nonclinical models MLN2238 has activity against both solid tumor and bortezomib-resistant xenografts.

In Vivo Pharmacology: To determine the activity of MLN2238 in vivo, pharmacodynamic studies were performed in immunocompromised mice bearing either CWR22 human prostate or WSU-DLCL2 (human diffuse large B-cell lymphoma [DLBCL]) tumors. Pharmacodynamic responses in xenograft tumors were analyzed by assessing 20S proteasome inhibition and by evaluating levels of accumulated protein markers such as deoxyribonucleic acid (DNA) damage-inducible protein 34 (GADD34) and activating transcription factor-3 (ATF-3) as well as measuring growth arrest. Increased expression of GADD34 and ATF-3 is indicative of a downstream biological response to proteasome inhibition. After a single dose of MLN2238, a clear dose response was observed in CWR22 xenografts as seen in both tumor 20S proteasome inhibition and in changes in GADD34 and ATF-3 expression. In WSU-DLCL2 xenografts, greater tumor proteasome inhibition was observed with MLN2238 compared to bortezomib and resulted in increased expression of GADD34 and ATF-3. MLN2238 efficacy experiments demonstrated strong antitumor activity in 4 xenograft models: CWR22 (a human prostate cancer cell line) and 3 human lymphoma cell lines (WSU-DLCL2, OCI-Ly7-7D1-luc, and PHTX-22L). In the case of the CWR22 xenograft model, significant antitumor activity was seen with both IV and PO dosing, demonstrating that this molecule has antitumor activity when administered via different dosing routes. In all 3 lymphoma lines, MLN2238 demonstrated stronger antitumor activity than did bortezomib. In summary, MLN2238, similar to bortezomib, is a dipeptide boronic acid proteasome inhibitor that potently, reversibly, and selectively inhibits the proteasome. There are several features, such as sustained pharmacodynamic effects and activity in a bortezomib-refractory lymphoma xenograft model, that suggest that it may have activity that extends beyond that seen with bortezomib.

Nonclinical Pharmacokinetics and Pharmacodynamics: Nonclinical Pharmacokinetics: The pharmacokinetic (PK) properties of MLN2238 were studied in severe combined immunodeficient (SCID) mice bearing human CWR22 tumor xenografts, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Because of the extensive red blood cell (RBC) partitioning of MLN2238, both blood and plasma PK parameters were determined in these studies. MLN2238 had a very low blood clearance (CLb) and a moderate blood volume of distribution at steady-state (Vss,b) after IV administration. The concentration-versus-time curve of MLN2238 displayed a distinct bi-exponential profile with a steep initial distribution phase and a long terminal $t_{1/2}$ (> 24 hr) in all species tested. MLN2238 had higher plasma clearance (CLp) and a larger plasma volume of distribution at steady-state (Vss,p) than in blood, largely because of the extensive RBC partitioning. The PK properties of MLN2238 after oral administration were studied in rats and dogs. The plasma oral bioavailability (F) was 41% in rats and nearly 100% in dogs. A clinical prototype formulation of the ixazomib capsule demonstrated that MLN2238 had excellent oral F and an excellent absorption profile in dogs. In addition, interindividual variability, as measured by %CV, in Cmax and $AUC_{0\text{-}24hr}$ after oral administration was low to moderate, similar to that after IV administration. The terminal $t_{1/2}$ after oral administration was also similar to that after IV administration. Comparison of the PK profiles after IV or PO administration in the dog is reported in further

detail in the IB. MLN2238 is predicted to have very low CLb (0.0045 L/hr/kg) and a moderate Vss,b (0.79 L/kg) with a long terminal $t_{1/2}$ (> 24 hours) in humans. The human efficacious IV dose of MLN2238 is predicted to be 2.0 mg/m^2 (0.054 mg/kg) twice weekly. The human efficacious oral dose is predicted to be between 2 and 5 mg/m^2 twice weekly, based on a predicted oral F of between 41% (as seen in rats) and 100% (as seen in dogs). The efficacious dose projection for once weekly oral would be higher than twice weekly oral (data not provided).

Metabolism appears to be a major route of elimination for MLN2238 and urinary excretion of the parent drug was negligible (< 5% of dose). In vitro in liver microsomes, the metabolism of MLN2238 was high in mice and low to moderate in all other species studied. MLN2238 is metabolized by multiple cytochrome P450 (CYP) isozymes and non-CYP enzymes and proteins.

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.

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

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

Toxicology: All studies discussed in this section were conducted with a solution of either MLN2238 or MLN2238 in equilibrium with ixazomib citrate. Because ixazomib citrate 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 (ixazomib).

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. MLN2238 did not cause significant toxicities that have not been previously observed after dosing with bortezomib. Therefore, on the basis of the similarity in the toxicity profile in rats between MLN22338 and bortezomib, MLN2238 is not known to present any additional safety risks beyond those that occur after treatment with bortezomib. In addition, there were no significant findings at tolerated exposures in dogs observed after PO administration that were not seen after IV administration, and similar exposures were tolerated regardless of the route of administration.

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

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

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

Clinical Experience with ixazomib

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

Pharmacokinetics and Drug Metabolism: After oral dosing, absorption of ixazomib is rapid with a median first time to maximum observed plasma concentration (Tmax) of approximately 1 hour postdose. The plasma exposure (AUC) of ixazomib increases in a dose-proportional manner over a dose range of 0.2 to 10.6 mg based on population PK analysis. The absolute oral bioavailability (F) of ixazomib is estimated to be 58% based on population PK analysis. A high-fat meal reduced ixazomib Cmax by 69% and AUC0-216 by 28%. This indicates that a high-fat meal decreases both the rate and extent of absorption of ixazomib. Therefore, ixazomib should be dosed at least 2 hours after food or 1 hour before food.

The steady-state volume of distribution of ixazomib is large and is estimated to be 543 L based on a population PK model. Based on in vitro plasma protein binding measurements on samples from clinical studies (Studies C16015 and C16018), ixazomib is highly bound to plasma proteins (99%). Ixazomib concentrations are higher in whole blood than in plasma, indicating extensive partitioning of ixazomib into red blood cells, which are known to contain high concentrations of the 20S proteasome.

Metabolism appears to be the major route of elimination for ixazomib. In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450 (CYP) and non-CYP proteins. At concentrations exceeding those observed clinically (10 μM), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (<1%). At 0.1 and 0.5 μM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, non-CYP proteins contribute to the clearance of ixazomib and no specific CYP isozyme predominantly contributes to the clearance of ixazomib. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor would be expected.

Ixazomib is neither a time-dependent inhibitor nor a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYPs 1A2, 2B6, and 3A4/5 activity or corresponding immunoreactive protein levels. Thus, the potential for ixazomib to produce DDIs via CYP isozyme induction or inhibition is low.

Ixazomib is not a substrate of BCRP, MRP2 and OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Ixazomib is unlikely to cause or be susceptible to clinical DDIs with substrates or inhibitors of clinically relevant drug transporters.

The geometric mean terminal half-life (t1/2) of ixazomib is 9.5 days based on population PK analysis. For both IV and oral dosing, there is an approximately average 3-fold accumulation (based on AUC) following the Day 11 dose for the twice-weekly schedule and a 2-fold accumulation (based on AUC) following the Day 15 dose for the once-weekly schedule.

Mean plasma clearance (CL) of ixazomib is 1.86 L/hr based on the results of a population PK analysis. Taken together with the blood-to-plasma AUC ratio of approximately 10, it can be inferred that ixazomib is a low clearance drug. Using the absolute oral bioavailability (F) estimate of 58% (also from a population PK model), this translates to an apparent oral plasma clearance (CL/F) of 3.21 L/hr. The geometric mean renal clearance for ixazomib is 0.119 L/hr, which is 3.7% of CL/F and 6.4% of CL estimated in a population PK analysis.

Therefore, renal clearance does not meaningfully contribute to ixazomib clearance in humans. Approximately 62% of the administered radioactivity in the ADME study (Study C16016) was recovered in the urine and 22% of the total radioactivity was recovered in the feces after oral administration. Only 3.2% of the administered ixazomib dose was recovered in the urine as unchanged ixazomib up to 168 hours after oral dosing, suggesting that most of the total radioactivity in urine was attributable to metabolites.

The PK of ixazomib was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor, and hence no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. Consistently, in a population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. Based on information from the clinical rifampin DDI study, ixazomib Cmax and AUC0-last were reduced in the presence of rifampin by approximately 54% and 74%, respectively. Therefore, the co-administration of strong CYP3A inducers with ixazomib is not recommended.

Mild or moderate renal impairment (CrCL ≥ 30 mL/min) did not alter the PK of ixazomib based on the results from a population PK analysis. As a result, no dose adjustment is required for patients with mild or moderate renal impairment. In a dedicated renal impairment study (C16015), unbound AUC0-last was 38% higher in patients with severe renal impairment or ESRD patients requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is appropriate in patients with severe renal impairment or ESRD requiring dialysis. Pre- and post-dialyzer concentrations of ixazomib measured during the hemodialysis session were similar, suggesting that ixazomib is not readily dialyzable, consistent with its high plasma protein binding (99%).

The PK of ixazomib is similar in patients with normal hepatic function and in patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (total bilirubin <1.5 times the upper limit of normal [ULN]), based on the results from a population PK analysis. Consequently, no dose adjustment is required for patients with mild hepatic impairment. In a dedicated PK study in patients with moderate (total bilirubin >1.5 to 3 times the ULN) or severe (total bilirubin >3 times the ULN) hepatic impairment (Study C16018), unbound dose-normalized AUC0-last was 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. Therefore, a reduced starting dose of ixazomib is appropriate in patients with moderate or severe hepatic impairment.

There was no statistically significant effect of age (23-91 years), sex, body surface area (1.2-2.7 m2), or race on the clearance of ixazomib based on the results from a population PK analysis.

Overview of the Oral Formulation of ixazomib

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

Relapsed MM: Single-agent, Weekly ixazomib (Study C16004):[13]

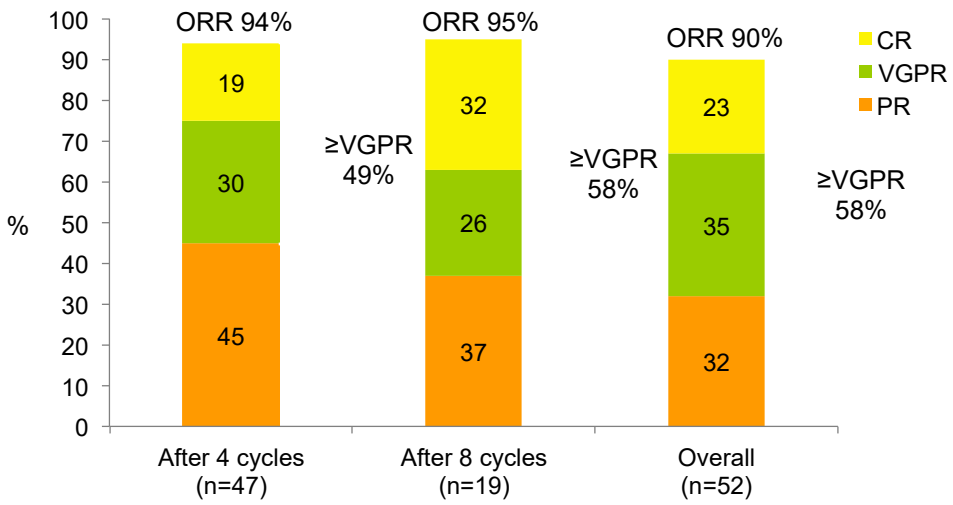
Study C16004 is an open-label, dose-escalation, phase 1 study of ixazomib administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have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

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

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

Sixty patients with relapsed and/or refractory multiple myeloma were enrolled. The MTD was determined to be 2.97 mg/m^2. Dose-limiting toxicities were grade 3 nausea, vomiting, and diarrhea in 2 patients, and grade 3 skin rash in 1 patient. Common drug-related adverse events were thrombocytopenia (43%), diarrhea (38%), nausea (38%), fatigue (37%), and vomiting (35%). The observed rate of peripheral neuropathy was 20%, with only 1 grade 3 event reported. Nine (18%) patients achieved a partial response or better, including 8 of 30 (27%) evaluable patients treated at the MTD. Pharmacokinetic studies suggested a long terminal half-life of 3.6 to 11.3 days, supporting once-weekly dosing.

Newly Diagnosed Multiple Myeloma *(C16005):* [14]
In Study C16005, ixazomib is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle.[15] Patients with newly diagnosed MM were enrolled and treated with oral ixazomib (days 1, 8, and 15) plus lenalidomide 25 mg (days 1-21) and dexamethasone 40 mg (days 1, 8, 15, 22) for up to twelve 28-day cycles, then maintenance therapy with ixazomib (same schedule) every 28 days until progression. Patients were allowed to undergo stem cell collection after 3 cycles and discontinue for autologous stem cell transplant (ASCT) after 6 cycles. Overall, 65 patients were enrolled, 15 in Phase 1 and 50 in Phase 2. Patients received a median of 6 cycles (range 1-19) with 27 (42%) remaining on treatment as of November 2012. Of those who have undergone stem cell mobilization, a median yield was 11.3 x 10^6 CD34+ cells/Kg (range 5-28). ixazomib MTD was established as 2.97 mg/m2 and RP2D was selected as 2.23 mg/m2; RP2D translates to a 4.0 mg fixed dose based on population PK results. Among the 64 evaluable patients, the overall response rate was 92%, including 55% VGPR and 23% CR (Figure 3 below). Median time to first response was 0.92 months (range 0.89-6.44).



Potential Risks and Benefits of ixazomib:

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

1.4 Lenalidomide in myeloma

Lenalidomide has significant activity in the setting of multiple myeloma; both in relapsed and in newly diagnosed disease. Initial phase I/II study of lenalidomide in relapsed myeloma determined the ideal dose to be 25 mg once daily given for 3 of 4 weeks.[16] The initial trial in the relapsed disease also demonstrated increased activity in combination with pulsed doses of dexamethasone. These findings led to the initial trials of the combination in newly diagnosed disease as well as randomized trials of the combination in relapsed myeloma.[17] In the phase III trials of lenalidomide and dexamethasone, the combination was demonstrated to be superior to dexamethasone in terms of response rates and progression free and overall survival.[18] The initial phase II study of lenalidomide and dexamethasone in newly diagnosed myeloma, conducted at the Mayo Clinic, also employed the combination of lenalidomide and pulsed dose dexamethasone (40 mg daily on four days on four days off schedule) for the first four cycles followed by 40 mg weekly for the subsequent cycles. The phase II study demonstrated significant response rates and long term follow up demonstrated sustained responses and 1-year survival rates of over 90%. The subsequent phase III trial in the ECOG (E4A03) compared the same dosing strategy to one that employed a lower dose of dexamethasone (40 mg weekly) right from the start of therapy.[18] The results of the trial demonstrated a superior overall survival for the lower dose dexamethasone arm.

1.5 Daratumumab in 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. It is not approved for initial therapy of myeloma, and hence considered investigational for the current trial.

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. A large phase 3 trial of Daratumumab and Rd versus Rd has completed accrual.

1.6 Rationale for the current trial: Ixazomib in combination with lenalidomide and dexamethasone results in high response rates and deep responses in patients with newly diagnosed myeloma. It is well tolerated and patients are able to stay on it long term as a maintenance therapy. More recently, addition of daratumumab to lenalidomide and dexamethasone has resulted in significant activity in relapsed myeloma. The combination of the ixazomib, lenalidomide, daratumumab and dexamethasone presents the potential to further enhance the response to therapy with four different drug classes with no significant overlapping toxicities. We hypothesize that this combination will lead to deep response including a higher proportion of MRD negative disease that will translate into longer survival in these patients.

Rationale for Arm B: Long term therapy with dexamethasone is associated with various side effects including osteoporosis, adrenal suppression, muscle weakness, and increased risk of opportunistic infections. Given the efficacy of the daratumumab, ixazomib and lenalidomide, it is likely we will be able to decrease the dexamethasone doses and potentially eliminate it after the initial cycles. We will add a similar cohort of patients and treat them with dexamethasone only for the first two cycles of treatment and then discontinue. The endpoints of the trial will not be altered.

2.0 Goals

2.1 Primary

To determine the complete response rate (CR) of the four-drug combination of Ixazomib, lenalidomide, dexamethasone and daratumumab in patients with previously untreated symptomatic MM.

2.2 Secondary

2.21 To determine the overall response rate (ORR), and very good partial response (VGPR) rate with the four drug combination of ixazomib, lenalidomide, dexamethasone and daratumumab, when used as initial therapy in patients with previously untreated symptomatic MM

2.22 To determine the progression free survival and overall survival among patients with previously untreated symptomatic MM following treatment with the four drug combination of Ixazomib, lenalidomide, dexamethasone and daratumumab followed by ixazomib and daratumumab maintenance till progression.

2.22 To determine the toxicities associated with the four drug combination of Ixazomib, lenalidomide, dexamethasone and daratumumab in patients with previously untreated symptomatic MM.

2.3 Correlative Research

2.31 To examine the proportion of MRD negativity following induction therapy with the four-drug combination of Ixazomib, lenalidomide, dexamethasone and daratumumab

2.32 To assess the quality of life using patient completed FACT/GOG questionnaires.

3.0 Patient Eligibility

3.1 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 (ANC) ≥1500/mm^3
- Untransfused Platelet count ≥75000/mm^3
- Hemoglobin ≥8.0 g/dL
- Total bilirubin ≤ 1.5 x ULN
- ALT and AST ≤ 2.5 x ULN

*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 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.

3.14 ECOG performance status (PS) 0, 1 or 2 (Appendix IV)

3.15 Previously untreated for myeloma or have received no more than one cycle of any treatment regimen. NOTE: Prior radiation therapy for the treatment of solitary plasmacytoma is permitted. Prior therapy with clarithromycin, DHEA, anakinra, pamidronate or zoledronic acid is permitted. Any additional agents not listed must be approved by the Principal Investigator.

3.16 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 follow strict birth control measures.
Female patients: If they are of childbearing potential, agree to one of the following:
- Practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, AND must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

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

3.19a 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) (added as of addendum 9)
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.

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

3.19c Willing to follow the requirements of the Revlimid REMS program

3.19d Willing to provide bone marrow and blood samples for planned research

3.2 Exclusion Criteria

3.21 MGUS or smoldering myeloma.

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

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

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

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

3.25 Peripheral neuropathy ≥ Grade 2 on clinical examination or grade 1 with pain during the screening period.

3.26 Major surgery ≤14 days prior to registration.

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

3.28 Evidence of current uncontrolled cardiovascular conditions, including hypertension, cardiac arrhythmias, congestive heart failure, unstable angina, or myocardial infarction ≤6 months. Note: Prior to entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.

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

3.29b Known human immunodeficiency virus (HIV) positive.

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

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

3.29e Known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or Investigator's Brochure), or known sensitivity to mammalian-derived products.

3.29f Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib, lenalidomide or dexamethasone including difficulty swallowing.

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

4.0 Test Schedule

4.1 Schedule of assessments

	Days Prior to Registration		*Every 14 days (cycles 1 - 3)*[1]	*Every cycle, Induction*[1,10,11]	*Maintenance Phase:*
	≤30 days	*≤14 days*			*(every cycle)*[1, 10]
Complete medical history	X				
Adverse Event monitoring		X		X	X[14]
Physical exam, weight and vital signs		X		X	X[14]
Height		X			
Performance status (ECOG scale)		X		X	X[14]
CBC with diff.		X	X	X	X[14]
Prothrombin time (PT)	X				
Blood type and screen	X				
Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; Total and Direct bilirubin; SGOT (AST);ALT serum creatinine, calcium		X	X	X	X[14]
sTSH, T3, T4	X				
LDH, $Beta_2$-microglobulin, C-reactive protein	X				
Viral hepatitis panel including HBsAg, HB core antibody, and HB antibody	X[13]			X[13]	X[13]
Electrophoresis of serum and urine		X		X[10]	X[10,14]
Affected Immunoglobulin		X		X[8]	X[8,14]
Immunofixation serum and urine	X			X[2]	X[2,14]
Immunoglobulin free light chain		X		X[5]	X[5,14]
X-ray skeletal survey or WBLDCT	X			X[4]	X[4]
Bone marrow aspirate and biopsy	X			X[6]	X[6]
Research bone marrow and blood sample[R,12]	X			X[6]	X
Chest x-ray	X				

	Days Prior to Registration		*Every 14 days (cycles 1 - 3)*[1]	*Every cycle, Induction*[1,10,11]	*Maintenance Phase:*
	≤30 days	*≤14 days*			*(every cycle)*[1, 10]
Serum pregnancy test		X[3]			
Patient Medication Diary (Appendix V)[7].				X	X
QOL questionnaire (Appendix VII)		X		X[9]	X[9]

1) All scheduled visits will have a window of ± 4 days unless otherwise stated
2) Immunofixation (IF) needed only in the absence of M-spike to document CR or sCR.
3) For women of childbearing potential only. Must be done ≤7 days prior to registration. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for cycle 1. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods) potential only.
4) WBLDCT-whole body low dose CT, Every 12 cycles or if clinically indicated.
5) FLC is required only if used to assess disease response during active phase
6) At the end of 4 cycles, 12 cycles, after 12 and 24 cycles of maintenance (Cycles 24 and 36) and to document CR or disease progression.
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, IgD, or IgM. Not applicable if patient "non-secretory" or if patient has no heavy chain, i.e. light chain myeloma. Affected immunoglobulin is required after baseline only if it used for disease monitoring instead of SPEP (for e.g. IgA myeloma)
9) The QOL questionnaire will be filled out by the patient at baseline, every cycle for the first 4 cycles, and then every 3 cycles.
10) Urine Electrophoresis required only if used to assess disease response
11) Does not need to be repeated at Cycle 1 Day 1. Baseline values can be used for Cycle 1.
12) Not mandatory at baseline or disease progression
13) Patients enrolled prior to amendment 9 and within the past 6 months, will be need to tested as soon as feasible. Note: 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.
14) **As of amendment 12** 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.

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

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	q. 3 months until PD	At PD	After PD q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.

5.0 Stratification Factors: None

6.0 Registration Procedures

6.1 Registration

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/ randomization application. The registration/randomization 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 Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c and 14.0).

6.3 Verification

Prior to accepting the registration, registration/randomization 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

6.4 IRB approval

Documentation of IRB approval must be on file in the Registration Office 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 Registration Office is no longer necessary.

6.5 Treatment requirements

As of amendment 12:
Treatment on this protocol must commence under the supervision of a hematologist from the enrolling institution.

6.6 Treatment start

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

6.7 Pretreatment

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

6.8 Baseline symptoms

All required baseline symptoms (see Section 10.5) must be documented and graded.

6.9a Study drug

Study drug is available on site.

6.9b Blood kits

Blood kit is available on site for this patient.

6.9c Patient questionnaire booklets

Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

6.9d GCP

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

7.0 Protocol Treatment

- Stem cell collection and transplant: Patients are allowed to collect stem cells at any time after completion of treatment on Cycle 4 if eligible for stem cell transplant. Details should be recorded on the Stem Cell Harvest form. If patient goes to transplant, they will go directly to event monitoring per Section 4.2 and the transplant should be reported on the event monitoring and Transplant and Engraftment forms. In the case that patients are unable to go to transplant due to other reasons, they can continue on study. In those cases, therapy may be interrupted for up to 4 weeks for the purpose of stem cell collection. Stem cells can be collected using standard institutional protocols. Any delay beyond 4 weeks should be discussed with the study PI prior to reinitiating protocol therapy.

- Lack of Response: Patients will go off treatment to event monitoring if an MR is not seen after 2 cycles and a PR is not seen after 4 cycles. Confirmation of MR or PR is not required.

- Dose modifications for toxicity are outlined in Section 8.

- An individual subject will be considered off-treatment following a 28-day safety follow-up period after the last cycle of treatment.

7.1 Treatment Schedule Arm A

Table 7.1

Induction phase (Cycles 1-12)

Drug	**Route**	**Dose**	**Schedule** **Each cycle is 28 days**
Ixazomib	Oral	4 mg	Days 1, 8 and 15
Lenalidomide	Oral	25 mg (if CrCl >60 ml/min)	Days 1-21
		10 mg (if CrCl 30-60 ml/min)	
Daratumumab	IV	16 mg/kg	Cycles 1 and 2: Days 1, 8, 15, 22
			Cycles 3, 4, 5, and 6: Days 1, 15
			Cycles 7 and beyond: Day 1
Dexamethasone	IV/ Oral*	40 mg	Days 1, 8, 15 and 22 **Arm A: Cycles 1-12**
* On days when daratumumab is given, dexamethasone is given IV over 15 minutes within 1 hour prior to daratumumab			
Maintenance Phase (Cycle 13 + up to 36 months from registration)			
Ixazomib	Oral	4 mg	Days 1, 8 and 15
Daratumumab	IV	16 mg/kg	Day 1
Cycle = 28 days			

NOTE: Once the creatinine clearance is >60 mL/min during the course of the treatment, lenalidomide can be increased to 25 mg.

Treatment Schedule Arm B

Table 7.1			
Induction phase (Cycles 1-12)			
Drug	**Route**	**Dose**	**Schedule Each cycle is 28 days**
Ixazomib	Oral	4 mg	Days 1, 8 and 15
Lenalidomide	Oral	25 mg (if CrCl >60 ml/min)	Days 1-21
		10 mg (if CrCl 30-60 ml/min)	
Daratumumab	IV	16 mg/kg	Cycles 1 and 2: Days 1, 8, 15, 22
			Cycles 3, 4, 5, and 6: Days 1, 15
			Cycles 7 and beyond: Day 1
Dexamethasone	IV/ Oral*	40 mg	Days 1, 8, 15 and 22 **Arm B: Cycles 1-2**
* On days when daratumumab is given, Dexamethasone is given IV over 15 minutes within 1 hour prior to daratumumab			
Maintenance Phase (Cycle 13 + up to 36 months from registration)			
Ixazomib	Oral	4 mg	Days 1, 8 and 15
Daratumumab	IV	16 mg/kg	Day 1
Cycle = 28 days			

NOTE: Once the creatinine clearance is >60 mL/min during the course of the treatment, lenalidomide can be increased to 25 mg.

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 Lenalidomide (Cycles 1-12 only)

- Subjects will receive lenalidomide orally once daily on days 1-21 of the 28 day cycle.
- Lenalidomide 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.
- Lenalidomide 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 12:
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 (Cycles 1-12 for Arm A / Cycles 1 and 2 only for Arm B)

- Dexamethasone may be self-administered by the subject on an outpatient basis.
- **Arm A**:
  Dexamethasone may be permanently discontinued after 12 cycles at the treating physician's discretion or sooner if needed to manage toxicity related to dexamethasone.

  Arm B:
  Dexamethasone will be discontinued after 2 cycles or sooner if needed to manage toxicity related to dexamethasone. Dexamethasone as part of infusion reaction prophylaxis may 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 12**: **Exception noted above in 7.4.**

As of amendment 12:
The patient must return to the consenting institution for ixazomib 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. If the toxicity is attributable to one drug, only that needs to be dose reduced. If overlapping toxicities are observed, the dose reductions can be alternated between the suspected drugs, starting with the drug most likely related to the adverse event. Thereafter, these modifications should be regarded as guidelines to limit to 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.

NOTE: If ixazomib, lenalidomide or daratumumab is discontinued, the patient can continue on the other drugs, unless specified otherwise in the dose modification tables. If all three are discontinued, the patient will go to event monitoring (Section 4.2).

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

8.1 Dose Levels for each drug in the combination

(Based on Adverse Events in Tables 8.2-5)

NOTE: Toxicities attributable to dexamethasone should lead to dose reduction only for dexamethasone.

Table 8.1 Dose reduction steps

Step	*Ixazomib*	*Lenalidomide*	*Daratumumab*	*Dexamethasone*
0	4 mg	25 mg	NA	40 mg
-1	3 mg	15 mg		24 mg
-2	2.3 mg	10 mg		12 mg
-3	Discontinue	5 mg		4 mg
-4	Discontinue	Discontinue		Discontinue

8.11 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 -related adverse event that may have occurred has resolved to ≤Grade 1 or baseline severity.

If these conditions are not met on Day 1 of a new cycle, 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 due to non-resolution of drug related toxicities, the patient will be removed from protocol therapy and will go to event monitoring.

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

8.2 Dose modifications for ixazomib based on adverse events during a cycle

CTCAE System/Organ/ Class (SOC)*	**ADVERSE EVENT**	**ACTION****
Investigations	If platelet count $<30 \times 10^9$/L or ANC $<1.0 \times 10^9$/L or ANC $>1.0 \times 10^9$/L (up to LLN) with fever (temperature >38.5°C)	Days 2-15: Ixazomib dose should be omitted on Day 8 and/or 15 as applicable Complete blood count (CBC) with differential should be followed weekly. If ANC is $\geq 1.0 \times 10^9$/L and/or platelet counts $\geq 30 \times 10^9$/L, ixazomib may be reinitiated with 1 dose level reduction. The subsequent cycle will use the reduced dose.
Skin and subcutaneous tissue disorders	Rash, Any skin, ≥Grade 2	Omit ixazomib till rash resolves to ≤Grade 1 (See Section 9.9a). Restart at same dose. If the rash recurs, reduce dose by one dose level.
	Any skin, Grade 4	Discontinue ixazomib and remove patient from all study treatment
Nervous System Disorders	Newly developed Grade 1 peripheral neuropathy with pain, ≥Grade 2 peripheral neuropathy	Reduce dose of ixazomib to the next lower dose level
Nervous System Disorders	Grade 2 neuropathy with pain or Grade 3 peripheral neuropathy	Omit ixazomib until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate ixazomib at the next lower dose level.
	Grade 4 peripheral neuropathy	Permanently discontinue ixazomib.
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	Omit ixazomib depending on the attribution, until resolution to Grade ≤1 or baseline Restart at next lower dose. If a patient is already at the lowest drug level, go to event monitoring
	Grade 4 Nonhematologic Toxicities	Consider permanently discontinuing ixazomib – Exception if the investigator determines the patient is obtaining a clinical benefit

* Located at [redacted]

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

➢ Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time

- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

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

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION
Blood and lymphatic system disorders	febrile neutropenia associated with fever (temperature ≥ 38.5º C)	• Omit lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21 and fever has resolved, restart lenalidomide at next lower dose level and continue the cycle through Day 21. If febrile neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the lenalidomide dose maintained.
Investigations	If platelet count $<30 \times 10^9$/L or ANC $<1.0 \times 10^9$/L or ANC $>1.0 \times 10^9$/L (up to LLN) with fever (temperature >38.5°C)	• Omit lenalidomide dose. • Follow CBC weekly. • Hold anticoagulation until platelets > 50,000 • If platelet count resolves to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the lenalidomide dose maintained.
Skin and subcutaneous tissue disorders	Rash maculo papular Grade 2 or 3.	• Omit lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.
	Any rash Grade 4	• Discontinue lenalidomide. Remove patient from all study treatment. • Go to event monitoring.
Nervous system disorders	Peripheral sensory Neuropathy Grade 3	• Omit lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION
	Grade 4	• Discontinue lenalidomide. Remove patient from all study treatment. • Go to event monitoring.
Immune system disorders	Allergic reaction Grade 2-3	• Omit dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 15 restart at next lower dose level and continue the cycle until Day 21.
	Grade 4	• Discontinue lenalidomide. Remove patient from all study treatment. • Go to event monitoring.
Vascular disorders	Thromboembolic event ≥ Grade 3	• Omit dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
	Hyperthyroidism or Hypothyroidism ≥ grade 2	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
Other non-hematologic adverse event	Other non-hematologic toxicity ≥ Grade 3	• Omit lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.

Lenalidomide dose modifications for renal impairment developing during treatment, considered not related to lenalidomide

Renal Function	Dose
CrCl 30-60 ml/min	10 mg daily
CrCl < 30 mL/min (not requiring dialysis)	15 mg every 48 hours
CrCl < 30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose after dialysis

* Located at [redacted]

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

➢ Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time

➢ Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.

➢ Discontinue = The specified drug(s) are totally stopped.

8.4 Dose modifications for dexamethasone (Dex) based on adverse events during a cycle

CTCAE System/Organ/Class (SOC)*	**ADVERSE EVENT**	**ACTION****
Gastrointestinal disorders	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL)	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)	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.
Gastrointestinal disorders	Pancreatitis ≥Grade 3 (Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support))	Discontinue dexamethasone and do not resume
General disorders and administration site conditions	Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)	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
Psychiatric disorders	Confusion or Mood alteration ≥Grade 2 (Severe disorientation; limiting self-care ADL)	Omit dexamethasone until symptoms resolve Restart with one dose level reduction If symptoms persist despite above measures, discontinue dexamethasone and do not resume
Musculoskeletal and connective tissue disorders	Muscle weakness ≥ Grade 2 Weakness limiting self-care ADL; disabling	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
Metabolism and nutrition disorders	Hyperglycemia Grade 3 or higher (>250 - 500 mg/dL; >13.9 - 27.8 mmol/L); hospitalization indicated	Treatment with insulin or oral hypoglycemics as needed If uncontrolled despite above measures, decrease dose by one dose level at a time until levels are satisfactory

* Located at [redacted]

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

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

8.5 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.

8.51 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 nonhematologic 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 lenalidomide, ixazomib or dexamethasone 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 Oral hydration

Patients are encouraged to drink at least 6 to 8 cups of liquid per day.

9.2 Disallowed concurrent treatment

The following treatments are not permitted during the trial:

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

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

9.3 Nausea and/or vomiting

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

9.4 Blood products and growth factors

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.

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.

9.5 Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals such as loperamide once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before

initiation of treatment and during treatment. Additional doses of loperamide at 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.
Please monitor patients carefully for development of ileus.

9.6 Renal failure and Ixazomib

Two cases of acute renal failure have been reported in patients treated at or above the MTD for intravenous ixazomib (see Section 1.4.3). Volume depletion should be corrected before initiation of study drug. Until further information is available, intake of nonsteroidal anti-inflammatory drugs immediately prior to the administration of ixazomib should be discouraged and requires consultation with the principal investigator. All necessary supportive care consistent with optimal patient care shall be available to patients as necessary.

9.7 Herpes Zoster prophylaxis

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis with acyclovir 400 mg PO BID is should be used while on study therapy and for 3 months beyond the end of therapy.

9.8 Prohibited medications

9.81 Prohibited enzyme inducers

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

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

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

9.9a Erythematous Rash with or without Pruritus

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

limiting, and is typically Grade 1 to 2 in severity. Rash can also be seen with lenalidomide, and usually responds to dose interruption and dose decrease.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (e.g., prednisone ≤10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

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

9.9b Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib and lenalidomide administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 8). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

9.9c Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Section 8). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

9.9d Fluid Deficit

Vitals should be assessed prior to start of each cycle as per Table 4.1. Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Patients should be encouraged to maintain adequate fluid intake. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously

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

9.9e Hypotension

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

9.9f Posterior Reversible Encephalopathy Syndrome

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

9.9g 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.

9.9h 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.

9.9i Management of Infusion-related Reactions

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 an infusion-related reaction develops, then the infusion should be temporarily interrupted or slowed down. 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.

9.9j Thromboprophyaxis:

All patients should be on 325 mg ASA daily while receiving lenalidomide. If they are unable to take ASA or are at high risk of VTE per investigator assessment, full dose anticoagulation is recommended.

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 10.2 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 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15 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).

10.4 Required Reporting

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 10.6.
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.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore2, 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.

10.41 Special Situations for Expedited Reporting

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

An expedited report may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events 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 **supersede** 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]; see Footnote 1):

System Organ Class (SOC)	Adverse event/ Symptoms*	CTCAE Grade at which the event will not be expeditedly reported[1]
General disorders and administrations site conditions	Fatigue	≤Grade 3
Gastrointestinal	Vomiting	≤Grade 3
	Nausea	≤Grade 3
	Diarrhea	≤Grade 3
Investigations	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	Lymphocyte count decreased	≤Grade 4
	White blood cell count	≤Grade 4
Blood and lymphatic system disorders	Anemia	≤Grade 4
Metabolism and Nutrition Disorders	Hyperglycemia	≤Grade 3

[1] These exceptions only apply if the adverse event does not result in hospitalization or any other serious criteria outlined in Section 10.42. 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.

10.411 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 abnormalities 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).

10.412 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.

10.413 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 must be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic 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.

10.414 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.

10.42 Expedited Reporting Requirements for IND/IDE Agents

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

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

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

Expedited AE reporting timelines are defined as:

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

○ "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.
[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 3 calendar days for:** • All Grade 4, and Grade 5 AEs **Expedited 7 calendar day reports for:** • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events

10.43 Additional instructions:
Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies of MedWatch 3500A, along with the UPIRTSO cover sheet, by email to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist at [redacted] who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator.

10.5 Required routine 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:

CTCAE SYSTEM/ORGAN/CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
General disorders and administration site conditions	Fatigue	X	X
	Infusion related reaction		X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of Stools	X	
	Diarrhea		X
Infections and infestations	Sepsis	X	X
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Skin and subcutaneous tissue disorders	Rash- maculopapular	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X

10.52 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 10.6:

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)

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

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
- Infections
- Cytopenias
- HBV Reactivation
- Other malignancies

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 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 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

The International Myeloma Working Group (IMWG) uniform response criteria[21] will be used to assess response to therapy.

11.1 Terms and definitions

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

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

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

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

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

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

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

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

- Serum M-protein ≥1 g/dl
  NOTE: Quantitative IgG may not be used for defining measurable disease
- Urine M-protein ≥ 200 mg/24 h
- Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
- Bone marrow plasma cells ≥ 30%

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

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

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

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

11.2 Clarification of test indications

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

Table 11.2

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

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

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

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

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

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

11.3 Confirmed response

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

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

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

11.4 Bone progression

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

11.5 Response and Progression

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

Table 11.5

IMWG MRD NEGATIVITY CATEGORY	**RESPONSE CRITERIA** [a]
Sustained MRD	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD [k]	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD [k]	Absence of clonal plasma cells by NGS on bone marrow aspirates in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging Plus MRD [k]	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less than mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
STANDARD IMWG RESPONSE CATEGORY	**RESPONSE CRITERIA** [a]
Stringent Complete Response (sCR) [b]	CR as defined *plus* Normal FLC ratio *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry [i]
Complete Response (CR) [b]	• Negative immunofixation of serum and urine [c] *and* • Disappearance of any soft tissue plasmacytoma *and* • <5% PCs in Bone Marrow *and* • If the only measurable disease is FLC, a normal FLC ratio [d]

Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis [c] *or* • ≥90% reduction in serum M-protein and urine M-protein <100 mg/24 h [c] • If the only measurable disease is FLC, a >90% reduction in the difference between involved and uninvolved FLC levels
Partial Response (PR)	• If present at baseline, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24hrs [c] • If the only measurable disease is FLC, a ≥50% reduction in the difference between involved and uninvolved FLC levels • If the only measurable disease is BM, a ≥ 50% reduction in BM PCs (provided the baseline PCs was ≥ 30%) • If present at baseline, ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas [j]
Minimal Response (MR)	• If present at baseline, ≥25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours [c] *and* • If present at baseline, ≥50% reduction in the size (SPD) of soft tissue plasmacytoma [j]
Stable Disease (SD)	• Not meeting criteria for sCR, CR, VGPR, PR, MR or PD
Progressive Disease (PD) [b, h]	Increase of 25% from lowest value in any of the following [f, g]: • Serum M-protein (absolute increase must be ≥ 0.5 g/dL) *and/or* • Urine M-protein (absolute increase must be ≥ 200 mg/24 hrs) *and/or* • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) *and/or* • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be ≥ 10%) [e] Or any one or more of the following: • Development of new bone lesion or soft tissue plasmacytoma or ≥50% increase from nadir in the size (SPD) of existing bone lesions or soft tissue plasmacytoma or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis [j] • 50% increase in circulating plasma cells (minimum of 200 cells per L) if this is the only measure of disease
Clinical Relapse	One or more of the following direct indicators of increasing disease and/or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder: 1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L) 4. Decrease in hemoglobin of more than 2 g/dL (1.25mM) or to less than 10 g/dL 5. Rise in serum creatinine by more than or equal to 2 mg/dL

	(≥177mM/L) 6. Hyperviscosity

[a] All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy. MRD tests should be initiated only at the time of suspected complete response. sCR, CR, VGPR, PR, MR and SD categories and MRD require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported. 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. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

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

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

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

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

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

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

[h] Progressive disease should be confirmed on two consecutive evaluations, where the timing of confirmation is per the treating physician and can be done immediately within the same cycle or on the next cycle. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

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

[j] Plasmacytoma 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 the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).

[k] Requires a complete response as defined in the table. MRD tests should be initiated only at the time of suspected complete response. MRD requires no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

NOTE: Interference with Determination of Complete Response: Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

12.0 Descriptive Factors

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

12.2 High risk vs. standard risk by mSMART (see Appendix II)

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation

Patients who are sCR, CR, VGPR, PR, or SD (or usCR, uCR, uVGPR, uPR) will continue treatment per protocol. Patients will go off treatment to event monitoring if an MR is not seen after 2 cycles and a PR is not seen after 4 cycles. Confirmation of MR or PR is not required.

13.2 Patients who receive transplant

Patients who receive a transplant will go to event monitoring per Section 18.0. The transplant should be reported on the event monitoring form. Details should be recorded on the Stem Cell Harvest and Transplant and Engraftment Forms.

13.3 Progressive Disease

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

13.4 Off protocol for reasons other than PD

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

13.5 Discontinuation for unacceptable AEs

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

13.6 Criteria for Discontinuation of Treatment

Patients may discontinue treatment for the following reasons:

- Progressive multiple myeloma
- Patient refuses further treatment on the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions over 2 years)
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation

All attempts should be made to complete the End of Study procedures when the patient discontinues treatment. Patients should go to event monitoring per Section 4.2, unless the patient refuses further study participation or is lost to follow-up.

13.7 Criteria for Study Discontinuation

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

- Safety concerns
- Poor enrollment

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

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

13.8 Ineligible

A patient is deemed *ineligible* 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 4.2 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.9a Major violation

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 4.2 of the protocol.

13.9b Cancel

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 Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Table 14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Correlative Study	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Study Entry*	End of cycle 4, 12, 24, 36	At suspected CR	At PD*	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Flow cytometry for circulating plasma cells	Mandatory	Peripheral blood	ACD (yellow)	6 mL (3)	X	X	X	X	No	Cool Pak
Flow cytometry for MRD	Mandatory	Bone marrow aspirate	ACD (yellow)	6 ml (2)	X	X	X	X	No	Cool Pak

* Samples at baseline and at time of disease progression are not mandatory

14.2 Shipping and Handling

14.21 Kits

14.211 Kits will be used for this study. Kits will contain supplies and instructions for collection, processing and shipping specimens

14.212 Participating sites may obtain kits by emailing: [redacted] Email requests should include address, contact information and number of kits being requested.

14.213 Kits will be sent via FedEx Ground at no additional cost to participating sites. Allow 3-4 business days to receive kits.

14.22 Shipping

Bone marrow and blood samples can be shipped with Cool Pak the same day they are collected (Monday-Thursday). They should be shipped priority overnight taking care to avoid Friday collection and shipping.

If unavoidable, Friday shipping with Saturday delivery can be arranged contacting the laboratory **in advance**.

Please notify Mayo Clinic by email [redacted] or phone [redacted] to notify laboratory when specimens are being shipped.

[redacted]

15.0 Drug Information

15.1 Ixazomib (MLN9708, Ninlaro®)

15.11 **Background**: Ixazomib (MLN9708) is a second-generation small molecule inhibitor of the 20S proteasome that is under development for the treatment of non-hematologic malignancies, lymphoma, and multiple myeloma.

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

15.12 **Formulation**: The ixazomib (MLN9708) 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 (MLN9708) 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 (MLN9708) 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 (MLN9708) capsules 0.2 mg, 0.5 mg, 2.0 mg), individually packaged in blisters, can be stored at 2ºC to 8ºC or “Do not store above 25°C. Do not freeze." Ixazomib capsules (2.3 mg, 3.0 mg, 4.0 mg, and 5.5 mg), individually packaged in blisters can be stored at “2°C - 8°C” or “Do not store above 30°C. Do not freeze."

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

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

15.14 **Administration:** Ixazomib (MLN9708) 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.

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. A high-fat meal decreased both the rate and extent of absorption. Therefore, ixazomib should be administered on an empty stomach.
b) Distribution: The steady state volume of distribution is large and is estimated to be 543 L. Ixazomib is 88-94% protein bound.
c) Metabolism: Metabolism is the primary route for elimination of ixazomib by both CYP and non-CYP enzymes. CYP3A4 and 1A2 comprise the major CYP isozymes that contribute to ixazomib metabolism.
d) Excretion: The mean terminal half-life is 9.5 days. Renal elimination is a minor clearance pathway for ixazomib. Dosing adjustment is not required in patients with mild and moderate renal impairment in studies. However, in a dedicated renal impairment study (C16015), unbound AUC0-last was 38% higher in patients with severe renal impairment or
end-stage renal disease (ESRD) requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is recommended in patients with severe renal impairment and ESRD requiring dialysis. Unbound systemic exposures of ixazomib are 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. A reduced starting dose of ixazomib is recommended for patients with moderate or severe hepatic impairment.

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

Pharmacokinetic parameters for ixazomib coadministered with lenalidomide and dexamethasone (LenDex) are similar to those observed when ixazomib is administered as a single agent. This suggests that there

is no readily apparent effect of coadministration of LenDex on the clinical PK of ixazomib.

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

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

Very common (≥10%): anemia, neutropenia, thrombocytopenia, constipation, diarrhea, nausea, vomiting, fatigue, decreased appetite, peripheral neuropathy,

Common (≥1% to <10%): Herpes zoster, peripheral sensory neuropathy, erythema, rash, erythematous rash, pruritic rash, macular rash, peripheral edema, upper respiratory tract infection, back pain, maculo-papular rash, papular rash

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

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

15.18 **Drug procurement:** Investigational product will be supplied free of charge to trial participants by Millennium Pharmaceuticals, Inc (Takeda)

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 hours before or 2 hours after meals) with 8 oz of water.

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

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

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

15.196 Assess patients concomitant medications, including over the counter and supplements. MLN9708 is metabolized through both CYP and non-CYP enzymes, and drug to drug interactions exist. Instruct patients not to start any new medications or supplements without checking with the study team first.

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

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

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

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

15.2 Lenalidomide (Revlimid®, CC-5013, CDC-501)

Please consult the most current Investigator's Brochure and package insert for complete drug information.

15.21 **Background**: Lenalidomide has a wide range of effects, including the inhibition of hematopoietic tumor cell proliferation, the enhancement of T cells and natural killer (NK) cell activity, the modulation of stem cell differentiation, the inhibition of angiogenesis, and the inhibition of inflammation.

15.22 **Formulation**: For clinical study, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for oral administration. Each capsule contains

lenalidomide as the active ingredient and the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Placebo capsules for the 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg lenalidomide capsules are available for use in blinded studies. Each placebo capsule visually matches the drug product.

The lenalidomide and placebo capsules are supplied in push-through blister foil or tamper-evident, child-resistant, opaque, high-density polyethylene (HDPE) containers with HDPE caps.

15.23 **Preparation and storage**: Lenalidomide should be stored at room temperature, between 59 and 86ºF (15-30ºC). Store drug away from direct sunlight.

15.24 **Administration:** Capsules are administered by mouth daily with water. Patients should not break, chew or open the capsules.

15.25 **Pharmacokinetic information**:
a) Absorption – Lenalidomide is rapidly absorbed following oral administration to subjects with multiple myeloma or MDS, with maximum plasma concentrations occurring between 0.5 and 1.5 hours post-dose. Co-administration with a high-fat and high-calorie meal in healthy subjects reduced the extent of absorption, resulting in an approximately 20% decrease in AUC and 50% decrease in C_{max} in plasma.

In the pivotal MM and MDS registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Multiple dosing (up to 100 mg BID) did not cause marked drug accumulation.

b) Distribution – In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

c) Metabolism – Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

d) Excretion – Elimination is primarily renal. Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The half-life of elimination is approximately 3 to 4 hours (2 to 3 hours in patients 5 to 21 years) at the clinically relevant doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days.

15.26 **Potential Drug Interactions**: In vitro studies demonstrate that lenalidomide is not a substrate of CYP enzymes. In addition, lenalidomide shows little inhibitory or induction potential towards the CYP enzymes in vitro. Hence,

coadministration of CYP substrates, inhibitors, or inducers with lenalidomide is not likely to result in clinically relevant drug-drug interactions in humans.

In vitro, lenalidomide is not a substrate of BCRP, MRP1, MRP2, MRP3, OAT1, OAT3, OATP1B1, OCT1, OCT2, MATE1, OCTN1, or OCTN2. Thus, it is unlikely that substrates or inhibitors of these transporters would affect lenalidomide disposition in humans.

Lenalidomide is not an inhibitor of BSEP, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. Thus, lenalidomide is not anticipated to cause any significant drug-drug interactions due to inhibition of these transporters.

Lenalidomide is not an inhibitor of UGT1A1 and is not anticipated to cause any significant drug-drug interactions due to UGT1A1 inhibition.

In vitro, lenalidomide is a weak substrate, but not an inhibitor of P-glycoprotein (P-gp).

Erythropoietic agents or other agents that may increase the risk of thrombosis, such as hormone replacement therapy and oral contraceptives, should be used with caution in patients with multiple myeloma receiving lenalidomide with dexamethasone.

Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant lenalidomide therapy. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

15.27 Known potential toxicities:

Pregnancy Warning: Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, a teratogenic effect of Lenalidomide in humans cannot be ruled out. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Very Common AEs (≥ 10%): anemia, febrile neutropenia, granulocytopenia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, cataracts, blurred vision, abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, asthenia, chills, edema including peripheral, fatigue, pyrexia, abnormal liver function tests, bronchitis, gastroenteritis, influenza, nasopharyngitis, sinusitis**,** pneumonia, rhinitis, upper respiratory tract infection, urinary tract infection weight decreased, decreased appetite, hyperglycemia, hypocalcemia, hypokalemia, arthralgia, back pain, bone pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity, dizziness, dysgeusia, headache, hypoesthesia, neuropathy peripheral, neuropathy, paresthesia, tremor, depression, insomnia, renal failure, cough, dyspnea, epistaxis, pharyngitis, pulmonary embolism, dry skin, pruritus, rash, and deep vein thrombosis.

Common (≥ 1% and < 10%): hemolytic anemia, pancytopenia, acute myocardial infarction, atrial fibrillation, cardiac failure, congestive heart failure, myocardial ischemia, tachycardia, vertigo, upper abdominal pain, dry mouth, toothache, chest pain, fall, cholestasis, arthritis infective, bacteremia, cellulitis, erysipelas, herpes simplex, herpes zoster, infection, lower respiratory infection, respiratory infection, lung infection, meningitis, ophthalmic herpes zoster, sepsis, contusion, alanine aminotransferase increased, c-reactive protein increased, gamma-glutamyltransferase increased, dehydration, diabetes mellitus, gout, hypercalcemia, hyperuricemia, hypophosphatemia, hypomagnesemia, hyponatremia, iron overload, muscular weakness, acute myeloid leukemia, basal cell carcinoma, Myelodysplastic syndrome, squamous cell carcinoma of skin, T-call type acute leukemia, tumor flare, tumor lysis syndrome, cerebrovascular accident, lethargy, peripheral sensory neuropathy, syncope, mood altered, respiratory distress, erythema, hyperhidrosis, night sweats, hematoma, hypertension, hypotension, thrombosis, and vasculitis.

Uncommon, limited to important or life-threatening (< 1%): appendicitis, bursitis infective, clostridium difficile colitis, infective exacerbation of chronic obstructive airways disease, pyelonephritis, hypersensitivity, Graft vs. Host Disease, viral reactivation (such as hepatitis B virus or herpes zoster), DRESS.

The following additional adverse reactions have been reported in Celgene-sponsored clinical studies and are considered by the company to be at least possibly related to the administration of lenalidomide: pneumonitis, transient abnormal liver laboratory tests, hyperthyroidism, viral reactivation (such as hepatitis B or herpes virus), acute graft-versus-host disease following allogeneic hematopoietic transplant, solid organ rejection, TLS, TFR, rhabdomyolysis, and allergic conditions, including angioedema,. These reactions are reported voluntarily from a population of uncertain size, so it is not possible to reliably estimate their frequency.

Lenalidomide may have minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

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

15.28 Drug procurement: Commerical supply. Per standard requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Celgene REVLIMID REMS™ program. Prescriptions must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Any unused lenalidomide should be returned for disposition in accordance with the REVLIMID REMS™ program

15.29 **Nursing Guidelines:**

- Myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction. Monitor CBC w/diff regularly. Instruct patient to report any unusual bruising or bleeding (thrombocytopenia); signs and symptoms of infection (neutropenia); and energy conserving lifestyle (anemia).

- Lenalidomide can have thrombotic adverse events (i.e DVT and PE). Instruct patient to report any limb swelling or pain, and to seek medical attention for shortness of breath or chest pain.

- Because of the potential for birth defects patients should be instructed in effective methods of birth control. Female patients should use 2 forms of birth control during treatment and for 4 weeks after discontinuing therapy. Males must be instructed to use a latex condom during any sexual contact with a woman of child bearing potential (even if they have had a vasectomy), because it is unknown if lenalidomide is present in semen.

- Patents may experience pruritus, rash and dry skin. Because of the rare risk of Steven's Johnson Syndrome, patients should immediately report any rash to their provider.

- Drug may cause hyperglycemia. Patients with diabetes or impaired fasting glucose may need to have their glucose levels monitored more closely.

- Gastrointestinal side effects (diarrhea, constipation, nausea, dyspepsia, anorexia, etc) are commonly seen. Manage patient symptomatically and monitor for effectiveness.

- Patients may experience myalgias, arthralgias, parasthesias and other generalized pain. Administer analgesics as ordered and monitor for their effectiveness. Rarely infective bursitis and arthritis have been reported. Instruct patients to report any joint pain or redness to study team immediately.

- Upper respiratory symptoms (nasopharyngitis, cough, epistaxis, etc.) can be seen. Manage symptomatically and monitor for effectiveness.

- Agent may cause fatigue, dizziness, vertigo or blurred vision. Instruct patients to use caution when driving or operating machines.

- Monitor LFT's and report any elevations to the study team. Instruct patient to report abdominal pain and/or jaundice to the study team.

- All prescribers and patients must be enrolled into the REVLIMID REMS program. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

- Rarely secondary malignancies have been seen after lenolidamide therapy, including MDS, squamous/basal cell carcinomas of the skin, T-cell type acute leukemia.

- Monitor Renal function, renal failure has been reported.

15.3 Dexamethasone for Oral Administration

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.

15.4 Daratumumab (Darzalex®)

Please consult the most current Investigator's Brochure and package insert for complete drug information.

15.41 **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.

15.42 **Formulation**:
IV formulation:Daratumumab IV solution is a colorless to yellow liquid and sterile concentrate of 20 mg/mL in a vial with a nominal fill of 5 mL or 20mL. It will be manufactured and provided under the responsibility of Janssen Biotech. Refer to the Product Insert for a list of excipients.

15.43 **Preparation and storage**:
IV drug formulation: Daratumumab is supplied in glass vials containing daratumumab at a concentration of 20 mg/mL. 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.

All 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 does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

Daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration. Refer to Section 7 of the protocol, the Investigational Product Preparation Instructions or Investigational Product Procedures Manual for details regarding dose preparation, storage, and handling of diluted solutions.

15.44 **Administration:**
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.
- 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.

15.45 **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. Clearance decreased with increasing dose and repeated dosing, indicating target-mediated pharmacokinetics. The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (332) µg/mL.

The half-life of daratumumab is both concentration and time dependent. After the first dose of 16 mg/kg of daratumumab, the observed half-life was 9±4 days. The model-derived half-life associated with linear elimination was approximately 18±9 days; this is the half-life that can be expected following repeat dosing of

daratumumab. Apparent steady state seems to be reached approximately 5 months into the every 4 weeks 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 (approximately 11 months of treatment in total).

As expected with subcutaneous administration, concentration-time curves following administration in all cohorts indicate a later T_{max} of approximately 72h post-dose, compared with IV administration when T_{max} occurs at or near the end of infusion. The range of C3D1 C_{trough} observations for the SC cohort is within the range observed following 16 mg/kg IV dosing, and the variability appeared to be similar for the daratumumab SC and 16 mg/kg IV cohorts. The observed C_{max} values from the daratumumab SC cohort is within the range observed for daratumumab 16 mg/kg IV.

Special Populations

Renal Impairment: The population PK analysis included 71 patients with normal renal function (creatinine clearance [CrCL] ≥90 mL/min), 78 patients with mild renal impairment (CrCL <90 and ≥60 mL/min), 68 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.

Hepatic Impairment: The population PK analysis included 189 patients with normal hepatic function (TB and AST ≤ULN) and 34 with mild hepatic impairment (TB 1.0× to 1.5× ULN or AST>ULN) patients. No clinical differences in the exposure to daratumumab were observed between patients with mild hepatic impairment and those with normal hepatic function. Daratumumab has not been studied in patients with moderate (TB>1.5× to 3× ULN and any AST) or severe (TB>3× ULN and any AST) hepatic impairment.

15.46 **Potential Drug Interactions**: No drug interaction studies have been performed.

15.47 **Known potential toxicities**:

Very common known potential toxicities, ≥ 10%:
Injury, poisoning, and procedural complications: infusion related reaction
Infections and infestations: pneumonia, upper respiratory tract infection, bronchitis, pneumonia
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, anemia, lymphopenia
Vascular disorders: hypertension
Nervous system disorders: headache, peripheral sensory neuropathy
Respiratory, thoracic, and mediastinal disorders: cough, dyspnea
Gastrointestinal disorders: nausea,vomiting, diarrhea
Musculoskeletal and connective tissue disorders: muscle spasms
General disorders and administration site conditions: fatigue, pyrexia, peripheral edema

Common known potential toxicities, 1% - <10%:
Injury, poisoning, and procedural complications: infusion related reaction

Infections and infestations: respiratory tract infection, influenza, lower respiratory tract infection, sepsis, sinusitis, rhinitis, pharyngitis, viral respiratory tract infection, 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
Gastrointestinal disorders: diarrhea

Uncommon and rare known potential toxicities, <1%:
Infections and infestations: metapneumovirus infection, tracheitis, acute sinusitis, bronchiolitis, epiglottitis, oropharyngeal candidiasis, tracheobronchitis, upper respiratory tract infection bacterial, bronchitis bacterial, respiratory syncytial virus infections, laryngitis, streptococcal pharyngitis, viral rhinitis
Blood and Lymphatic Disorders: neutropenic sepsis, neutropenic infection
Please refer to the Investigator Brochure for a more comprehensive list of treatment-emergent adverse events.

15.48 **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.

15.49 **Nursing Guidelines:**

- Daratumumab can cause severe infusion reactions, usually during the first infusion. Patients who have experienced 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.

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

- Patients may experience gastrointestinal side effects including diarrhea and nausea. Treat symptomatically and monitor for effectiveness.
- Warn patients about the possibility of peripheral neuropathy, dizziness, and insomnia.

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

- 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.

15.5 Dexamethasone commercial supply for Infusion Administration

15.51 Formulation and storage: Dexamethasone sodium phosphate is supplied as 4mg/ml IV solution in 5ml vials. Store intact vials at controlled room temperature, do not refrigerate. Protect from heat and light.

15.52 Preparation: The sterile solution from the vial may be further diluted in D5W or NS (refer to the treatment section of the protocol).

15.53 Stability: Refer to expiration date on the vial.

15.54 Administration: IV push or infusion (see treatment section of the protocol).

15.55 Known potential toxicities: 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.

15.56 Drug procurement: Commercially available from several commercial sources.

15.57 **Nursing guidelines:**

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

15.572 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.

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

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

15.575 Monitor blood glucose frequently.

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

15.577 Advise patient that easy bruising is a side effect.

16.0 Statistical Considerations and Methodology

16.1 Overview

This study is designed to assess the confirmed complete response rate with daratumumab added to ixazomib, lenalidomide and dexamethasone, when used as initial therapy in patients with previously untreated symptomatic MM using a one-stage binomial phase II study design in each arm. This study will include 2 treatment arms: Arm A (Dexamethasone cycles 1-12) and Arm B (Dexamethasone cycles 1-2 only).

16.11 Primary Endpoint

The primary endpoint in each arm of this trial is the confirmed complete response rate. A confirmed complete response is defined as objective status of CR or sCR that is maintained on two consecutive evaluations at least 2 weeks apart. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.12 Sample Size

The one-stage binomial design to be used in each arm is fully described below. A maximum of 36 evaluable patients will be accrued to each arm of this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 4 patients in each arm to account for ineligibility, cancellation, major treatment violation, or other reasons for a maximum of 40 patients accrued in each arm, and 80 patients overall.

16.13 Accrual Rate and Study Duration

The anticipated accrual rate is 3 evaluable multiple myeloma patients per month, translating to a duration of approximately one year for accrual in each arm. Accrual to Arm A will be completed before accrual is opened to Arm B. In each arm, the total duration before any results may be available is expected to be approximately 1.5 years from the date of activation for that arm, or until the last patient accrued to that arm has been observed for at least 6 months. The maximum total study duration is expected to be 5 years, or until the last patient accrued has been followed for 3 years.

16.2 Statistical Design (to be evaluated in each arm independently)

16.21 Decision Rule

In a prior phase I/II study of previously untreated multiple myeloma patients, the efficacy of a combination of ixazomib, lenalidomide and dexamethasone was evaluated.[14] A total of 53 patients were treated at the recommended phase II dose of 4.0 mg ixazomib, where a complete response rate of 27% was seen. This study will add daratumumab to the combination of ixazomib, lenalidomide and dexamethasone. An increase in complete response rate with this four-drug combination would be of interest.

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%.

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16.211 Final Decision Rule: Enter 36 evaluable patients into the study. If 12 or fewer successes are observed in the first 36 evaluable patients, we will consider this regimen ineffective in this patient population. 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.

16.212 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the final decision rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.313.

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

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

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

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. In each arm, it is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient in that arm has been followed for at least 6 months.

16.31 Primary Outcome Analyses (to be evaluated in each arm independently): :

16.311 Definition: The primary endpoint in each arm of this trial is the proportion of patients who achieve a confirmed complete response. A confirmed complete response is defined as an sCR or CR noted as the objective status on two consecutive evaluations at least two weeks apart. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.312 Estimation: The proportion of successes in each arm will be estimated by the number of successes divided by the total number of evaluable patients. An exact binomial 95% confidence interval for the true success proportion will be calculated.

16.313 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.

16.32 Secondary Outcome Analyses (to be evaluated in each arm independently)

16.321 The overall response rate will be estimated by the number of patients who achieve an sCR, CR, VGPR or PR divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportions will be calculated.

16.322 The rate of ≥ VGPR will be estimated by the number of patients with a VGPR, CR, or sCR divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportions will be calculated.

16.323 Overall survival is defined as the time from registration to death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier.[22]

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

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

16.33 Correlative Analyses: Due to the small overall sample size, the results of these analyses will be considered exploratory and hypothesis-generating in nature.

16.331 Minimal residual disease will be assessed on bone marrow aspirate in all patients achieving CR. The proportion of patients who achieve MRD negative status will be estimated by the number of patients who are MRD negative divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true MRD negative rate will be calculated.

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

16.4 Data & Safety Monitoring:

16.41 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

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

Accrual will be temporarily suspended to this study if at any time we observe events with an attribution of possibly, probably, or definitely related to study treatment that satisfy one of the following:

- if 5 or more patients in the first 13 treated patients experience a grade 4 or higher non-hematologic adverse event
- if after the first 13 patients have been treated, 40% of all patients experience a grade 4 or higher non-hematologic adverse event.

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.

16.5 Results Reporting on ClinicalTrials.gov:

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time all patients registered have achieved a confirmed complete response or have discontinued treatment without achieving a confirmed complete response.

16.6 Inclusion of Women and Minorities

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

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

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

16.631 Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	2	0	2
Not Hispanic or Latino	28	50	0	78
Ethnic Category: Total of all subjects*	28	52	0	**80**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	2	2	0	4
Native Hawaiian or other Pacific Islander	0	0	0	0
White	26	50	0	76
Racial Category: Total of all subjects*	28	52	0	**80**

Ethnic Categories:

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

Not Hispanic or Latino

Racial Categories:

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

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

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

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

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

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Event monitoring

See Section 4.2 and data submission table for the event monitoring schedule.

18.3 CRF completion for non-Mayo Clinic sites

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each co-sponsor/participant will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy. Supporting documentation for diagnosis will include either a pathology report or a laboratory report demonstrating multiple myeloma with extramedullary disease or plasma cell leukemia (including bone marrow biopsy report; and SPEP, UPEP, FLC, FISH, and Cytogenetics reports). These reports should be submitted within 14 days of registration.
For progression of disease prior to study entry, supporting documentation includes the evidence needed to determine the patient's progression prior to enrollment. These documents should be submitted within 14 days of registration.
For response to treatment, supporting documentation includes SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, and X-ray skeletal survey.
For patients who progress after study therapy supporting documentation may include any of the following: SPEP, UPEP, FLC, serum and urine immunofixation, bone marrow biopsy and aspirate, and X-ray skeletal survey.

18.6 Labelling of materials

Each participant will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.8 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.9 Corrections forms

If a correction is necessary the QAS will query the co-sponsor/participant. The query will be sent to the appropriate co-sponsor/participant who will make the correction and return the query and documentation of correction back to the QAS.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: None

19.3 Other budget concerns: None

20.0 References

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Appendix I Multiple Myeloma Diagnostic Criteria

Clonal BMPC ≥10% or biopsy-proven plasmacytoma PLUS

***-Either a myeloma defining event*:**

C: Hypercalcemia: serum calcium >1 mg/dL higher than the upper limit of normal or >11 mg/dL

R: Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >2 mg/dL

A: Anemia: hemoglobin >20 g/L below the lower limit of normal, or a hemoglobin <100 g/L

B: Bone lesions: osteolytic lesions on x-ray, CT, or PET-CT

-OR a biomarker of early progression

- Clonal bone marrow plasma cell percentagen≥60%
- Involved: uninvolved serum free light chain ratio ≥100
- >1 focal lesion on MRI studies

Appendix II Mayo Risk Stratification (mSMART)

High Risk

FISH deletion 17p

FISH t(4:14)

FISH t(14:16)

Hypodiploidy

PCLI >3%

Standard Risk

Not high risk as defined above

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 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 V Revlimid REMS Required Pregnancy Information

Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods
Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.
Females of childbearing potential (FCBP)[†] must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Before starting study drug:
Female Subjects:

- FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10-14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure..
- Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure,
- Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

During study participation and for 28 days following discontinuation from the study:
All Subjects:

[†] A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.
- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, .

Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

- Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen, .

Appendix VI PATIENT MEDICATION DIARY FOR ARM A

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

Please swallow the ixazomib capsules whole, with water, and not to break, chew, or open the capsules. They should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

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

Week of: _____

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

Week of: _____

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

Week of: _____

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

Week of: _____

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

Patient signature: _____
Date:_____

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

Appendix VI PATIENT MEDICATION DIARY FOR ARM A (Maintenance)

Please complete this diary on a daily basis. Write in the amount of the dose of ixazomib that you took in the appropriate "Day" box.

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

Please swallow the ixazomib capsules whole, with water, and not to break, chew, or open the capsules. They should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

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

Week of: _____

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

Week of: _____

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

Week of: _____

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

Week of: _____

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

Patient signature: _____
Date:_____

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

PATIENT MEDICATION DIARY FOR ARM B (Cycles 1 & 2)

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

Please swallow the ixazomib capsules whole, with water, and not to break, chew, or open the capsules. They should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

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

Dexamethasone will be taken for cycles 1 and 2 only (unless your doctor instructs you otherwise)

Week of: _____

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

Week of: _____

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

Week of: _____

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

Week of: _____

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

Patient signature: _____
Date: _____

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

PATIENT MEDICATION DIARY FOR ARM B (Cycles 3 and beyond)

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

Please swallow the ixazomib capsules whole, with water, and not to break, chew, or open the capsules. They should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

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

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Lenalidomide							
Ixazomib							

Week of: _____

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

Week of: _____

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

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Lenalidomide							
Ixazomib							

Patient signature: _____
Date: _____

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

PATIENT MEDICATION DIARY (Cycles 13 and beyond)

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

Please swallow the ixazomib capsules whole, with water, and not to break, chew, or open the capsules. They should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

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

Week of: _____

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

Week of: _____

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

Week of: _____

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

Week of: _____

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

Patient signature: _____

Date:_____

My next scheduled visit is: _____

If you have any questions, please call: _____

Appendix VII FACT/GOG NTX (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

Appencix VIII – Patient Information Sheet

Patient Completed Booklet

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

1. This booklet contains one set of questions:
   FACT GOG NTX (Version 4) Questionnaire (38 questions)

2. Please select one answer for each question.

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

Thank you for taking the time to help us.