

line of therapy	1 or more cycles of a planned treatment program; this may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by ASCT, followed by maintenance is considered 1 line of therapy) [1]. Typically, each line of therapy is separated by PD. Discussion with the medical monitor may help clarify the number of prior lines of therapy for each prospective study participant.
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NSAIDs	nonsteroidal anti-inflammatory drugs
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
pom+dex	pomalidomide+dexamethasone (control study therapy; given in Arm B)
PP	per-protocol
PR	partial response
QOL	quality of life
REMS	Risk Evaluation and Mitigation Strategies
RRAL	relapsed and/or refractory systemic light-chain amyloidosis
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SPEP	serum protein electrophoresis
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TMA	thrombotic microangiopathy
TTP	time to progression
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VD	bortezomib with dexamethasone
VGPR	very good partial response

[55], or death from any cause, whichever occurs first.

### **5.2.2 Secondary Endpoints**

Secondary endpoints are:

- OS, measured as the time from randomization to death from any cause.
- ORR, defined as PR, very good partial response (VGPR), or complete response (CR), as evaluated by the investigator, according to IMWG criteria [55].
- Duration of response, defined as the time from the first documentation of PR or better to first documentation of PD.
- Time to response, defined as the time from randomization to the first documentation of PR or better.
- TTP, defined as the time from randomization to first documentation of PD.
- Health-related QOL as measured by the physical functioning domain of the EORTC QLQ-C30.
- Health-related QOL as measured by other domains of the EORTC QLQ-C30, by the EORTC QLQ-MY20, and by the EQ-5D-5L.
- HU as measured by the number and duration of medical encounters.

### **5.2.3 Safety Endpoint**

The safety endpoint is the safety/tolerability of ixa+dex versus pom+dex.

### **5.2.4 Exploratory Endpoint**

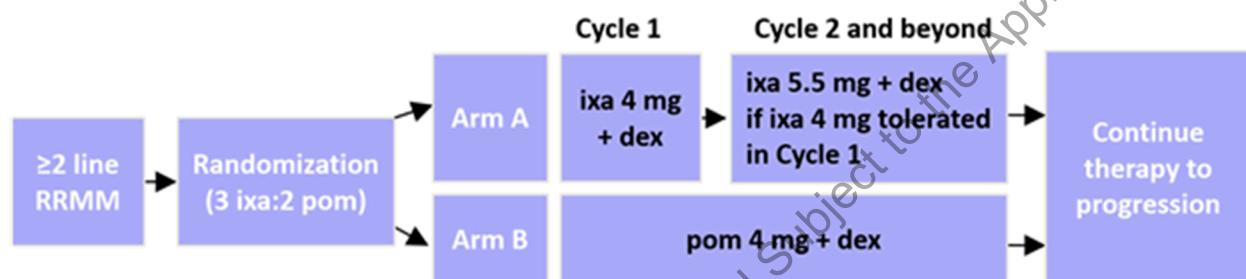


## 6.0 STUDY DESIGN

### 6.1 Overview of Study Design

This is a prospective open-label, randomized, 2-arm, multicenter phase 2 study of patients with RRMM who have received at least 2 prior lines of therapy. Eligible patients will be randomized to receive ixa+dex (Arm A) or pom+dex (Arm B) in a 3:2 ratio via interactive response technology (IRT). The study design is illustrated in [Figure 6.a](#).

**Figure 6.a Study Schema, From Randomization Through End of Therapy**



Ixa=ixazomib; pom=pomalidomide; RRMM=relapsed and/or refractory multiple myeloma.

Note: There are 3 stratification factors in the study: International Staging System stage (I or II vs III at study entry), prior lines of therapy (2 vs 3 or more), and age (<65 vs ≥65 years).

#### 6.1.1 Study Population

The patient population will consist of adult patients (aged ≥18 years) who have an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2; who have been diagnosed with MM according to IMWG criteria [55]; and who have measurable disease and documentable isotype. All patients must have had a relapse or PD after having received 2 or more prior lines of systemic therapy. (A line of therapy is defined as 1 or more cycles of a planned treatment program; this may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous SCT, followed by maintenance is considered 1 line of therapy [1]. Typically, each line of therapy is separated by PD. Discussion with the medical monitor may help clarify the number of prior lines of therapy for each prospective study participant.)

1. All patients must be refractory to lenalidomide, defined as having received at least 2 consecutive cycles of lenalidomide as a single agent or within a lenalidomide-containing regimen and having had PD during treatment with or within 60 days after the last dose of lenalidomide. The starting dose of lenalidomide should have been 25 mg (or as low as 10 mg in the case of renal function impairment or other safety concern), and the final dose should have been a minimum of 10 mg. In addition, all patients must have received at least 2 consecutive cycles of a bortezomib- or carfilzomib-containing regimen. Further, all patients must not be refractory to proteasome inhibitors (ie, must have achieved at least a PR and not have had PD during treatment with or within 60 days after the last dose of bortezomib or carfilzomib) or

have bortezomib and/or carfilzomib intolerance (ie, must have discontinued because of drug-related AEs before completion of the planned treatment course) without PD before the start of the next regimen. A Millennium project clinician or designee will confirm patient eligibility before randomization by the investigator.

2. Patients with a prior allogenic bone marrow transplantation in any prior line of therapy are excluded. Patients with a prior autologous SCT in the last prior line of therapy are excluded, unless the autologous SCT was done a year or more before disease progression. Exclusion of patients on this basis aims not to interfere with the immune profiling endpoint.

The 3 stratification factors that will be used are ISS stage (I or II vs III) at study entry, prior lines of therapy (2 vs 3 or more), and age (<65 vs  $\geq$ 65 years).

### **6.1.2 Study Therapy Dosing**

Patients randomized to Arm A will receive oral ixazomib on Days 1, 8, and 15 of every 28-day cycle, as well as 20 mg oral dexamethasone (or 10 mg if patient is aged  $\geq$ 75 years) on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every 28-day cycle. In cases where only 4 mg tablets for dexamethasone are available (eg, 4 mg dexamethasone is the only dosage available), the following dexamethasone schedule is recommended for patients aged  $\geq$ 75 years: 12 mg dexamethasone will be given on Days 1, 8, 15, and 22 of every 28-day cycle; and 8 mg dexamethasone will be given on Days 2, 9, 16, and 23 of every 28-day cycle.

For Cycle 1, all patients will receive a starting dose of 4 mg of ixazomib. Patients who do not experience any new Grade 1 peripheral neuropathy with pain or other ixazomib-related Grade  $\geq$ 2 nonhematologic or Grade  $\geq$ 3 neutropenia or thrombocytopenia in Cycle 1 will dose escalate to 5.5 mg of ixazomib on the same schedule at the start of Cycle 2. Patients who have had any dose reductions, holds, or delays because of ixazomib toxicities will not dose escalate. Dose escalation beyond the start of Cycle 2 is permitted only when dose escalation was inadvertently missed at Cycle 2 and will require consultation with a Millennium project clinician or designee.

Patients randomized to Arm B will receive oral pomalidomide at a dose of 4 mg daily on Days 1 to 21 of each 28-day cycle, as well as 40 mg oral dexamethasone (or 20 mg if patient is aged  $\geq$ 75 years) on Days 1, 8, 15, and 22 of each 28-day cycle until PD.

Neither pomalidomide nor dexamethasone will be dose escalated in this study.

### **6.1.3 Study Assessments**

Section 9.4 provides more information on study procedures, and [Appendix A](#) contains the detailed, updated Schedule of Events for this study (the previous, full Schedule of Events is now moved to [Appendix L](#) for reference only).

Only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. As no further formal statistical analyses will be performed, only assessments contributing to long-term safety data are required. Most study assessments besides safety are discontinued to ease the burden of protocol-mandated assessments on patients.

Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib or pomalidomide, as well as dexamethasone, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care.

Upon implementation of Amendment 06, data collection requirements will be limited to collection of AEs and SAEs. All other study assessments are no longer required. All central laboratory assessments are discontinued. Quality of life and HU assessments are discontinued. Patients will not be followed for the PFS or OS follow-up periods, because PFS and OS data are no longer being collected. See the updated Schedule of Events in [Appendix A](#) (the previous, full Schedule of Events is now moved to [Appendix L](#) for reference only).

#### *6.1.3.1 Assessments During the Treatment Period*

##### Assessments Effective Only Before Amendment 06

Patients will have study assessments performed at regular intervals while they are participating in the study: weekly (Days 1 and 15) for 2 cycles and then once a cycle (on Day 1) for the remainder of the Treatment period, until PD or discontinuation. In addition, in Arm B only, on Day 8 and Day 22 of Cycles 1 and 2, hematologic laboratory assessments will be performed. Patients will receive study therapy until documented, confirmed PD (on the basis of the IMWG criteria), intolerable toxicities, withdrawal of consent, or sponsor termination of study, whichever comes first.

Patients will be assessed for disease response and progression, according to the IMWG criteria by the investigator, for the purpose of treatment decisions, at every cycle during the Treatment period. ECOG performance score and AEs will be assessed, and laboratory values and vital signs will be obtained to evaluate the safety and tolerability of the study therapy. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010. Clinical, laboratory, response, and QOL data, with an emphasis on tolerability and symptom burden, will be collected.

QOL assessments will be collected at Screening. QOL and HU assessments will be collected on Day 1 of every treatment cycle and at the EOT visit (as well as during the PFS Follow-up period and, for EQ-5D-5L only, the OS Follow-up period; see next section). QOL and HU assessments should be completed on the same day as the study visit, before any other study procedures are performed or study therapy is administered.

##### Assessments Still in Effect as of Amendment 06

Unscheduled visits may occur between treatment cycles as required. For example, symptomatic pain progression should result in an interim unscheduled visit, as would ongoing Grade 3 or worse AEs.

Patients will attend an EOT visit 30 days (+1 week) after receiving their last dose of study therapy or prior to the start of a new line of anti-myeloma treatment, should that line start within 30 days of the last dose. In the event a patient withdraws consent or has a death prior to the EOT visit, the last

date of contact with the patient will be utilized as the EOT visit date. AEs/SAEs will be monitored for all patients up to 30 days after administration of the last dose of study therapy regardless of whether a patient starts a new line of therapy.

Note: Related SAEs occurring during follow-up periods after the EOT visit must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study therapy that occur during posttreatment follow-up. In addition, new primary malignancies that occur during follow-up periods, irrespective of causality to study therapy, must be reported to the Global Pharmacovigilance department or designee. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

#### *6.1.3.2 Assessments During the Follow-up Periods: PFS and OS*

The following section describes the study design before Amendment 06 was implemented and is no longer relevant after that time but is retained below for reference only.

After a patient completes the EOT visit or a patient discontinues study therapy before confirmed PD, he/she will enter either a PFS or OS follow-up period ([Figure 6.b](#)). Information about any new primary malignancies will be collected during the study, including during both follow-up periods.

Patients who have stopped treatment for any reason other than PD will enter the PFS Follow-up period. Patients who have PD while on study therapy will skip the PFS Follow-up period and will enter directly into the OS Follow-up period. Patients in the PFS Follow-up period who have PD or start subsequent anticancer therapy during this follow-up period will end PFS Follow-up and will enter into the OS Follow-up period.

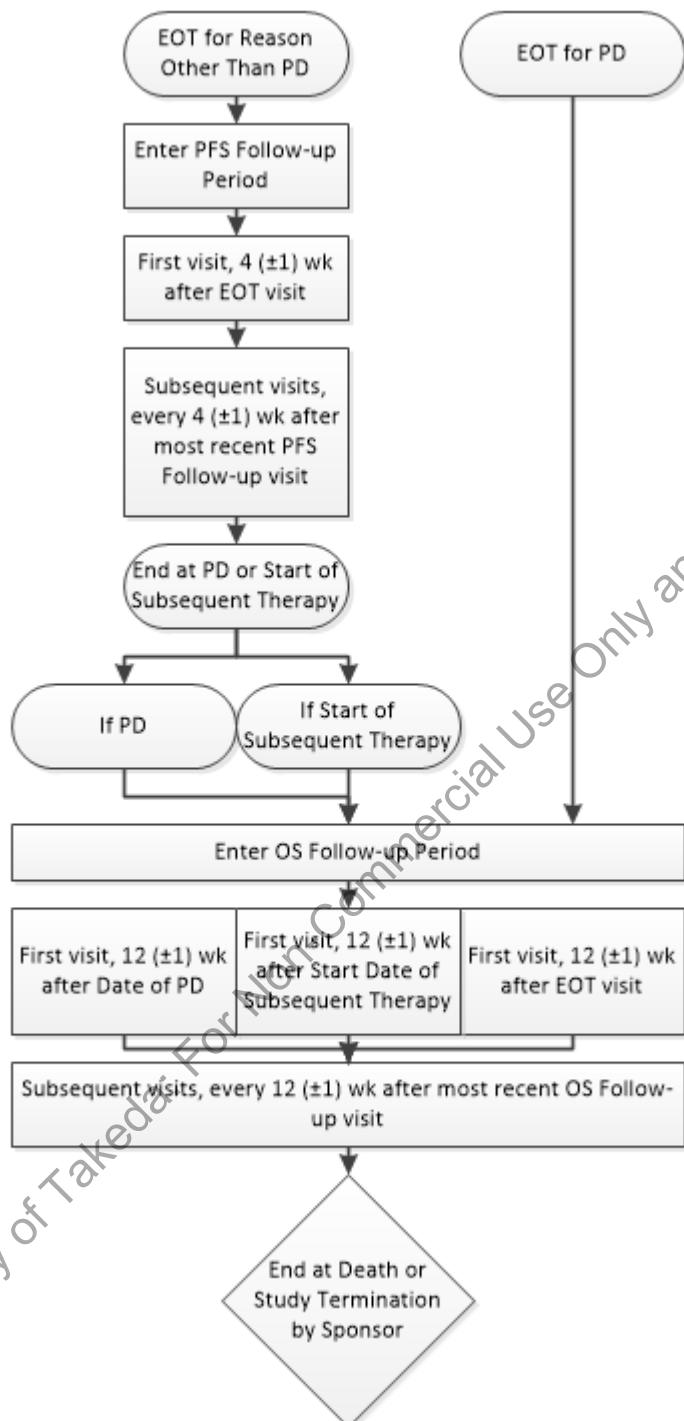
[Figure 6.b](#) provides more detail about both follow-up periods.

QOL and HU assessments will be collected during the PFS Follow-up period at every PFS Follow-up visit. QOL and HU assessments should be completed on the same day as the follow-up visit, before any other study procedures are performed.

The only QOL assessment collected during the OS Follow-up period is the EQ-5D-5L assessment. This assessment will be collected during the OS Follow-up period at every OS Follow-up visit. The assessment should be completed on the same day as the follow-up visit, before any other study procedures are performed.

All assessments during the OS Follow-up period (including the EQ-5D-5L) may be made over the telephone by trained site staff and do not require a clinic visit. Data may be collected by methods that include, but are not limited to, telephone, email, mail, and social security indexes. Both the patient and the current treating physician will be contacted during the OS Follow-up period to provide information about all MM treatments (best response, date of progression, drug regimen, start/stop date).

**Figure 6.b Flow of Patients Through Follow-up Periods After the EOT Visit (Only in Effect Before Amendment 06)**



**Table 6.a Primary and Secondary Endpoints for Disclosures**

<b>Endpoint</b>	<b>Definition</b>	<b>Maximum Time Frame</b>
Primary: PFS	The time from randomization to the first occurrence of confirmed PD, as evaluated by the investigator, according to IMWG criteria [55], or death from any cause, whichever occurs first	Up to 4 years
Secondary: OS	The time from randomization to death from any cause	Up to 4 years
Secondary: ORR	PR, VGPR, or CR, as evaluated by the investigator, according to IMWG criteria	Up to 4 years
Secondary: Duration of response	The time from the first documentation of PR or better to first documentation of PD	Up to 4 years
Secondary: Time to response	The time from randomization to the first documentation of PR or better	Up to 4 years
Secondary: TTP	The time from randomization to first documentation of PD	Up to 4 years
Secondary: Health-related QOL related to physical functioning	The physical functioning domain of the EORTC QLQ-C30	Up to 4 years
Secondary: Other health-related QOL	Health-related QOL as measured by other domains of the EORTC QLQ-C30, by the EORTC QLQ-MY20, and by the 5-level classification system of the EQ-5D-5L	Up to 4 years
Secondary: Health care utilization (HU)	HU as measured by the number and duration of medical encounters	Up to 4 years

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EORTC QLQ-MY20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–multiple myeloma module; IMWG: International Myeloma Working Group; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; TTP: time to progression; QOL: quality of life.

### **6.3.4 Total Study Duration**

It is anticipated that this study will last for approximately 28 months. However, the study duration is dependent on rate of accrual and of maturation of the different endpoints.

### **Nausea or Vomiting**

Prophylaxis with standard antiemetics, including serotonin 5-hydroxytryptamine 3 receptor antagonists, is recommended for emesis. In addition, it is recommended that the dexamethasone dose be administered at least 2 hours before ixazomib to maximize the potential antiemetic effect (see Section 8.3). Any fluid deficit occurring during treatment should be promptly corrected.

### **Diarrhea**

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Any fluid deficit occurring during treatment should be promptly corrected.

### **Erythematous Rash With or Without Pruritus**

Rash may range from limited erythematous areas, macular 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 predominantly 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 and self-limiting and is typically Grade 1 or 2 in severity. If rash occurs, consideration should be given to alternate causes of the rash such as concomitant medications, infections, etc.

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

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

The rare risks of Stevens-Johnson syndrome, TEN, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and pemphigus vulgaris have been reported in oncology studies when ixazomib (or placebo) was given with concomitant medications that are known to cause rash (eg, Bactrim, lenalidomide, aspirin), and/or in the setting of confounding treatment-emergent adverse events (TEAEs). These severe, potentially life-threatening or deadly conditions may involve rash with skin peeling and mouth sores and should be clinically managed according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator. Additional information regarding these reactions can be found in the IB.

### **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

#### *9.4.10.1 QOL*

The patient-reported health-related QOL will be directly self-reported by patients on paper versions of the EORTC QLQ-C30 ([Appendix H](#)), EORTC QLQ-MY20 ([Appendix I](#)), and EQ-5D-5L ([Appendix J](#)), at multiple points throughout the study: at the Screening visit, on Day 1 visits of every cycle during the Treatment period, at the EOT visit, and at the PFS Follow-up visits, every 4 ( $\pm 1$ ) weeks during the PFS Follow-up period (see the previous, full Schedule of Events in [Appendix L](#)). Upon implementation of Amendment 06, PRO and PFS data will no longer be collected.

The EQ-5D-5L will also be assessed at the OS Follow-up visits, every 12 ( $\pm 1$ ) weeks during the OS Follow-up period; however, if a patient is unable to attend a study visit during the OS Follow-up period, EQ-5D-5L assessments may be collected from the patients via a telephone interview by trained site staff, who record the patient's responses on the patient's behalf. Upon implementation of Amendment 06, PRO and OS data will no longer be collected.

#### *EORTC QLQ-C30*

Cancer-specific health-related QOL will be assessed using the EORTC QLQ-C30 [[59](#)] ([Appendix H](#)). The EORTC QLQ-C30 contains 30 items across 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties) and a global health status/QOL scale. Most of the 30 items have 4 response levels (not at all, a little, quite a bit, and very much), with 2 questions relying on a 7-point numeric rating scale. Raw scores are converted into scale scores ranging from 0 to 100. For the functional subscales and the global health status/QOL subscale, higher scores represent better QOL; for the symptom subscales, lower scores represent better QOL.

The physical functioning domain of EORTC QLQ-C30 consists of 5 items covering the patient's daily physical activities. It has been validated to measure physical activity changes in patients with MM [[60,61](#)]. Because of the relevance of physical function in MM, the physical functioning domain of EORTC QLQ-C30 has been used as a primary endpoint in some MM studies [[61](#)].

Upon implementation of Amendment 06, PRO data will no longer be collected.

#### *EORTC QLQ-MY20*

The EORTC QLQ-MY20 is an MM disease-specific 20-item questionnaire module, designed to assess the QOL of MM patients with EORTC QLQ-C30. The 20 items are across 2 functional subscales and 2 symptom subscales ([Appendix I](#)). The EORTC QLQ-MY20 has also been validated and used in clinical studies of MM and has been demonstrated to have excellent measurement properties (validity, reliability, responsiveness).

Raw scores are converted into scale scores ranging from 0 to 100. For the functional subscales, higher scores represent better QOL; for the symptom subscales, lower scores represent better QOL.

Upon implementation of Amendment 06, PRO data will no longer be collected.

CCI

use

child  
cle 1  
table  
y test  
sults  
sing  
ring  
we  
ne ter  
before  
durin

y Ev  
y tes  
rep

ache  
Dav  
ay b  
on D  
at C  
ays  
cyc'



Table 9.b will be obtained and recorded in the eCRFs as specified in the updated Schedule of Events (Appendix A). (For the previous, full Schedule of Events, see Appendix L.)

**Table 9.b Clinical Chemistry and Hematology Tests**

Hematology	Serum Chemistry
Hemoglobin	Albumin
Leukocytes with differential	Alkaline phosphatase
Neutrophils ANC	Alanine aminotransferase
Platelet (count)	Aspartate aminotransferase
	$\beta$ 2-microglobulin (at Screening only)
	Bilirubin (total)
	Blood urea nitrogen
	Calcium
	Creatinine
	Gamma glutamyl transferase
	Lactate dehydrogenase (at Screening only)
	Magnesium
	Potassium
	Urate
	C-reactive protein

**CCI**

Quantification of B cells, T cells, and natural killer cells  
Measles  
Varicella-zoster virus  
Tetanus

If creatinine clearance is to be estimated, the Cockcroft-Gault formula will be employed as follows:

**Estimated creatinine clearance**

$$= [(140 - \text{Age}) \times \text{Weight (kg)}] / [72 \times \text{serum creatinine(mg/dL)}]$$

For female patients, the result of the formula above should be multiplied by 0.85.

#### 9.4.15.2 Clinical Laboratory Evaluations for Disease Assessments

Upon implementation of Amendment 06, all central laboratory assessments are no longer required. See the updated Schedule of Events (Appendix A) for more information.

A blood sample will be collected during Screening for measurement of serum  $\beta_2$ -microglobulin and albumin for determination of disease stage according to the ISS; these results will be analyzed centrally and recorded on the eCRF.

Clinical laboratory evaluations for disease assessments (serum protein electrophoresis [SPEP], urine protein electrophoresis [UPEP], serum free light chain, immunofixation, and immunoglobulin) must be sent to the central laboratory for evaluation.

Immunofixation will also be done to confirm CR. Undetectable M-protein by protein electrophoresis in both serum and urine will lead the central laboratory to perform immunofixation testing in both serum and urine. Blood samples for IgM, IgG, and IgA will be obtained at Screening and throughout the study at the time points specified in the as indicated in the previous, full Schedule of Events ([Appendix L](#)). Note that 24-hour urine collection is permitted before Screening if it is part of standard clinical practice at the site. Quantitative IgD and IgE will be done at Screening (and Baseline if needed) only. For the rare patient with documented IgD or IgE MM, the quantitative test for that antibody will be followed at the same time points as IgG and IgA.

Bone marrow aspirate or biopsy disease assessment is to be performed at a local laboratory to assess disease status at Screening and will be repeated if the patient is considered possibly to have resolution of serum and urine M-protein consistent with CR or to investigate suspected PD. A clinically indicated bone marrow aspirate or biopsy drawn prior to consent is acceptable for the Baseline assessment provided that it is collected within 42 days before the first dose.

#### **9.4.16 AEs**

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events ([Appendix A](#)). Refer to Section [10.0](#) for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

When peripheral neuropathy occurs, each subsequent monthly evaluation will record the grade of peripheral neuropathy at that visit. (This is in contrast to other AEs where only increases in grade are recorded until the maximum grade is reached and then followed at that grade until complete resolution or return to Baseline.) Peripheral neuropathy will be followed monthly until:

- 1) resolution of peripheral neuropathy, 2) the start of a second-line alternative antineoplastic treatment, or 3) 6 months after PD has occurred, whichever occurs first.

#### **9.4.17 Concomitant Medications and Procedures**

Concomitant medications and therapeutic procedures will be recorded in the eCRFs as specified in the Schedule of Events ([Appendix A](#)). See Section [8.5](#) and Section [8.6](#) for a list of medications and therapies that are prohibited and allowed, respectively, during the study.

#### **9.4.18 PK Samples and Measurements**

PK data will be collected in Arm A (ixa+dex) only, as indicated Table A of the previous, full Schedule of Events ([Appendix L](#)). Plasma concentrations of ixazomib (the complete hydrolysis product of ixazomib citrate) will be measured using a validated liquid chromatography

tandem-mass spectrometry assay. Details regarding the preparation, handling, and shipping of the PK samples are provided in the Study Manual. Blood samples (3 mL) for the determination of plasma concentrations of ixazomib (the complete hydrolysis product of ixazomib citrate) will be collected during Cycles 1 through 4. The exact date and time of each PK sample collection should be recorded in the source documents and eCRF.

Upon implementation of Amendment 06, PK sample collection will be considered complete and no additional PK samples will be collected or quantified.

### **9.5 Completion of Study Treatment (for Individual Patients)**

Patients will be considered to have completed study treatment if they experience PD, discontinue treatment because of unacceptable toxicity, or withdraw consent for any reason. Before an investigator discontinues a patient from treatment for PD, the pertinent data must be confirmed by a Millennium project clinician or designee. Patients will attend an EOT visit 30 days (+1 week) after receiving their last dose of study therapy or prior to the start of a new line of anti-myeloma treatment. In the event a patient withdraws consent or has a death prior to the EOT visit, the last date of contact with the patient will be utilized as the EOT visit date. AEs/SAEs will be monitored for all patients up to 30 days post last study drug dose regardless if a patient starts a new line of therapy. Patients will continue to be followed for other follow-up assessments specified in Section 6.1.3.2. Also refer to the updated Schedule of Events ([Appendix A](#)) for EOT visit assessments.

Upon implementation of Amendment 06, only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib or pomalidomide, as well as dexamethasone, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care. The reason for treatment discontinuation must be recorded in the eCRF but no approval is required.

### **9.6 Completion of Study (for Individual Patients)**

Patients will be considered to have completed the study when the analysis for the study (PFS and secondary endpoints) is completed or when the sponsor terminates the study. The study will be considered complete after the study analysis is completed or the study has been terminated (see Section 9.9).

### **9.7 Discontinuation of Treatment With Study Therapy**

Study therapy must be permanently discontinued for patients who become pregnant.

Treatment with study therapy may also be discontinued for any of the following reasons:

- AE.
- Protocol deviation.

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.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [62]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm<sup>3</sup> to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

## **10.2 Procedures for Recording and Reporting AEs and SAEs**

All AEs 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 will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). 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 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

The paper SAE forms should be submitted via fax (see fax numbers below) within 24 hours of awareness. In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day. Email submission of paper SAE forms with a PDF attachment should only be used in the case where fax is not possible within 24 hours of receiving the event. In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day. If SAEs are reported via fax or by email, the EDC application must be updated as soon as possible with the appropriate information.

<b>NINLARO</b> <b>(ixazomib)</b>	<b>CCI</b>				<b>AX</b>
-------------------------------------	------------	--	--	--	-----------

Product complaints or medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, an SAE Form should be completed and sent to [redacted] (refer to Section 10.2).

## **10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities**

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

Time to response is defined as the time from randomization to the first documentation of PR or better. Time to response will be summarized descriptively.

TTP is defined as the time from randomization to the date of first documented PD. Patients without documentation of PD at the time of analysis will be censored at the date of the last response assessment. TTP will be analyzed on the basis of the ITT population using methods similar to those used for PFS.

#### **13.1.4 PK Analysis**

PK data collected in this study may contribute to population PK and exposure/response (safety and efficacy) analyses. These analyses may include data from other ixazomib clinical studies and will be separately developed and reported.

#### **13.1.5 QOL and HU Analyses**

Analyses of patient-reported QOL outcomes will be performed for patients with data at baseline and at least 1 postbaseline measurement. Analyses of HU will be performed for the ITT population.

The QOL analyses will be completed for all subscales, but particular emphasis will be placed on the Physical Functioning subscale. The main health-related QOL endpoint is time to maintained deterioration of Physical Functioning domain scores from the EORTC QLQ-C30, based on a minimally important difference of 10 (primary analysis) [63-65] and 5 (sensitivity analysis) [66]. The summary and subscale scores of EORTC QLQ-C30 and subscale scores of QLQ-MY20 will also be analyzed. Specifically, the actual value and change from baseline scores will be summarized using descriptive statistics by treatment group over time. The change from baseline on summary and subscale scores may also be analyzed using linear mixed models by incorporating the measurements across different time points. Additionally, the number and percentages of patients showing a clinically meaningful change from baseline will be summarized by treatment group over time. Questionnaire compliance will also be summarized.

Published manuals/guidance for these questionnaires will be used for scoring and handling of missing data. Sensitivity analyses may be conducted to study the impact of missing data.

EQ-5D-5L item scores and visual analogue scale (VAS) scores will be summarized using descriptive statistics by treatment group over time.

HU as measured by hospitalizations, emergency room visits, non-protocol-directed outpatient visits, and missed days of work by patients and/or caregivers will be summarized using descriptive statistics by treatment group.

#### **13.1.6 Safety Analysis**

All available safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

## **14.0 QUALITY CONTROL AND QUALITY ASSURANCE**

### **14.1 Study-Site Monitoring Visits**

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC. The CRO may also monitor the site remotely as described in the Monitoring Plan.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by applicable local regulations and permitted by the IRB/IEC.

### **14.2 Protocol Deviations**

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and the protocol.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form or equivalent form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The procedure below applies to Japanese sites only.

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal

investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained. The investigator should document all protocol deviations.

#### **14.3 Quality Assurance Audits and Regulatory Agency Inspections**

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

## **7.0 STUDY POPULATION**

### **7.1 Inclusion Criteria**

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

1. Male or female patients aged 18 years or older.
2. Must have a confirmed diagnosis of MM requiring therapy according to IMWG criteria (see [Appendix D](#)).
3. ECOG performance status of 0 to 2 (see [Appendix E](#)).
4. Must have had a relapse or PD after having received 2 or more prior lines of systemic therapy.  
Note: A line of therapy is defined as 1 or more cycles of a planned treatment program; this may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous SCT, followed by maintenance is considered 1 line of therapy [1]. Typically, each line of therapy is separated by PD. Discussion with the medical monitor may help clarify the number of lines of therapy that a prospective study participant had.
5. Must be refractory to lenalidomide, defined as having received at least 2 consecutive cycles of lenalidomide as a single agent or within a lenalidomide-containing regimen and having had PD during treatment with or within 60 days after the last dose of lenalidomide. The starting dose of lenalidomide should have been 25 mg (or as low as 10 mg in the case of renal function impairment or other safety concern), and the final dose should have been a minimum of 10 mg.
6. Must have received at least 2 consecutive cycles of a bortezomib- or carfilzomib-containing regimen, and either:
  - Achieved at least a PR and did not have PD during treatment with or within 60 days after the last dose of bortezomib or carfilzomib, OR
  - Had bortezomib and/or carfilzomib intolerance (defined as discontinuation because of drug-related AEs before completion of the planned treatment course) without PD before the start of the next regimen.
7. Patients must have measurable disease defined by:
  - Serum M-protein  $\geq 1$  g/dL ( $\geq 10$  g/L), OR  
Urine M-protein  $\geq 200$  mg/24 hours and must have documented MM isotype by immunofixation (central laboratory).
8. Patients must meet all of the following clinical laboratory criteria:
  - Absolute neutrophil count (ANC)  $\geq 1000/\text{mm}^3$  and platelet count  $\geq 75,000/\text{mm}^3$ , without growth factor or transfusion support.
  - Total bilirubin  $\leq 1.5$  times the upper limit of normal (ULN).

Study Procedures	Treatment Period (a) Cycle X and Beyond, Day 1 of Each 28-day Cycle	EOT 30 Days After Last Dose or Before Start of New Line of Treatment
	Window, $\pm$ 1 week	Window, + 1 week
Concomitant medications/procedures	Recorded from the signing of informed consent form through 30 days after last dose of study therapy	
NPM assessment	Continuous from start of study therapy administration until death or termination of study by sponsor	

NPM: new primary malignancy; PI: package insert.

Follow this Schedule of Events at the start of the next full treatment cycle upon implementation of Amendment 06. Patients who do not continue treatment must complete the End of Treatment assessments, which should occur 30 days (+1 week) after the last dose of study drug or prior to the initiation of subsequent antineoplastic therapy, whichever comes first.

- (a) Tests and procedures should be performed on schedule, within a 1-week window for Day 1 of each cycle. Unless otherwise specified, occasional changes are allowable within an additional 2-day window for holidays, vacations, and other administrative reasons. If a visit or procedure cannot be performed within the window, then the Millennium project clinician or designee should be consulted. If the study schedule is shifted, assessments should be shifted to be aligned with the new schedule. Note that, except for hematology and chemistry laboratory samples (see footnote f below), all required tests and procedures for a specific visit should be done on the same day as the study visit.
- (b) Before dosing on Day 1 of the next full treatment cycle upon implementation of Amendment 06, patients must be reconsented. Reconsenting should be done in person. Remote reconsenting is permitted as long as the process adheres to site, IRB/IEC, and GCP standards and local regulations.
- (c) Patients should be assessed and treated according to local standard of care. Collect and record only clinically significant findings as AEs in the eCRF.
- (d) Alternative methods for administering study procedures/assessments may be considered when it is not possible for the patient to come to the study site due to extenuating circumstances (eg, due to the COVID-19 pandemic). Alternative methods should be considered for performing the assessments by other means than the patient presenting to the clinic (eg, remote assessment, having laboratory assessment performed at a facility closer to the patient's home). If any of the following study procedures/assessments is missed because a site visit is done remotely, the study procedure/assessment is waived: symptom-directed physical examination, hematology, clinical chemistry.
- (e) In Arm A, 3 serum pregnancy tests must be performed for women of childbearing potential. The Cycle 1 Day 1 pregnancy test may be collected up to 3 days before dosing and results must be available and negative before dosing. In Arm B, for women of childbearing potential, 2 pregnancy tests (with 1 or both being a serum test) must be performed before starting pom+dex and results must be available and negative before dosing—the first within 10 to 14 days before dosing and the second within 24 hours before dosing. Then testing must be performed weekly during the first month and monthly thereafter in women with regular menstrual cycles, or every 2 weeks (at Day 15) in women with irregular menstrual cycles. In Arm B at the EOT visit, the test must be a serum pregnancy test. The results of each test must be available and negative before the study therapy is administered. Pregnancy tests may also be repeated during the study upon request by IECs/IRBs or if required by local regulations.
- (f) Hematology and chemistry laboratory samples will be collected locally and may be collected up to 3 days before Day 1 of each cycle or prior to dosing on Day 1. For Cycles 1 and 2 in both arms, the laboratory samples may be collected 24 hours prior to dosing on Day 15 or before dosing on Day 15. In addition, for Arm

**CONFIDENTIAL**

**Previous Schedule of Events (continued)**

Study Procedures	Screening	Treatment Period (a)										EOT (b)	Follow-up (c)	
		28-Day Cycles											PFS	OS
Cycle			C1		C2 (d)			C3	C4 and Beyond		30 days after last dose or before start of new line of treatment	Every 4 wk, Until PD or Subsequent Therapy	Every 12 wk, After PD or Subsequent Therapy	
Days	-28 to -1	1	8	15	22	1	8	15	22	1	1			
Window						± 2 days					+1 wk	± 1 wk	± 1 wk	
EORTC QLQ-C30 (g)	X	X				X				X	X	X	X	
EORTC QLQ-MY20 (g)	X	X				X				X	X	X	X	
EQ-5D-5L (g)	X	X			X					X	X	X	X	
HU assessment (g)			X			X				X	X	X	X	
Imaging disease assessment														
Bone (h)	X													
Soft-tissue plasmacytoma (i)	X	X								X (& every 3 cycles hereafter)				
Investigator's assessment of disease response/status					X					X	X	X	X	
Determination of dose escalation						X (d)								

Footnotes are on last table page.

### **3.4 Corporate Identification**

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

#### **6.1.3.3 Other Assessment Details**

An independent data monitoring committee (IDMC) will review safety data at regular intervals, approximately every 6 months or per IDMC request.

After the data cutoff date for the study analysis has occurred, no further analyses are planned, and all central efficacy and investigator assessments of disease response (ie, PFS, response rates, and TTP) for protocol purposes will be discontinued. As such, no further laboratory samples related to response assessments will be sent to the central laboratory.

#### **6.1.4 Statistical Analyses**

Upon completion of this study, approximately 120 patients will have been enrolled globally. The study analysis for PFS will occur after approximately 81 PFS events have been observed (after approximately 28 months from first patient enrollment), for 80% power at a 2-sided 0.20 level of significance. Analysis of all secondary endpoints will occur at the same time as this study analysis, which is the only planned formal analysis for this study; no further formal analyses are planned. Long-term safety data collected after the data cutoff date for the study analysis will be summarized descriptively in a clinical study report addendum.

See Section [13.0](#) for more information.

### **6.2 Number of Patients**

Upon completion of this study, approximately 120 patients will have been enrolled at approximately 100 study sites globally: approximately 72 in Arm A (ixa+dex) and approximately 48 in Arm B (pom+dex). Enrollment is defined as randomization to a study therapy.

### **6.3 Duration of Study**

#### **6.3.1 Duration of an Individual Patient's Study Participation**

Patients, including those who achieve a clinical response, may receive study therapy until they experience PD, have an unacceptable toxicity, or withdraw consent, or until the sponsor terminates the study.

#### **6.3.2 End of Study/Study Completion Definition**

The study will be considered complete after the study analysis (for PFS and all secondary endpoints) has been completed or the study has been terminated by the sponsor. The estimated time frame for study completion is approximately 28 months.

#### **6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures**

Refer to [Table 6.a](#) for disclosures information for all primary and secondary endpoints.

manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified according to dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 8.4.3). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS), are rare, serious blood disorders that cause low levels of platelets and red blood cells and result in blood clots in small blood vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders, including fatal cases, have been reported in patients receiving ixazomib. TMA should be managed according to standard medical practice.

### **Neutropenia**

Blood counts should be monitored regularly with additional testing, as appropriate, 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 according to dose modification recommendations in the protocol when neutropenia occurs (see Section 8.4.3). Febrile neutropenia should be managed as per local guidelines. Therapy can be reinitiated at a reduced level upon recovery of ANC.

### **Fluid Deficit**

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

Fluid deficit should be promptly corrected before administration of ixazomib and as needed during treatment to avoid dehydration.

### **Hypotension**

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored as per standard of care 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 decreased appetite. Patients taking medications or diuretics to manage their blood pressure (for either hypotension 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 administration of ixazomib and as needed during treatment to avoid dehydration.

### **Posterior Reversible Encephalopathy Syndrome**

Posterior reversible encephalopathy syndrome has been reported with ixazomib. This condition is usually transient and reversible. It is characterized by headache, seizures, and visual loss, and abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI) or computed tomography (CT). 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.

**EQ-5D-5L**

The EQ-5D-5L consists of 2 pages: the EQ-5D-5L descriptive system and the EuroQol visual analogue scale (EQ VAS) ([Appendix J](#)). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each rated on 5 levels. The EQ VAS records the respondent's self-rated health on a 20 cm, vertical, visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Upon implementation of Amendment 06, PRO data will no longer be collected.

**9.4.10.2 HU**

HU data will be collected on Day 1 visits of every cycle during the Treatment period, at the EOT visit, and at the PFS Follow-up visits, every 4 ( $\pm 1$ ) weeks during the PFS Follow-up period (see the previous, full Schedule of Events ([Appendix L](#)). Only non-protocol-directed health care encounters (ie, those not scheduled per this study protocol) are to be entered into the HU form ([Appendix K](#)). The form is to include all hospitalizations, emergency room visits, and non-protocol-directed outpatient visits (eg, physician/clinic visits, laboratory/pathology/radiology/biomedical imaging workups); missed work by the patient and/or caregiver is also collected on the form.

Note that the HU form is NOT intended to be completed by patient directly. At each HU assessment, the data collection recall timeframe is from the time of the previous study visit.

Upon implementation of Amendment 06, HU and PFS data will no longer be collected.

**9.4.11 Imaging Disease Assessment**

Imaging to assess status of bone disease will be performed at Screening (within 8 weeks before randomization) for all patients by means of skeletal survey, CT, MRI, or positron emission tomography (PET)-CT. Additional assessments can be done at the discretion of the investigator (ie, for suspected increased or new bone lesions or PD), and should be done by the same modality. At least the following areas should be assessed: head, neck, chest, abdomen, pelvis, arms, and legs.

Imaging to assess extramedullary disease will be done at Screening (within 8 weeks before randomization) for all patients by means of CT, MRI, or PET-CT. In patients for whom extramedullary disease is found at Screening, additional assessments should be done, using the same modality, at Cycle 1 Day 1 and every 3 cycles thereafter, unless the Screening assessment is completed before 14 days before Cycle 1 Day 1; then the next assessment can be on Cycle 3 Day 1.

Imaging assessments will be analyzed locally and reports maintained with the patient record for review during monitoring visits.

Upon implementation of Amendment 06, imaging will no longer be performed at specified times per the Schedule of Events.

- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Pregnancy (patient must be discontinued).
- Progressive disease.
- Death.
- Other.

Upon implementation of Amendment 06, only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib or pomalidomide, as well as dexamethasone, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care. The reason for treatment discontinuation must be recorded in the eCRF but no approval is required.

## **9.8 Withdrawal of Patients From Study**

A patient will be withdrawn from the study for any of the following reasons:

- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

Upon implementation of Amendment 06, PFS and OS follow-up will no longer be performed. Patients will now complete the study immediately following the EOT visit. The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

## **9.9 Study Closure**

The study will be considered complete after the study analysis is completed or the study has been terminated. In addition to PFS, at the time of the study analysis, OS and other secondary endpoints will be assessed, with no later analyses to follow. Only patients who continue to demonstrate clinical benefit but who do not have other means of access to the study drugs will continue on the study. Patients continuing their current study treatment may do so until such time as other means of accessing the study drugs are arranged. When possible, patients should complete an EOT visit and transition onto an alternative supply of (eg, commercially available) ixazomib or pomalidomide, as well as dexamethasone, or onto another standard of care treatment. Discontinued patients will be treated by their physician per local standard of care.

		US and Canada
CCI		
CCI		
		<u>Japan</u>
Emergency Center for Safety Information (available 24 hours a day, 365 days a year)		
CCI		

Planned hospital admissions or surgical procedures for an illness or disease that existed before study therapy was given are **not** to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study therapy administration. For serious pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [62]. The criteria are provided in the Study Manual.

Relationship of the event to study therapy administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: “Is there a reasonable possibility that the AE is associated with the study therapy?”



Proprietary Information - Not for Distribution or Subsequent Use

Applicable Terms of Use

## **11.0 STUDY-SPECIFIC COMMITTEES**

An IDMC will be used in this study.

### **11.1 IDMC**

An IDMC supported by an independent statistician will review safety data, including the feasibility and safety of the intrapatient dose escalation of ixazomib from 4 mg to 5.5 mg at regularly scheduled meetings prespecified in the IDMC charter.

The IDMC will provide a recommendation regarding study continuation based on the safety parameters. If the study is terminated early based on the IDMC recommendation, Millennium will notify the appropriate regulatory authorities.

Study accrual will not be interrupted because of the scheduled safety reviews. The IDMC or ixazomib study team may request an ad hoc meeting for any reason, including a significant unexpected safety event, unplanned unblinding of study results, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, subject incidence rates of AEs (including all SAEs, treatment-related AEs, serious treatment-related events, and events requiring the discontinuation of study therapy) will be tabulated by system organ class, preferred term, and severity grade. Listings and/or narratives of on-study deaths and other serious and significant AEs, including any early withdrawals because of AEs, will be provided. Records of all meetings will be archived. The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Millennium. Further details will be provided in the IDMC charter.

Property of Takeda: For Non-Commercial Use Only  
Subject to the Applicable Terms of Use

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to study therapy and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study therapy and through 30 days after the last dose of study therapy will be tabulated.

AEs will be tabulated according to MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 TEAEs.
- Grade 4 or higher TEAEs.
- Grade 3 drug-related TEAEs.
- Grade 4 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those reported by  $\geq 10\%$  of all patients).
- All SAEs.
- Grade  $\geq 2$  peripheral neuropathy.
- New primary malignancies.
- Any AE resulting in dose modification or discontinuation of any study therapy.
- Any other AE that in the opinion of the investigator is a clinically significant event.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from Baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from Baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG performance scores will be summarized using a shift table.

Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the ixazomib safety profile.

All concomitant medications collected from the first dose of study therapy throughout the study period will be classified to preferred terms according to the World Health Organization drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of ixazomib.

## **15.0 ETHICAL ASPECTS OF THE STUDY**

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix B](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

The rationale for the open-study design is primarily to reduce the treatment burden on study patients. A placebo control would require patients to ingest a large number of additional pills (23 additional placebo tablets per cycle for patients receiving pom+dex, and 41 additional placebo tablets per cycle for patients receiving ixa+dex). Furthermore, any QOL benefit attributed to taking oral medications during just 8 out of 28 days (ixa+dex arm) versus 22 out of 28 days (pom+dex arm) would be lost.

Pom+dex was selected as the control regimen for many reasons. Pom+dex is a US- and EU-approved treatment regimen for RRMM. Because the investigational regimen is an entirely oral therapy, the all-oral standard-of-care comparator of pom+dex provides a more balanced treatment burden between the 2 regimens than would a study where 1 regimen required periodic intravenous infusions. In addition, a comparison of ixa+dex to a single-agent comparator such as daratumumab would not allow for the characterization of the ixazomib contribution to the observed treatment effect, unlike the comparison of ixa+dex to pom+dex, in which the dexamethasone contribution would be similar in both treatment groups.

### **15.1 IRB and/or IEC Approval**

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol’s review and approval. This protocol, the IB, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. In

- Alanine aminotransferase and aspartate aminotransferase  $\leq 3 \times \text{ULN}$ .
  - Calculated creatinine clearance  $\geq 30 \text{ mL/min}$  (see Section 9.4.15.1).
9. Female patients who:
- Are postmenopausal for at least 1 year before the Screening Visit, OR
  - Are surgically sterile, OR
  - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, for 4 weeks before signing the informed consent through 90 days after the last dose of study therapy, OR
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.), AND
  - In women of childbearing potential (if randomized to Arm B), agree to have 2 negative pregnancy tests before initiating therapy, with 1 or both being a serum test (the first test should be performed within 10-14 days before; the second, within 24 hours before); then have a negative pregnancy test weekly during the first month and monthly thereafter in women with regular menstrual cycles or every 2 weeks thereafter in women with irregular menstrual cycles; and have a negative pregnancy test 4 weeks after the last dose of study therapy.
10. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
- Agree to practice effective barrier contraception during the entire study Treatment period and through 90 days after the last dose of study therapy, OR
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.), AND
  - Do not donate semen or sperm during treatment and for 90 days after the last dose of study therapy.
11. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12. Suitable venous access for the study-required blood sampling, including PK sampling.
13. Patient is willing and able to adhere to the study visit schedule and other protocol requirements including blood sampling and bone marrow aspiration.
14. Recovered (ie, Grade  $\leq 1$  nonhematologic toxicity) from the reversible effects of prior anticancer therapy.

B (pom+dex) only, hematology samples will be collected at Cycle 1 and at Cycle 2 Days 8 and 22. Samples may be collected 24 hours before, or prior to dosing on, Days 8 and 22. Laboratory reports must be reviewed by the investigator prior to dosing for all cycle visits, and clinical significance must be indicated. In addition, the investigator must assess any AEs or concomitant medication changes prior to dosing. Local laboratory evaluations and evaluation of SPEP and UPEP for confirmation of PD may be done more frequently at the investigator's discretion (ie, for acute management of TEAEs).

- (g) All central laboratory assessments are discontinued. Patients should be assessed and treated according to local standard of care using local laboratory evaluations. Abnormal hematology and chemistry data are to be collected and recorded in the eCRF only to the extent that they are needed to document or support an AE. Laboratory assessments to inform dosing decisions and routinely monitor patients do not need to be recorded in the eCRF.
- (h) Patients should be assessed and treated per local standard of care. All AEs/SAEs will be recorded in the eCRF according to the criteria outlined in Section 12.0. Patient safety outside the protocol assessments should be monitored during the time between on-site visits at the investigator's discretion, per standard of care. At minimum, there will be a phone call with an investigator within the specified-visit window timeframe, which will include an assessment of AEs/SAEs.

## Previous Schedule of Events (continued)

Study Procedures	Screening	Treatment Period (a)								EOT (b)	Follow-up (c)		
		28-Day Cycles									PFS	OS	
		C1	C2 (d)			C3	C4 and Beyond				Every 4 wk, Until PD or Subsequent Therapy	Every 12 wk, After PD or Subsequent Therapy	
Cycle										30 days after last dose or before start of new line of treatment			
Days	-28 to -1	1	8	15	22	1	8	15	22	1	1		
Window		$\pm 2$ days								+1 wk	$\pm 1$ wk	$\pm 1$ wk	
Pregnancy test, Arm A (j)	X	X								X			
Pregnancy test, Arm B (j) (increased frequency required per pom PI)	X	X	X	X		X			X	X			
Hematology laboratory tests, Arm A (k)	X	X		X	X	X		X	X	X	X		
Hematology laboratory tests, Arm B (k) (increased frequency required per pom SmPC)	X	X	X	X	X	X	X	X	X	X	X		
Chemistry laboratory tests (k)	X	X			X			X	X	X	X		
LDH and $\beta_2$ -microglobulin	X												
M-protein (SPEP)	X	X (l)			X			X	X	X	X		
M-protein (UPEP [24-h urine])	X	X (l)			X			X	X	X	X		
Serum free light chain assay	X	X (l)			X			X	X	X	X		
Immunofixation: serum and urine (m)	X	X (l)			X			X	X	X	X		
Quantification of immunoglobulins (n)	X	X (l)			X			X	X	X	X		
BMA or biopsy for disease assessment (o)	X												
CCI													
CCI													

Footnotes are on last table page.

CONFIDENTIAL